Post-thrombotic syndrome: Impact and potential prevention

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# Disclosures

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<tr>
<th>Category</th>
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Overview of session

What is the post-thrombotic syndrome (PTS) and what is its impact?

Why does it occur after DVT?

How is PTS prevented and treated?
Mr. G.
27 year old chef
Received prompt, appropriate anticoagulant treatment of acute DVT

8 months later
Unable to stand for extended periods of time due to leg pain and aching
No longer able to work
**Typical clinical features of PTS**

<table>
<thead>
<tr>
<th>Leg Symptoms</th>
<th>Signs</th>
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<tr>
<td>Heaviness</td>
<td>Edema</td>
</tr>
<tr>
<td>Pain</td>
<td>Peri-malleolar telangiectasiae</td>
</tr>
<tr>
<td>Swelling</td>
<td>Venous ectasia</td>
</tr>
<tr>
<td>Itching</td>
<td>Hyperpigmentation</td>
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<tr>
<td>Cramps</td>
<td>Redness</td>
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<tr>
<td>Paresthesia</td>
<td>Dependent cyanosis</td>
</tr>
<tr>
<td>Bursting pain</td>
<td>Lipodermatosclerosis</td>
</tr>
<tr>
<td></td>
<td>Healed ulcer</td>
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<tr>
<td></td>
<td>Open ulcer</td>
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- May be intermittent or persistent
- **Worsen** with standing, walking; **improve** with rest, leg elevation
- Range: mild symptoms to severe leg pain that limits activity and work, intractable edema and leg ulcers.
Post-thrombotic ulcers

- Occur in 1-3% of patients with PTS
- May be precipitated by minor trauma
- Chronic, painful, slow to heal, often recur
- Require close medical attention

Management of venous ulcer disease, van Gent WB et al., BMJ. 2010 Nov 12;341:c6045
Post Thrombotic Syndrome (PTS) is the most frequent complication of DVT

- Occurs in 25%-50% of patients with DVT, even when appropriate anticoagulation + compression therapy is used; ulcers occur in 1-3%

- Burdensome and potentially debilitating condition for which patients frequently seek medical advice.

- PTS
  - reduces quality of life and productivity
  - is costly, as measured by health resource utilization, direct costs and indirect costs
DVT patients who develop PTS have worse quality of life (QOL) during subsequent 2 yrs

Generic Physical QOL (SF-36 PCS)
DVT patients who develop PTS have worse quality of life (QOL) during subsequent 2 yrs

Generic Physical QOL (SF-36 PCS)

Average 2-year SF-36 PCS scores worse than age-matched U.S. patients with arthritis, chronic lung disease, diabetes.
Economic Burden of DVT and PTS

• Cost-of-illness study within a multicenter prospective cohort study (VETO Study; n=355)

• Objectives: To quantify medical and non-medical resource use and costs incurred by DVT during the 2 years after the diagnosis, and to identify determinants of costs after DVT

• 355 consecutive patients with objectively diagnosed acute symptomatic DVT at one of 7 clinical centers in Quebec, Canada (recruited from 2001-2004)

• Patients followed for 2 years after diagnosis, and attended clinical visits at 1, 4, 8, 12 and 24 mths

Guanella et al, J Thromb Haemost 2011
Type of resource utilization identified during study follow-up

• **Medical**: DVT-related hospitalizations, physician and non-physician visits, prescription and OTC medications, compression stockings and assistive devices

• **Non-medical**: DVT-related lost workdays, assistance and transportation

• i.e. all resources identified were related to DVT
Distribution of costs over time

Can$ 5094 (95% CI 4274 to 5915)

Can$ 5094 (95% CI 4274 to 5915)

- Up to 4 months: Can$ 5094 (95% CI 4274 to 5915)
- Months 4-12: Can$ 0
- Months 12-24: Can$ 0

Medical: 53%
Non-medical: 47%
Distribution of non-medical costs

Can$ 2647 (95%CI 2081 to 3214)
Cost, by category, in patients with vs. without PTS

* P < 0.05
Conclusions

• Economic burden of DVT over 2 years after diagnosis is substantial, with average cost of Can$ 5094 (95%CI 4274 , 5915)

