Iliofemoral DVT: Minimizing Post-Thrombotic Syndrome

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Acute Deep Venous Thrombosis Incidence & Outcomes

- 117 of 100,000 person years in US
- Recurrent DVT in ~30% within 5-10 years
- Post-thrombotic syndrome (PTS) in ~40% within 2 years

Post-thrombotic syndrome (PTS)

- 20-50% of DVT patients in 1-2 years
- Symptoms and signs vary
- Severe in 5-10%

PTS: Villalta scale

PTS after Acute DVT

- Prospective study of 387 patients
- Villalta scale from 1 to 24 months

PTS Severity

<table>
<thead>
<tr>
<th>Prevalence</th>
<th>Mild: 5-9</th>
<th>Moderate: 10-14</th>
<th>Severe: &gt;14 or ulcer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>30%</td>
<td>10%</td>
<td>3%</td>
</tr>
</tbody>
</table>

Predictors of Higher Scores

<table>
<thead>
<tr>
<th>Increase in Score</th>
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</thead>
<tbody>
<tr>
<td>Common femoral or iliac DVT: +2.23 (+1.29 to +3.16)</td>
</tr>
<tr>
<td>Previous ipsilateral DVT: +1.78 (+0.69 to +2.87)</td>
</tr>
<tr>
<td>Severity at 1 month: +2.97 (+3.03, +5.00)</td>
</tr>
</tbody>
</table>

DVT Classification

Proximal vs distal
LET classification
I - isolated calf vein thrombosis
II - femoral-popliteal vein thrombosis
III - common femoral and/or iliac vein thrombosis
IV - IVC thrombosis

Non-occlusive thrombus in common femoral vein graded as class II
Iliofemoral DVT: Natural History

- Common channel of venous drainage from involved lower extremity obliterated
- Sequela with anticoagulation alone
  - Persistent obstruction 70%
  - Chronic venous insufficiency >90%
  - Venous claudication 40%
  - Venous ulceration 15%
  - Recurrent VTE 11.8% in 3 months
    - OR 2.4 (95% CI 0.95 to 5.9)


Treatment of Acute DVT

- Anticoagulation
- Compression stockings
- Catheter directed thrombolysis (CDT)
  - Pharmacomechanical adjuncts
  - Venoplasty and stenting

4 studies: thrombolysis vs anticoagulation
Quality generally low

CDT: Meta-analysis

- 4 studies: thrombolysis vs anticoagulation
- Quality generally low

Egypt Trial

- 1st randomized controlled trial – N=35
  - CDT + anticoagulation (N=18)
  - Anticoagulation alone (N=17)
- Iliofemoral DVT <10 days old
  - Streptokinase: pulse spray → continuous infusion → venogram 12 hour intervals
- Venous function at 6 months
  - Extent of residual thrombus
  - Venous reflux and venous outflow
Egypt Trial

- No major bleeding complications
- Symptomatic PE 6% - anticoagulant group

CaVenT Trial

- Norwegian randomized trial – N=209
  - CDT + anticoagulation (N=101)
  - Anticoagulation alone (N=108)
  - 1st DVT above mid thigh ≤ 21 days
  - Alteplase infusion → venogram daily
    - Adjunctive angioplasty and stenting (<50% stenosis)
  - Co-primary outcomes
    - Iliofemoral patency at 6 months
    - PTS by Villalta score at 24 months

CaVenT Trial

- Iliofemoral DVT <50%
- Compliance with compression stockings higher in CDT group
Adjunctive Procedures

CaVenT Trial

Extent of Thrombolysis Achieved

48% 17% 25% 57%

Complete <50% 50-99% ≥100%

AngioJet Venous stents Balloon angioplasty ± stenting

CaVenT Trial

48% 17% 25% 57%

Complete <50% 50-99% ≥100%

AngioJet Venous stents Balloon angioplasty ± stenting

CaVenT Trial: Results at 5 years

• N=176 patients (84% of initial 209)

