What is the optimal time window for treating deep venous thrombosis? Acute vs subacute vs chronic

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Disclosure

Peter A. Schneider:

I have the following potential conflicts of interest to report:

- Scientific Advisory Board (not compensated): Medtronic, Abbott, Cardinal Health
- Intellectual property: modest Royalty, Cook
- Chief Medical Officer: Intact Vascular
# Catheter-based Intervention for Ilio-femoral DVT

## Beneficial Effects


<table>
<thead>
<tr>
<th>Outcome</th>
<th>RR</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>Events / Total</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postthrombotic syndrome</td>
<td></td>
<td></td>
<td></td>
<td>lysis</td>
<td>anticoag</td>
</tr>
<tr>
<td>AbuRahma, 2001</td>
<td>0.32</td>
<td>0.13</td>
<td>0.78</td>
<td>4 / 18</td>
<td>23 / 33</td>
</tr>
<tr>
<td>Markevicius, 2004</td>
<td>0.10</td>
<td>0.03</td>
<td>0.29</td>
<td>3 / 43</td>
<td>47 / 64</td>
</tr>
<tr>
<td><strong>Pooled RR</strong></td>
<td>0.18</td>
<td>0.05</td>
<td>0.62</td>
<td>7 / 61</td>
<td>70 / 97</td>
</tr>
<tr>
<td>Venous reflux</td>
<td></td>
<td></td>
<td></td>
<td>11 / 60</td>
<td>84 / 90</td>
</tr>
<tr>
<td>Markevicius, 2004</td>
<td>0.20</td>
<td>0.11</td>
<td>0.34</td>
<td>2 / 18</td>
<td>7 / 17</td>
</tr>
<tr>
<td>Elsharawy, 2002</td>
<td>0.27</td>
<td>0.06</td>
<td>1.12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enden, 2009</td>
<td>0.91</td>
<td>0.67</td>
<td>1.22</td>
<td>30 / 50</td>
<td>35 / 53</td>
</tr>
<tr>
<td><strong>Pooled RR</strong></td>
<td>0.39</td>
<td>0.16</td>
<td>1.00</td>
<td>43 / 128</td>
<td>126 / 160</td>
</tr>
<tr>
<td>Venous obstruction</td>
<td></td>
<td></td>
<td></td>
<td>8 / 18</td>
<td>26 / 33</td>
</tr>
<tr>
<td>AbuRahma, 2001</td>
<td>0.56</td>
<td>0.33</td>
<td>0.97</td>
<td>1 / 60</td>
<td>21 / 90</td>
</tr>
<tr>
<td>Markevicius, 2004</td>
<td>0.07</td>
<td>0.01</td>
<td>0.52</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elsharawy, 2002</td>
<td>0.31</td>
<td>0.15</td>
<td>0.68</td>
<td>5 / 18</td>
<td>15 / 17</td>
</tr>
<tr>
<td>Enden, 2009</td>
<td>0.56</td>
<td>0.37</td>
<td>0.85</td>
<td>18 / 50</td>
<td>34 / 53</td>
</tr>
<tr>
<td><strong>Pooled RR</strong></td>
<td>0.38</td>
<td>0.17</td>
<td>0.87</td>
<td>32 / 146</td>
<td>96 / 193</td>
</tr>
</tbody>
</table>

Favors thrombolysis   Favors anticoagulation
Catheter-based Intervention for Ilio-femoral DVT

Beneficial Effects: CaVenT Study

- Multicenter RCT of Ilio-femoral DVT
- Treatment initiated within 21 days
- Mean time to initiation of treatment 6.6 days

<table>
<thead>
<tr>
<th></th>
<th>Additional catheter-directed thrombolysis (n=90)</th>
<th>Standard treatment only (n=99)</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>% (95% CI)</td>
<td>n</td>
<td>% (95% CI)</td>
</tr>
<tr>
<td>Post-thrombotic syndrome at 24 months†</td>
<td>37  41.1% (31.5–51.4)</td>
<td>55</td>
<td>55.6% (45.7–65.0)</td>
</tr>
<tr>
<td>Iliofemoral patency at 6 months†‡</td>
<td>58  65.9% (55.5–75.0)</td>
<td>45</td>
<td>47.4% (37.6–57.3)</td>
</tr>
</tbody>
</table>

Post-thrombotic Syndrome

• Miserable, time consuming, exhausting.
• I manage a lot of chronic venous insufficiency, the resources and diligence required are grossly underestimated, in my opinion.
Better Thrombus Removal = Less Post-thrombotic Syndrome

**Fig 1.** Plot of clinical class of CEAP at follow-up vs residual thrombus at treatment end. Data points may represent more than one patient.

2.1. We suggest a strategy of early thrombus removal in selected patients meeting the following criteria: (a) a first episode of acute iliofemoral deep venous thrombosis, (b) symptoms <14 days in duration, (c) a low risk of bleeding, and (d) ambulatory with good functional capacity and an acceptable life expectancy.
Timing DVT Treatment
We Can’t All Be Correct!