• Costs are almost equally distributed between medical and non-medical resource use

• Development of PTS → significant predictor of costs during the 2 years follow-up

Guanella et al, J Thromb Haemost 2011
Why does PTS develop after DVT?
Proposed pathophysiology of PTS

Acute DVT
Thrombus + Inflammatory mediators

Venous valve disruption $\rightarrow$ **REFLUX**
Residual venous **OBSTRUCTION**

**Venous hypertension**
Impaired venous return, reduced calf muscle perfusion, perforator valve incompetence, abnormal microcirculation, tissue hypoxia, injury, capillary leak

**Characteristic symptoms and signs of PTS**
Correlation between residual thrombus after catheter-directed thrombolysis and PTS

Prospective study of 71 consecutive patients with iliofemoral DVT treated with catheter-directed thrombolysis; Mean age 45 years; Mean follow-up 19 months

Comerota AJ et al., JVS 2012
Overall, obstruction appears to be more important than reflux in development of PTS

- Persistent obstruction (with/without reflux) predicted PTS [RR1.69; 95% CI 1.23 2.32] but reflux alone did not [1.01; 95% CI, 0.47–2.18] (Prandoni 2005)

- CavenT Study (Enden 2012) : Irrespective of treatment group, among those with iliofemoral patency at 6 months, 36.9% developed PTS vs. 61.3% with insufficient canalisation

- Interim analysis of CavenT (Enden 2009) : no difference in frequency of valvular reflux at 6 months in CDT vs. standard treatment arms
Biomarkers may provide insight into pathophysiology of PTS

Recent studies: elevated levels of markers of inflammation * (e.g. ICAM-1, IL-6, C-reactive protein) and D-dimer # early after DVT diagnosis or within a few months of DVT were associated with development of PTS.

* Shbaklo, Thromb Haemost 2009
* Roumen-Klappe, J Thromb Haemost 2009
# Stain, J Thromb Haemost 2005
# Latella, J Thromb Haemost 2010

IL-6 levels (4 mos) in patients with and without PTS at 2 years

Adj P=0.03

Shbaklo, Thromb Haemost 2009
Management of PTS

Will not address thrombolysis in detail: to be addressed by other speakers
Preventing PTS

Prevent the initial DVT
• Improve rates of use of thromboprophylaxis in patients at risk for VTE (high-risk patients, high-risk settings)

Prevent ipsilateral recurrence
• Optimize duration of anticoagulation for initial DVT

Ensure high quality of anticoagulation for DVT
• During 1st 3 months, INR<2 more than 50% of time → 2-3 fold increased risk PTS (van Dongen, JTH 2005; Chitsike, JTH 2012)
Elastic compression stockings (ECS) to prevent PTS and recurrent DVT

- 5 randomized trials * evaluated ECS (30-40 mm Hg pressure at the ankles) used at various times after diagnosis of acute proximal DVT to prevent PTS

- Results suggest ECS started within 2 weeks of DVT and continued for 2 years reduce PTS by ~50% and do not alter risk of recurrent VTE.

- Overall, evidence is of moderate quality because assessment of PTS, which includes a large subjective component, was not blinded, and estimates for recurrent VTE was imprecise.

Recommendation:

In patients with acute symptomatic DVT of the leg, we suggest the use of compression stockings (Grade 2B).

Remarks:

Compression stockings should be worn for 2 years, and we suggest beyond that if patients have developed PTS and find the stockings helpful.

Patients who place a low value on preventing PTS or a high value on avoiding the inconvenience and discomfort of stockings are likely to decline stockings.
Thigh-length versus below-knee ECS for Prevention of PTS

- 267 patients with 1st episode proximal DVT randomized to either thigh-length or below-knee ECS for 2 years.

- PTS developed in 32.6% thigh-length vs. 35.6% below-knee (adj HR 0.93 [95% CI, 0.62 to 1.41])

- Stockings-related side-effects occurred in 40.7% thigh-length vs. 27.3% below-knee (p=0.017) → led to premature discontinuation in 21.5% and 13.6%, respectively.

