Ileo Femoral DVT
“Review and Update”

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Interventional Cardiology & Endovascular Medicine
Venous thromboembolism is a major national health problem, with an overall incidence of more than 1 per 1,000 annually.

Deep Vein Thrombosis (DVT) is a potentially life-threatening pathology that can lead to pulmonary embolism (PE), and/or post-thrombotic syndrome (PTS).

The spectrum of DVT to pulmonary embolism can be referred to as venous thromboembolic disease (VTE).

**VTE: A Major Source of Mortality and Morbidity**

Over **200,000** deaths per year due to PE annually in the U.S. alone.

More than HIV, MVAs & Breast Cancer combined

Over **600,000** patients diagnosed with DVT annually in the US alone

10% of Hospital Deaths most common preventable death

Huge Costs and Morbidity

Recurrence of DVT, post-thrombotic syndrome and chronic PE / PAH are long term sequelae

<table>
<thead>
<tr>
<th>Some Causes of Death in the US</th>
<th>Annual Number of Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>PE</td>
<td>Up to 200,000</td>
</tr>
<tr>
<td>AIDS</td>
<td>16,371</td>
</tr>
<tr>
<td>Breast Cancer</td>
<td>40,580</td>
</tr>
</tbody>
</table>
Venous Thromboembolism (VTE) remains a major health problem.

In addition to the risk of sudden death:

- 30% of survivors develop recurrent VTE within 10 years.
- 28% of survivors develop venous stasis syndrome within 20 years.
Icoper: Cumulative Mortality After Diagnosis of PE

Mortality (%) vs. Days From Diagnosis

17.5% At 90 days

Risk Factors and DVT

Most hospitalized patients have at least one risk factor for DVT
VTE is a Disease of Hospitalized and Recently Hospitalized Patients

Cases per 10,000 person-years

Hospitalized patients

Community residents

Recently hospitalized

Heit – Mayo Clin Proc 2001;76:1102
## Risk of DVT in Hospitalized Patients

No prophylaxis + routine objective screening for DVT

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>DVT Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical patients</td>
<td>10 - 26 %</td>
</tr>
<tr>
<td>Major gyne/urol/gen surgery</td>
<td>15 - 40 %</td>
</tr>
<tr>
<td>Neurosurgery</td>
<td>15 - 40 %</td>
</tr>
<tr>
<td>Stroke</td>
<td>11 - 75 %</td>
</tr>
<tr>
<td>Hip/knee surgery</td>
<td>40 - 60 %</td>
</tr>
<tr>
<td>Major trauma</td>
<td>40 - 80 %</td>
</tr>
<tr>
<td>Spinal cord injury</td>
<td>60 - 80 %</td>
</tr>
<tr>
<td>Critical care patients</td>
<td>15 - 80 %</td>
</tr>
</tbody>
</table>

Heit – Mayo Clin Proc 2001;76:1102
### VTE According to Service (N=384)

<table>
<thead>
<tr>
<th>Service</th>
<th>Total VTE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical</td>
<td>44</td>
</tr>
<tr>
<td>General surgery</td>
<td>16</td>
</tr>
<tr>
<td>Medical oncology</td>
<td>10</td>
</tr>
<tr>
<td>Orthopaedic surgery</td>
<td>9</td>
</tr>
<tr>
<td>Thoracic surgery</td>
<td>8</td>
</tr>
<tr>
<td>Other</td>
<td>14</td>
</tr>
</tbody>
</table>

Number of VTE events:
- **Total VTE**:
  - 44 events
- **PE**:
  - 16 events
- **DVT**:
  - 10 events

# DVT Prophylaxis

## DVT risk and prophylaxis in the hospitalized patient

<table>
<thead>
<tr>
<th>Low Risk</th>
<th>Moderate Risk</th>
<th>High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ambulatory patient <em>without</em> additional VTE Risk Factors</td>
<td>All other patients. Most patients (not LOW or HIGH category)</td>
<td>Elective major lower extremity arthroplasty</td>
</tr>
<tr>
<td>Ambulatory patient with expected LOS ≤ 2 days, or same day/minor surgery</td>
<td></td>
<td>Hip, pelvic, or sever lower extremity fractures</td>
</tr>
<tr>
<td>Only a few patients!</td>
<td></td>
<td>Acture spinal cord injury with paresis</td>
</tr>
<tr>
<td><strong>Ambulation and Education</strong></td>
<td><em>Px indicated</em></td>
<td><em>Px indicated</em></td>
</tr>
</tbody>
</table>

Physicians at UCSD use these checklists to assess all adult inpatients when they are admitted, transferred between units, or post-op.
DVT and Your Cancer Patient

Patients with cancer who develop VTE are at higher risk of both *recurrence and death* than other patients with VTE. Because of improved treatment and longer survival, patients with cancer account for an increasing proportion of those with VTE.