<table>
<thead>
<tr>
<th>Procedure</th>
<th>N=87</th>
<th>N=89</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTS</td>
<td>43%</td>
<td>71%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Severe PTS</td>
<td>9%</td>
<td>5%</td>
<td></td>
</tr>
</tbody>
</table>

ARR 28% (95% CI: 14-42), NNT = 4
No difference in QOL

Haig et al. Lancet Haematol 2016; 3(2):e64-71

ATTRACT Trial

• Multicenter, randomized, open-label, assessor blinded, controlled trial
• Symptomatic, proximal DVT <14 days
  • Iliac, common femoral, &/or femoral vein DVT
  • No prior DVT within 2 years
• Randomization stratified
  • Anatomical extent (common femoral ± iliac vein)
• Primary outcome – PTS at 24 months
  • Villalta Scale

ATTRACT Trial

• Anticoagulation
  • Heparin + Coumadin
  • Duration ≥ 3 months
• PCDT
  • Pharmacomechanical catheter directed thrombolysis
  • 30-40 mmHg knee high compression stockings at 10 day FU

ATTRACT Trial

• PCDT
  • Good inflow into popliteal vein
    • "Isolated thrombolysis" – Trellis
    • "Powerpulse thrombolysis" – AngioJet
  • Poor inflow into popliteal vein
    • "Infusion-first thrombolysis"
      • rt-PA infusion at 0.01 mg/kg/hr
      • Max rt-PA 35 mg, 30 hours
  • Adjunctive treatment
    • PTA ± stenting of obstructive lesions

ATTRACT Trial
ATTRACT Trial

- N = 692 patients, 24 month FU

No difference in any PTS (Villalta >5 or ulcer)
No difference in QoL measures
No difference when stratified by level of DVT

Vedantham S et al. NEJM 2017; 377:2240-52

ATTRACT Trial

<table>
<thead>
<tr>
<th></th>
<th>PCDT N = 337</th>
<th>Anticoagulation N = 355</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTS</td>
<td>46.7%</td>
<td>48.2%</td>
<td>.56</td>
</tr>
<tr>
<td>Generic QoL (SF-36)</td>
<td>11.8%</td>
<td>10.1%</td>
<td>.37</td>
</tr>
<tr>
<td>Venous QoL (VEINES)</td>
<td>27.7%</td>
<td>23.5%</td>
<td>.08</td>
</tr>
</tbody>
</table>

PCDT reduced PTS severity
Difference in PTS severity seen mostly in iliofemoral DVT patients

Vedantham S et al. NEJM 2017; 377:2240-52

ATTRACT Trial

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<th>PCDT N = 337</th>
<th>Anticoagulation N = 355</th>
<th>P value</th>
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<tbody>
<tr>
<td>Moderate or Severe PTS</td>
<td>17.9%</td>
<td>23.7%</td>
<td>.035</td>
</tr>
<tr>
<td>Iliofemoral DVT</td>
<td>18.4%</td>
<td>28.2%</td>
<td></td>
</tr>
<tr>
<td>Femoropopliteal DVT</td>
<td>17.1%</td>
<td>18.1%</td>
<td></td>
</tr>
</tbody>
</table>

Removal of the residual thrombus associated with increased risk of PTS

Comparative Safety of CDT

- Observational study: NIS from 2005 – 2010
- Proximal or caval DVT
- CDT + Anticoagulation in 4.1%
  
  - Increase from 2.3% 2005 to 5.9% in 2010
- Propensity scores
  
  - 2 matched groups of N=3594 patients
- Outcomes
  
  - Primary: in-hospital mortality
  - Secondary: bleeding complications

Bashir R et al. JAMA Intern Med 2014; 174(9):1494-1501

No significant difference in mortality

Increased blood transfusion, ICH, PE and IVC filter placement with CDT.