• Goal: Preservation of valve function
• Timing: Best response to intervention when thrombus is acute.
  – 10 days: National Venous Registry
  – 14 days: ATTRACT Trial
  – 21 days: CaVenT Trial

Timing of DVT Treatment

• Time is a surrogate for describing the degree to which the clot has become organized.
  – Initially asymptomatic or mildly symptomatic and do not report.
  – Acute thrombus forms on top of old organized but previously asymptomatic clot.
  – In dehydrated patients and those in a pro-inflammatory state, the clot may organize faster.
  – High degree of variability in inflammatory process.
Timing of DVT Treatment
Inflammation Caused by Thrombus Formation

- **Endothelial activity:** Vasodilatory, local fibrinolysis
  - Thrombomodulin and Protein C activation
  - Production of heparin sulfate, anti-thrombin, TPA nitric oxide, prostacyclin, tissue factor pathway inhibitor

- **Thrombus initiates inflammation**
  - Platelet activating factor, endothelin-1

- **Prothrombotic:** vWF, TF, activated Factor V, PAI-1

- **Cell adhesion:** activated platelets, P-selectin, E-selectin, leukocyte activation and transmigration

- **Promote the inflammatory cycle:** TF, fibrinogen, phosphatidylserine, decreases thrombomodulin and Protein C
Timing of DVT Treatment

• Early phase treatment of acute DVT is best.
• The sooner treatment is initiated, whether medical or interventional, the better.
• The younger and more symptomatic the patient, the more proximal the DVT, active prior to DVT, the better.
• We wish it was that simple.
Timing of DVT Intervention
Poor Candidates in the Acute Setting

- Recent surgery
- Post-partum
- Pregnant
- Cancer
- Severe hypertension
- GI bleed
- Cerebral bleed
- Stroke
- Late presentation
Timing of DVT Treatment

Logistical Issues of DVT Presentation

• Patient presentation is often delayed.
• Contraindications to treatment.
• When patients do present who have no contraindications, only some will be good candidates and likely to benefit.
Timing of DVT Treatment
Technical Aspects: Acute vs chronic

<table>
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<th>Acute</th>
<th>Chronic</th>
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<tr>
<td>• Higher likelihood of clearing everything</td>
<td>• Less likely to clear anything</td>
</tr>
<tr>
<td>• If you leave thrombus behind, the lytic system plus</td>
<td>• Likely to leave chronic disease behind</td>
</tr>
<tr>
<td>anticoagulation may improve it</td>
<td>• More likely to need stents for reconstruction</td>
</tr>
<tr>
<td>• Less likely to need a stent unless a chronic lesion</td>
<td></td>
</tr>
<tr>
<td>is uncovered</td>
<td></td>
</tr>
</tbody>
</table>
Timing of DVT Treatment

Chronic Iliac Vein Occlusion

Fig 3. Cumulative primary, assisted-primary, and secondary patency rates of 603 limbs after iliofemoral stenting. The lower numbers represent limbs at risk for each time interval (all standard error of the mean $<10\%$).
Treatment of Chronic Occlusions

• Ideal patient for treatment of chronic occlusion
  – 6 months out
  – Patent common femoral vein
  – History of being physically active
  – No hypercoag state

Diseases of the Veins. 2nd edition, Browse et al. 1999
## Timing of DVT Treatment

### Why Does It Matter?

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<tr>
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<th>Acute (&lt;2 weeks)</th>
<th>Chronic (&gt;6 months)</th>
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<td>Results</td>
<td>Favorable results. Complete thrombus removal in many patients.</td>
<td>Acceptable results. Stent patency can be enhanced with technique, reintervention.</td>
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<td>Focus</td>
<td>Thrombus removal.</td>
<td>Stenting chronic lesions.</td>
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### Timing of DVT Treatment

**Why Does It Matter?**

<table>
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<tr>
<th></th>
<th><strong>Acute</strong> (&lt;2 weeks)</th>
<th><strong>Subacute</strong></th>
<th><strong>Chronic</strong> (&gt;6 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Results</strong></td>
<td>Favorable results. Complete thrombus removal in many patients.</td>
<td>Unknown</td>
<td>Acceptable results. Stent patency can be enhanced with technique, reintervention.</td>
</tr>
<tr>
<td><strong>Focus</strong></td>
<td>Thrombus removal.</td>
<td>Organized thrombus inflammation, and scar. Thrombus well formed but still mobile. Organized thrombus prevents full stent expansion. Much more of an adventure.</td>
<td>Stenting chronic lesions.</td>
</tr>
</tbody>
</table>
Timing of DVT Treatment

Conclusion

• Reasonable results in both the acute and chronic settings but indications, techniques and management are significantly different.

• We avoid the subacute setting except for special circumstances:
  – Phlegmasia
  – Re-thrombosis
    • especially if clear cut May-Thurner
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