- VTE can occur before cancer is evident, at the time of the cancer diagnosis and at any point in the clinical course of patients with known cancer.

- VTE is particularly likely to occur during intensive chemotherapy and as a complication of cancer surgery.

- For years, clinicians have been aware of so-called "warfarin failure"-the tendency to develop recurrent VTE despite an INR between 2.0 and 3.0-in patients with VTE and cancer. Recent clinical trials have shown that *long-term LMWH* in a treatment dose reduces the recurrence rate of VTE in cancer patients by 50% compared with warfarin (INR 2.0-3.0).
The Challenge - Approximately **half of patients with DVT are asymptomatic.**

Symptoms of DVT include swelling, pain, tenderness, warmth, and prominent superficial veins on the affected limb.

**Patients with suspected DVT** frequently present to hospital emergency departments. Since symptoms and signs of DVT can be non-specific and found in a wide variety of non-thrombotic disorders, timely diagnostic testing must be performed to correctly identify patients with VTE.
• The gold standard to diagnose DVT and PE remains **Doppler ultrasound** and CT, respectively. D-dimers, V/Q scans, and other modalities may be useful in some scenarios.

**Diagnosis of DVT**

*However, this range of diagnostic testing options has resulted in wide practice variations.*
What do we do with those patients that develop a DVT? And Why?

**GOALS**: Decrease the risk of:

1. Recurrence of DVT.
2. Fatal pulmonary embolism (PE)
3. Long term sequelae of DVT
Is current in-hospital treatment adequate?

Anticoagulation

Compression Stockings

Can we do better for these patients?

Using multidisciplinary team approach

What are the options for thrombus removal

Offering minimally invasive solutions
SOX Trial
Elastic Compression Stockings vs Placebo Control

Compression stockings to prevent post-thrombotic syndrome: a randomised placebo-controlled trial

Susan R Kahn, Stan Shapiro, Philip S Wells, Marc A Rodger, Michael J Kovacs, David R Anderson, Vicky Tagalakis, Adrielle H Hauweling, Thierry Ducruet, Christina Holcroft, Mira Johri, Susan Solymass, Marie-José Miron, Erik Yeo, Reginald Smith, Sam Schulman, Jeannine Kassis, Clive Kearon, Isabelle Chagnon, Tunny Wong, Christine Demers, Rajendar Hamniah, Scott Kaatz, Rita Selby, Suman Rathbun, Sylvie Desmarais, Lucie Opattany, Thomas J. Ortel, Jeffrey S Ginsberg, for the SOX trial investigators

- **Objective:** To evaluate the effectiveness of elastic compression stockings (ECS), compared with placebo stockings to prevent post-thrombotic syndrome (PTS)

- **Design:** Multicenter, randomized, placebo-controlled trial of active (N=410) vs placebo (N=396) ECS

- **Key Inclusion Criteria:** First indicative, proximal DVT (with or without coexisting pulmonary embolism or distal DVT)

- **Primary Endpoint:** PTS diagnosed at 6 months or later using Ginsberg’s criteria (ie, leg pain and swelling of ≥1 month)

SOX Trial Results
Elastic Compression Stockings vs Placebo Control

“ECS did not prevent PTS after a first proximal DVT”

**PTS incidence rate at 2 years:**
- 14.2% for active ECS vs. 12.7% for placebo (p=0.58)^a

Post-thrombotic Syndrome (PTS)

- *Chronic pain, edema* and fatigue of affected limb after DVT

- Severe PTS may result in venous claudication, stasis dermatitis, *subdermal fibrosis and ulceration* -> tissue loss

- $\geq 40\%$ of patients within 2 years of first lower extremity DVT
Post-thrombotic Syndrome (PTS)

- As assessed by Villalta score, more severe PTS is predicted by:
  - Common femoral or iliac DVT (IFDVT)
  - Higher BMI
  - Prior ipsilateral DVT
  - Older age
  - Female gender

- Patients with PTS have overall lower QOL scores and less improvement in symptoms over time with conventional therapy
## What is the Villalta Score?