- Overall: thigh-length ECS do not offer a better protection against PTS than below-knee ECS and are less well tolerated

*Prandoni P et al, Blood 2011*
Uncertainty regarding use of ECS to prevent PTS

- Lack of multicenter, placebo-controlled trials
  - SOX Trial n=803; 24 centres; 2 year follow-up ends Feb. 2012; results to be presented end 2012

- Not clear if ECS prevents vs. palliates PTS → may be as effective and more convenient to start using ECS at the time of PTS onset

- Many patients don’t wear them in “real life”, especially if asymptomatic

- Recent studies: suggest beyond initial 6-12 months use, no incremental benefit in prolonging use
6 months vs. longer use of compression stockings to prevent PTS

• After an initial 6 month course of daily ECS use, 169 patients with proximal DVT and no PTS skin changes or ulcers were randomized to continue or discontinue ECS.

• **Primary endpoint:** Progression to moderate or severe PTS

![Graph showing event-free rate over years since randomization.]

**HR 0.60**  
(95% CI 0.28, 1.28; p=0.19)

Stop at 6 mths
Continue stockings

Aschwanden M; J Vasc Surg 2008
ECS to prevent PTS: A reasonable clinical approach

- ECS unlikely to cause harm, but difficult to apply, uncomfortable, expensive and require replacement every few months.

- Prescribe knee-length, 30-40 mm Hg compression stockings to patients with residual leg pain or swelling after DVT, and continue as long as the patient gains benefit or is able to tolerate them.

- Contraindications: symptomatic claudication due to PAD, allergy to material
Can thrombolysis prevent PTS?

- Anticoagulant drugs do not eliminate thrombus

- Could immediate thrombus removal open veins, save venous valves, and prevent PTS?
2.9. In patients with acute proximal DVT of the leg, we suggest anticoagulant therapy alone over catheter-directed thrombolysis (CDT) (Grade 2C).

Remarks: Patients who are most likely to benefit from CDT (see text), who attach a high value to prevention of postthrombotic syndrome (PTS), and a lower value to the initial complexity, cost, and risk of bleeding with CDT, are likely to choose CDT over anticoagulation alone.

2.10. In patients with acute proximal DVT of the leg, we suggest anticoagulant therapy alone over systemic thrombolysis (Grade 2C).

Remarks: Patients who are most likely to benefit from systemic thrombolytic therapy (see text), who do not have access to CDT, and who attach a high value to prevention of PTS, and a lower value to the initial complexity, cost, and risk of bleeding with systemic thrombolytic therapy, are likely to choose systemic thrombolytic therapy over anticoagulation alone.
**CaVenT Study:** 200 patients with iliofemoral DVT and symptoms < 21 days randomized to receive additional catheter-directed thrombolysis (CDT) or standard anticoagulant treatment alone, to prevent PTS.

<table>
<thead>
<tr>
<th></th>
<th>Additional catheter-directed thrombolysis (n=90)</th>
<th>Standard treatment only (n=99)</th>
<th>p value*</th>
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<tr>
<td></td>
<td>n</td>
<td>% (95% CI)</td>
<td>n</td>
</tr>
<tr>
<td>Post-thrombotic syndrome at 24 months†</td>
<td>37</td>
<td>41.1% (31.5–51.4)</td>
<td>55</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>
<tr>
<td>Post-thrombotic syndrome at 6 months§</td>
<td>27</td>
<td>30.3% (21.8–40.5)</td>
<td>32</td>
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Post-thrombotic syndrome defined as Villalta score of 5 points or higher. *χ² test. †Co-primary outcomes. ‡Five patients had inconclusive patency assessments and one was lost to follow-up at 6 months. §Secondary outcome.

**Bleeding:** 20 bleeds related to CDT; 3 major, 5 clinically relevant. Major bleeds: abdominal wall hematoma + blood transfusion, compartment syndrome of calf needing surgery, and inguinal puncture site hematoma. No deaths or cerebral hemorrhages.

No bleeding complications in patients allocated control.