Bashir R et al. JAMA Intern Med 2014; 174(9):1494-1501

Pharmacomechanical adjuncts: Advantages

- Local administration of thrombolytic agent
- Reduced thrombolytic dose
- Reduced thrombolytic infusion time
- Decreasing bleeding complications
- Reduced ICU stay
- Reduced overall hospital treatment cost

TORPEDO Trial

- Randomized trial – N=183
- Anticoagulation ± PEVI (Percutaneous endovascular intervention)
- Symptomatic, proximal DVT
  
  - Femoropopliteal, iliac veins, or IVC
- Outcomes – 6 months, final FU
  
  - Recurrent VTE
  - PTS – 2 new symptoms + clinical sign (edema + reflux or venous stasis changes)


50% with no known history of DVT had venographic evidence of prior DVT

Infusion thrombolysis – 37%

Balloon venoplasty – 76%

Stenting – 30%

- Total 47 stents, 21 in femoropopliteal veins

TORPEDO Trial

TABLE 1

<table>
<thead>
<tr>
<th>Interventional Approaches Utilized in the 96 PEVI Patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infusion thrombolysis</td>
<td>37</td>
</tr>
<tr>
<td>Balloon venoplasty</td>
<td>76</td>
</tr>
<tr>
<td>Stenting</td>
<td>30</td>
</tr>
</tbody>
</table>

**TORPEDO Trial**

Primary Endpoints at 30 Months

<table>
<thead>
<tr>
<th></th>
<th>PEVI N=88/91</th>
<th>Control N=81/92</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTS</td>
<td>6 (6.8%)</td>
<td>24 (29.6%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>VTE</td>
<td>4 (4.5%)</td>
<td>13 (16.0%)</td>
<td>.02</td>
</tr>
</tbody>
</table>

PEVI is superior to anticoagulation alone in reducing PTS and VTE

Limitations
- PTS not defined by validated scale
- PEVI more likely to be on aspirin and Plavix
- Aspirin with RR 0.37 (95% CI 0.19 – 0.74) for PTS

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**Pharmacomechanical Catheter Directed Thrombolysis: Patient Selection!**

- Highest anatomical extent of DVT
- Iliofemoral DVT
- Length and degree of symptoms
  - Acute <14 days
  - Risk factors for PTS
  - Risk factors for bleeding
  - Functional status

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**Venous Stenting**

- Recognition and treatment of obstructive lesions of iliac veins impacts success of CDT
- Criteria for stenting
  - Pressure gradient of 5 mmHg?
  - ≥50% stenosis by IVUS
  - Venous collaterals
- Self expanding stents
  - Elastic recoil after venoplasty from fibrosis
  - Oversized (14-16 mm)

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**Venous Stenting**

- Pooled analysis – 19 studies (N=1046)
  - CDT ± percutaneous mechanical thrombectomy
  - Acute DVT in 88%, iliofemoral DVT 66%
  - Stents in 46%
- National Venous Registry
  - CDT in 303 limbs in 287 of 473 patients with DVT
  - Acute DVT in 85%, iliofemoral DVT 71%
  - Stents 33%
  - Patency 1 year: 74% with iliac stent vs 53% without (P<.001)

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**Durable Patency after Venous Stenting**

- Retrospective analysis
  - N=61: CDT + venous stenting
  - Acute iliofemoral DVT (<10 days)
**Durable Patency after Venous Stenting**

- Retrospective analysis
- N=32: CDT in 92% + iliac vein stenting
- Acute DVT 78%


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**Compression Stockings: Significant Reduction in PTS**

Proximal DVT
Active stockings vs no stockings for 2 years
Outcome – PTS (5 years FU)