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Clinical Signs</th>
<th>Scoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>Edema</td>
<td>No PTS</td>
</tr>
<tr>
<td>Cramps</td>
<td>Skin induration</td>
<td>Mild</td>
</tr>
<tr>
<td>Heaviness</td>
<td>Hyperpigmentation</td>
<td>Moderate</td>
</tr>
<tr>
<td>Pruritus</td>
<td>Redness</td>
<td>Severe</td>
</tr>
<tr>
<td>Paraesthesia</td>
<td>Pain during calf compression</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Venous ectasia</td>
<td></td>
</tr>
</tbody>
</table>

Each symptom is rated as: 0 (absent), 1 (mild), 2 (moderate), or 3 (severe)

Villalta Score is the only validated measure for PTS.

2. The Villalta PTS scale (sometimes called the Villalta-Prandoni scale) has been adopted by the International Society on Thrombosis and Haemostasis (ISTH) as a standard to diagnose and grade the severity of PTS in clinical studies: Kahn, Sr (2016).
Medical management is inadequate for many VTE patients

Anticoagulation therapy

- Does not reduce or eliminate the existing thrombus
- Does not prevent long-term damage to the vein and valves, leading to high levels of PTS\(^3,4\)
- While it reduces the risk of Pulmonary Embolism, the risk remains significant\(^5\)
- 50% of patients on oral therapy are at sub-therapeutic levels\(^1,2\)

New options to remove thrombus are being utilized for treatment of DVT. Interventional options can now offer the potential to provide:

| Immediate removal of thrombus providing flow restoration | Potential to reduce risks of pulmonary embolism | Quick restoration of flow providing symptom relief and return of valve function | Possible reduction of PTS with early thrombus removal |

Interventional treatment offers the option to quickly remove thrombus, which provides flow restoration and rapid symptom relief and the potential for decreasing PTS.
Interventional options in the treatment of DVT

<table>
<thead>
<tr>
<th>Catheter directed lytic use</th>
<th>Mechanical thrombectomy</th>
<th>Pharmacomechanical thrombus removal</th>
<th>IVC Filters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Used for older thrombus or larger clot burden where thrombolytic is delivered directly to the site of thrombus</td>
<td>Mechanical removal of acute thrombus, to debulk and restore flow</td>
<td>Combination treatment utilizing lytics with mechanical thrombectomy for quicker and improved thrombus removal</td>
<td>Filter designed to capture an embolism; a blood clot that has broken loose</td>
</tr>
</tbody>
</table>

Depending on the age and volume of the thrombus, additional techniques can be employed to remove or dissolve thrombus – assisting the body's natural ability to resolve the clot burden.
Thrombolysis for Acute DVT

- tPA
Mechanical thrombectomy is an interventional technique where medication is infused directly into the DVT, and then a device macerates and removes the clot.

These techniques offer:

• A *minimally invasive* procedure
• Potential to minimize treatment time
• *Shorter treatment time*
• Possibility to reduce the risk of PE
• Possibility to eliminate or decrease dose and duration thrombolytic
• Potential for *quick resolution of signs and symptoms*
• Provide improved short term & hopefully long term outcomes
An option for DVT thrombus Removal

Thrombectomy System

MECHANISM OF ACTION

1. The AngioJet Console monitors and controls the system.
2. The Console energizes the pump which sends pressurized saline to the catheter tip.
3. Saline Jets travel backwards to create a low pressure zone causing a vacuum effect.
4. Thrombus is drawn into the in-flow windows and the jets push the thrombus back down the catheter.
5. Thrombus is evacuated from the body and into the collection bag.
Catheter Directed Lytics

Pharmacologic thrombolytic agent delivery through an infusion catheter and/or wire that is embedded within the thrombosed vein being treated.

Thrombolytic therapy requires careful monitoring. In most clinical practices, this may occur in an intensive care unit or step-down unit.

Quality Improvement Guidelines for the Treatment of Lower Extremity Deep Vein Thrombosis with Use of Endovascular Thrombus Removal
J Vas Interv Radiol 2006; 17:435-448
Catheter-Directed Thrombolysis for Deep Vein Thrombosis (CaVenT) - Norway

- n=176 IFDVT patients followed to 5 years
- 1:1 randomization to catheter-directed thrombolysis (CDT) and anticoagulation vs. anticoagulation alone
- End-point: assess development of PTS
- 43% CDT group vs. 71% of control developed PTS (p = 0.0001)
- QOL scores not statistically significant between groups
- 28% Absolute risk reduction (95% CI 14-42%)

CaVenT Trial: Study Design

- Eligibility (n = 209)
  - Age: 18-75 years
  - First-time acute iliofemoral DVT
  - Objectively verified DVT above midthigh level
  - Symptom duration up to 21 days
  - No increased risk of bleeding

- Conventional treatment only* (n = 108)
- CDT + conventional treatment (n = 101)

*Initial low molecular weight heparin (LMWH) and warfarin followed by warfarin alone with target Intensity international normalized ratio (INR) of 2.0-3.0