Enden T et al. Lancet 2012
Pharmacomechanical Catheter-directed Thrombolysis (PCDT)

• Simultaneous use of catheter-directed lysis and mechanical clot fragmentation

• Image-guided, targeted, efficient method of eliminating thrombus

• Less major bleeding than systemic lysis
692 subjects with symptomatic proximal DVT (femoral vein or higher) will be randomized to receive PCDT* (with rt-PA) + standard DVT therapy, vs. standard DVT therapy alone, to prevent PTS.

Subjects enrolled in >50 U.S. Centers (2009-2013)

**Primary outcome: PTS during 24 months follow-up**

*PCDT=pharmacomechanical catheter directly thrombolysis*
Treatment of established PTS: Limited options, limited effectiveness

- ECS to reduce leg swelling, heaviness and aching, but requires patient compliance to maximize effectiveness

- Start by prescribing a knee length 30-40 mm Hg ECS
  - If too constricting or difficult to apply → 20-30 mm Hg ECS
  - Some patients require higher compression strengths (e.g. 40-50 mm Hg) to adequately control edema.
Other types of compression therapy

• Intermittent pneumatic compression devices to treat severe PTS (*Ginsberg CMAJ 1999*)
  - Effective but impractical (patients must remain stationary for two hours or more per day), expensive

• Portable, battery-operated lower-limb venous return assist device (*Venowave™*)
  - Use of the device alone or in combination with ECS led to improved quality of life and reduced severity of PTS (*O’Donnell, Thromb Haemost 2008*)
Recommendations, ACCP Guidelines 2012: Physical Treatment of PTS

4.2.1. In patients with PTS of the leg, we suggest a trial of compression stockings (Grade 2C).

4.2.2. In patients with severe PTS of the leg that is not adequately relieved by compression stockings, we suggest a trial of an intermittent compression device (Grade 2B).

Kearon, Akl, Comerota et al, Chest 2012
Recommendations ACCP Guidelines 2012: Pharmacologic Treatment of PTS

• In patients with PTS of the leg, we suggest that vеноactive medications (eg, rutosides, defibrotide, and hidrosmin) not be used (Grade 2C).

• Remarks: Patients who value the possibility of response over the risk of side effects may choose to undertake a therapeutic trial

Kearon, Akl, Comerota et al, Chest 2012
Meta-analysis for symptomatic relief associated with venoactive medication

Cohen JM, Akl E, Kahn SR. Chest 2012;141:308-320
Exercise training to treat PTS

Exercise training is effective treatment for arterial claudication. Role of exercise to treat PTS?

Six-month exercise training program to treat post-thrombotic syndrome: a randomized controlled two-centre trial

Susan R. Kahn MD MSc, Ian Shrier MD PhD, Stan Shapiro PhD, Adrielle H. Houweling MSc, Andrew M. Hirsch MD, Robert D. Reid PhD MBA, Clive Kearon MB PhD, Khalil Rabhi PhD, Marc A. Rodger MD MSc, Michael J. Kovacs MD, David R. Anderson MD, Philip S. Wells MD MSc

Kahn et al, CMAJ 2011
EXPO Trial study interventions:

**Exercise Training:**
- 6-month (26-week) exercise program with strengthening, stretching and aerobic (walking or jogging) components, designed to improve leg strength, leg flexibility and overall cardiovascular fitness.

**Vs.**

**Attention Control:**
- Standardized, 1-hour educational session on PTS; role of exercise kept neutral.
- Monthly phone calls to inquire about general well-being and PTS symptoms.
Difference in Baseline to 6 months change: Exercise training (n=21) vs. Control (n=23)

No adverse events in either group
PTS: Specific areas that require research

• Better characterization of pathophysiology of PTS
• Identification of clinical, anatomic, physiologic and genetic risk factors for PTS
• Derivation and validation of PTS risk prediction models that integrate clinical and biomarker information
• Investigation of link between inflammation and PTS → could lead to identifying new therapeutic targets to prevent or treating PTS
• Careful evaluation of long-term effectiveness, safety, costs:
  - Catheter-directed thrombolytic techniques to prevent PTS
  - Endovascular and surgical procedures to treat severe PTS