<table>
<thead>
<tr>
<th>Study</th>
<th>Timing</th>
<th>Group</th>
<th>N</th>
<th>PTS</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brandjes</td>
<td>2-3 weeks</td>
<td>Stockings</td>
<td>96</td>
<td>20%</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Control</td>
<td>98</td>
<td>47%</td>
<td></td>
</tr>
<tr>
<td>Prandoni</td>
<td>5-10 days</td>
<td>Stockings</td>
<td>90</td>
<td>24.5%</td>
<td>.011</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Control</td>
<td>90</td>
<td>49.1%</td>
<td></td>
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**Compression Stockings: Sox Trial**

- Multicenter, randomized trial
- 1st proximal DVT
  - <40% common femoral and iliac veins
  - Active vs placebo elastic compression stockings (ECS) for 2 years
    - 30-40 mmHg vs <5 mmHg at ankle
    - Applied within 2 weeks
  - Outcome: PTS at ≥ 6 months


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**Sox Trial: PTS by Ginsberg’s criteria**

1° outcome: Leg pain + swelling ≥ 1 month

HR 1.13, 95% CI (0.73 – 1.76)

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**Sox Trial: PTS by Villalta Score**

2° outcome: ≥ 5 or venous ulcer

HR 1.00, 95% CI (0.81 – 1.24)

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**No difference in outcomes**

Findings do not support routine use of elastic compression stockings after DVT

Sox Trial: Limitations in Methodology

- Timing of ECS application (delayed)
- Fitting of ECS (mailed, no training)
- Evaluation of compliance (interview, frequent defined as 3-6 days)
- Compliance low
- 69% by 24 months
- 56% used ECS ≥3 days/week at 24 months

Study Compliance

<table>
<thead>
<tr>
<th>Study</th>
<th>Compliance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brandjes</td>
<td>76% always</td>
</tr>
<tr>
<td>Prandoni</td>
<td>87% ≥80% of daytime hours</td>
</tr>
<tr>
<td>Kahn (SOX)</td>
<td>56% ≥3 days/week</td>
</tr>
</tbody>
</table>

Not justifiable to entirely abandon compression stockings to prevent PTS

Anticoagulation: Poor Quality and Increased PTS

- Calculated time spent < INR 2-3
- 1st DVT – treated with vitamin K antagonist
- N=244 – median FU 4.9 years
- 30% of time INR <2
- 33% developed PTS
- Patients with >50% subtherapeutic INR associated with increased risk of PTS
  - OR 2.7, 95% CI 1.4 to 5.1

Duration of Anticoagulation: >3 months for Unprovoked DVT

- 3 months + 24 months warfarin vs placebo

<table>
<thead>
<tr>
<th></th>
<th>Warfarin N=255</th>
<th>Placebo N=253</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent VTE</td>
<td>2.6%</td>
<td>7.2%</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Bleeding</td>
<td>0.9</td>
<td>0.4%</td>
<td>.25</td>
</tr>
</tbody>
</table>

Duration of Anticoagulation: >3 months for Unprovoked DVT

- Low vs conventional intensity warfarin

<table>
<thead>
<tr>
<th></th>
<th>Conventional N=169</th>
<th>Low Intensity N=369</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent VTE</td>
<td>0.7%</td>
<td>1.9%</td>
<td>2.8 (1.1-7.0)</td>
</tr>
<tr>
<td>Bleeding</td>
<td>0.9%</td>
<td>1.1%</td>
<td>1.2 (0.8-2.1)</td>
</tr>
</tbody>
</table>

- ACCP guidelines: Long term treatment
  - Unprovoked proximal DVT/PE + low/moderating bleeding risk
  - Cancer associated thrombosis

Conclusions

- Iliofemoral DVT associated with significant PTS
- PCDT can reduce PTS
  - Patient selection!
    - Mechanism to identify patients with iliofemoral DVT
    - Adjuncts to improve risks and outcomes of CDT
      - Minimize thrombolysis time
      - Treat residual stenosis
  - Compression stockings for ≥ 6 months
  - Indefinite anticoagulation if unprovoked