- Randomization was stratified for involvement of the pelvic veins.
- Primary outcomes:
  - Frequency of PTS at 24 months, assessed by the Villalta score
  - Iliofemoral patency after 6 months

PEARL Registry (Boston Scientific)

- n=329 patients with image-confirmed DVT (66% iliac involvement)
- Treatment groups
  - Rheolytic thrombectomy (RT) without lytics (4%)
  - Pharmacomechanical catheter-directed therapy (PCDT) (35%)
  - PCDT and catheter-directed thrombolysis (CDT) (52%)
  - RT and CDT (9%)
- End-point: assess procedure/patient outcomes of endovascular treatment of DVT with RT
PEARL Registry

- Median procedure times
  - RT alone: 1.4 h
  - PCDT: 2 h
  - PCDT/CDT: 22 h
  - RT/CDT: 41 h (P = 0.05, Kruskal–Wallis test)
- 36% procedures done within 6 hours; 86% required ≤ 2 sessions
- 3-, 6-, and 12-month freedom from re-thrombosis rates
  - 94%, 87%, and 83%, respectively
- Physical/mental SF-12 QOL scores sig. improved 3-, 6- & 12-month f/u
- Interpretation: **PCDT** may reduce need/duration of CDT for DVT tx


EKOS™ Acoustic Pulse Thrombolysis™ is a minimally invasive system for accelerating thrombus dissolution.
The “Open Vein Hypothesis”

- Development of PTS is associated with persistent venous thrombosis
- Does active elimination of DVT prevent PTS?
- Support comes from studies linking:
  - Poor thrombus clearance to venous valve dysfunction and recurrent VTE
  - Residual venous thrombus or valve incompetence and PTS
  - Systemic thrombolysis, surgical thrombectomy or CDT to reduced incidence of PTS
ATTRACT Trial Design

• Multicenter, randomized, open-label, assessor-blinded, parallel two-arm, controlled clinical trial sponsored by National Heart, Lung, and Blood Institute of the U.S. National Institutes of Health

• SIR Foundation, Boston Scientific, BSN Medical, Covidien/Medtronic,

• and Genentech provided additional support

• 692 subjects enrolled in 56 US Centers followed for 24 mo
  • 337 randomized to PCDT
  • 355 randomized to no PCDT
ATTRACTION Trial Objectives

• Primary objective:
  • Determine if PCDT with standard DVT therapy reduces development of PTS after 24 month follow-up compared to standard DVT therapy alone

• Secondary objectives:
  • Evaluate for major bleeding, symptomatic VTE and death
  • Venous disease-specific QOL
  • Relief of acute DVT symptoms
  • Pretreatment predictors of response to PCDT in preventing PTS
  • Compare medical costs and cost-effectiveness
  • Determining technical, anatomical and physiologic endpoints of therapy
ATTRACT Trial – Standard DVT Therapy

- Weight-based low molecular weight heparin or IV unfractionated heparin then Warfarin
- International guidelines for INR 2-3, duration of therapy (3 months or longer)
- 30-40 mmHg knee-high elastic compression stockings at 10 day follow-up
**ATTRACT Trial – PCDT Intervention**

- One of three methods for rt-PA delivery (max 25 mg initially; max 35 mg total)
  
  1. “Isolated Thrombolysis” with Trellis Peripheral Infusion System (Covidien, Inc.)
  
  2. “PowerPulse Thrombolysis” with AngioJet Rheolytic Thrombectomy System (Boston Scientific)
ATTRACT Trial – PCDT Intervention

• One of three methods for rt-PA delivery (max 25 mg initially; max 35 mg total)

3. “Infusion-First Thrombolysis” with multisidehole catheter through thrombus, up to 1 mg/h rt-PA for max 30 hours

• Subsequent therapy with balloon maceration, aspiration thrombectomy and/or mechanical thrombectomy allowed for residual thrombus

ATTRACT Trial – Endpoints and Efficacy

- ≥90% thrombus clearance with restored flow
- 35 mg maximum rt-PA dose or 30 h maximum infusion time reached
- Overt clinical bleeding or other complications necessitating cessation
- Evaluation for PTS in index limb at 6-24 months after randomization
- Villalta PTS scoring used
  - Combines patient and clinician evaluation
  - PTS defined as Villalta score > 5 or presence of ulcer
ATTRACTION Trial
“The Bad & Ugly”

• **PCDT not found to reduce incidence of PTS** compared to AC alone

  • PTS 46.7% for PCDT vs 48.2% for no-PCDT (p= 0.56)

  • Recurrent VTE higher in PCDT vs no-PCDT (12.5% vs 8.5%; p=0.09)

  • Major and any bleeding rates statistically higher in PCDT arm (1.7% vs 0.3%; p=0.49 and 4.5% vs 1.7%; p=0.034) – in line with prior studies
    • NO intracranial or fatal hemorrhages
ATTRACTION Trial

- IFDVT vs femoropopliteal DVT (FPDVT)
  - Trends to more **benefit in IFDVT**

- Study **not powered** to sufficient power to statistically significant differences between subgroups
ATTRACTION Trial
“The Good”

- Leg pain and swelling significantly improved in PCDT vs. no-PCDT out to 30 days (p=0.019 and p=0.05)
  - *PCDT helpful for acute symptoms*

- 25% fewer patients in PCDT arm developed *moderate or severe PTS* vs no-PCDT (17.9 % vs 23.7%; p=0.035)
  - “Open Vein hypothesis”
ATTRACTION Trial – Results SIR 2017 – “The Good”

• In IFDVT mod-severe PTS was 18.4% vs 28.2% in PCDT vs no-PCDT

• In FPDVT little difference (17.1% vs 18.1% moderate to severe PTS)

• PCDT was less effective in patients ≥ 65 y/o
ATTRACTION Trial
Summary and Learning points

• Ambitious well-designed RCT failed primary endpoint, but not the end

• Helps us strategize for appropriate care

• Who to and not to treat
  • Same as CaVenT: iliofemoral DVT, younger and functional patients
  • Femoropopliteal DVT alone patients do not derive same benefit
  • Older patients do not derive same benefit
  • Prevent bleeding and cost in inappropriate patients
ATTRACT Trial Learning points

• Do we fully understand the pathophysiology of PTS?
  • *Is the “Open Vein Hypothesis” enough?*

• We know thrombolysis works, but are *recent tech advances* enough to merit further trials (Boston-Scientific ZelanteDVT, Inari Flow-Triever, Penumbra Indigo, Argon Cleaner, etc.)?
ATTRACT Trial Learning points

• Same-session therapy vs. prolonged ICU time for thrombolysis?
  • Cost and resource analysis
  • Patient experience

• Role of IVUS in treatment of iliofemoral disease?
  • Likely to be an integral component of development of new technologies

• Femoropopliteal subgroup did not derive benefit
  • Did we look sufficiently at the iliac segments for evidence of compression?
A Word on Iliac Vein Compression

- 80% of Iliofemoral DVT have underlying external iliac venous compression

- Chang, et al. JVIR; 15:249-56
MAY-THURNER

IVC FILTER OCCLUSION
ANEURYSMS, ARTERIAL GRAFTS
TUMORS, CYSTS
SURGICAL INJURY
RADIATION FIBROSIS
Iliac Venous Compression

*Diagnosis*

- CT/MR Venogram
  - Anatomic details
  - *Do NOT evaluate flow*
  - *Timing of contrast* injection-flow issues
  - Dependent upon facility and radiology interest
Definitive diagnosis

- Venogram
  - Anatomic diagnosis
  - Assessment of flow: femoral inflow/iliac outflow
  - Collaterals
    - Will miss some stenosis and webs
Intra Vascular Ultrasound
IVUS

- The anatomic gold standard
- Evaluate compression in CFV, Iliac veins: morphology and CSA
- Evaluation of CFV, bilateral iliac veins and IVC
- Choosing diameter and length of balloon/stent
- Post stenting assessment
Word on Duration of Therapy

Proximal DVT or PE
- Provoked
  - 3 months
- Unprovoked
  - Low to moderate bleeding risk
  - 3 months
  - Extended therapy
  - High bleeding risk
  - 3 months
  - Extended therapy

Isolated Distal DVT
- Mild symptoms or high bleeding risk
  - Serial imaging x2 weeks
  - 3 months
  - Extending thrombus
  - Anticoagulate
- Severe symptoms or risk for extension
  - Anticoagulate

Cancer-associated
- Extended therapy
- Anticoagulate

Upper extremity DVT
- Anticoagulate
50%+ of DVT patients treated with the standard of care risk developing **Post Thrombotic Syndrome**

There may be a potential benefits of adding Interventional thrombolysis, mechanical thrombectomy, and/or pharmacomechanical thrombectomy for the treatment of DVT in **selected patients**.

---

Moving Forward

Multidisciplinary team approach to in-hospital DVT

Create best practice model

Develop treatment pathways to benefit patients for quicker recovery

Reduce the potential risks for those that develop DVT

Decrease hospital stay and cost associated with DVT

Potential to improve short and long term outcomes
Thank you

Questions