When is Thrombolysis Indicated for Femoral Vein DVT?

Marlene Grenon, MD
Assistant Professor of Surgery
University of California San Francisco
UCSF Vascular Surgery Symposium 2011

When is Thrombolysis Indicated for Femoral Vein DVT?

1. When should we thrombolyse patients with iliofemoral DVT (IFDVT)?
2. When should we thrombolyse patients for femoropopliteal DVT?

How often would you suggest thrombolysis in a good-risk patient with iliofemoral DVT?

1. Never
2. Often
3. Most of the time
4. Always

How often would you suggest thrombolysis in a good-risk patient with femoropopliteal DVT?

1. Never
2. Often
3. Most of the time
4. Always
Aims

- Review:
  - Morbidity of the post-thrombotic syndrome (PTS)
  - Medical therapies for proximal DVT

- Examine the evidence for:
  - Thrombolysis in IFDVT
  - Thrombolysis for femoro-popliteal DVT

Proximal DVT:
- Complete or partial thrombosis of the popliteal vein, femoral vein, deep femoral vein, common femoral vein, iliac vein and/or IVC
- Subgroups:
  - Femoropopliteal DVT
  - Iliofemoral DVT

Femoropopliteal DVT
- Complete/partial thrombosis of popliteal vein, femoral vein and/or deep femoral vein
- Iliofemoral DVT
- Complete/partial thrombosis of any part of the iliac vein and/or CFV +/- associated femoro-popliteal DVT

Post-thrombotic syndrome (PTS)
- Chronic venous insufficiency affects 5 million people in the US
- 1% of the population will develop a venous ulcer
- DVT increases the risk of chronic venous disease by 26x fold
- 6x fold increase in PTS with recurrent DVT
- Iliofemoral DVT treated with anticoagulation alone increases the risk of PTS by 2.4x fold compared to femoropopliteal DVT

Incidence of PTS
- Incidence PTS:
  - 25-46% of patients DVT
- If treated with anticoagulation alone, IFDVT patients:
  - 90% have ambulatory venous hypertension
  - 40% have venous claudication
  - 15% will develop ulceration within 5 years

<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 Risk Factors

<table>
<thead>
<tr>
<th>INCREASED</th>
<th>NO EFFECT</th>
<th>DECREASE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obesity</td>
<td>IVC filter</td>
<td>Compression therapy</td>
</tr>
<tr>
<td>Thrombophilia</td>
<td></td>
<td>Early clot removal</td>
</tr>
<tr>
<td>Ipsilateral</td>
<td></td>
<td>Thrombectomy, thrombolysis, combined</td>
</tr>
<tr>
<td>recurrence of</td>
<td></td>
<td>pharmacomechanical therapy</td>
</tr>
<tr>
<td>DVT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inadequate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>anticoagulation</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Guidelines Amer Venous Forum, P. Gloviczki, 2009*

### Pathophysiology

- Valvular incompetence
  - Dysfunction of the vein valves with vein wall fibrosis
  - Development of reflux
- Luminal venous obstruction
- Combination of the above

*Rutherford’s Vascular Surgery, 7th Edition, Chapter 51*

### Aims

- Review:
  - Morbidity of the post-thrombotic syndrome (PTS)
    - HIGH MORBIDITY, IFDVT> FPDVT
  - Medical therapies for proximal DVT

- Examine the evidence for:
  - Thrombolysis in IFDVT
  - Thrombolysis for femoro-popliteal DVT

### What Medical Treatment Should We Offer Patients with Proximal DVT?
Recommendations for the Use of Compression Therapy

- Compression therapy (30-40 mm Hg) knee-high graduated stockings recommended
  - AHA: Class I, level of evidence B
  - Chest: Grade 1A
- Should be worn for 2 years after initial DVT
- Also consider intermittent sequential pneumatic compression if patients have severe edema

Kearon et al., Antithrombotic Therapy for Venous Thromboembolism, CHEST 2008; Jaff et al., Circulation 2011.

Recommendations for Initial Anticoagulation for Patients with IFDVT

- AHA Guidelines 2011
  - IV UFH, s/c UFH, LMWH, Fondaparinux
  - Direct thrombin inhibitor if HIT +
- Duration of treatment
  - 3 months: if reversible RF
  - 6 months – indefinite: if unprovoked or recurrent
- Cancer patients:
  - LMWH for 3-6 months or duration of cancer

Kearon et al., Antithrombotic Therapy for Venous Thromboembolism, CHEST 2008; Jaff et al., Circulation 2011.
Evaluation of iliofemoral DVT

Anticoagulation

IVC filter

Thrombus removal:
- CDT
- PCDT
- venous thrombectomy

IVC Filter Indications

- An IVC filter should not be used routinely in the treatment of IFDVT (Class III; Level of Evidence B).


Aims

- Review:
  - Morbidity of the post-thrombotic syndrome (PTS)
    - HIGH MORBIDITY, IFDVT > FPDVT
  - Medical therapies for proximal DVT
    - COMPRESSION THERAPY: 30-40mm Hg
    - ANTICOAGULATION as per guidelines
    - IVC Filters… Let’s wait to see what Dr. Kerlan has to say…

- Examine the evidence for:
  - Thrombolysis in IFDVT
  - Thrombolysis for femoro-popliteal DVT
**ANATOMY**

- Considering that the common femoral vein and iliac veins are the single outflow channel for the lower extremity and, it appears intuitive that eliminating thrombus and restoring patency will result in improved outcomes in iliofemoral DVT.

**Goals of “Clot Removal”**

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

**Venous Thrombectomy Trial Results**

Results of a Multicenter Randomized Trial of Operative Venous Thrombectomy with Antieplatelet Fibrinolysis Plus Anticoagulation versus Anticoagulation Alone in Patients with Iliofemoral Deep Venous Thrombosis

Guidelines Amer Venous Forum, P. Gloviczki, 2009

**Systemic Thrombolytics: Phlebographic Outcomes (Lysis)**

12 Randomized trials

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No lysis (%)</th>
<th>Partial lysis (%)</th>
<th>Significant/complete lysis (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heparin (n=212)</td>
<td>81</td>
<td>14</td>
<td>5</td>
</tr>
<tr>
<td>Lytic (n=253)</td>
<td>40</td>
<td>15</td>
<td>45</td>
</tr>
</tbody>
</table>

**Lytics:**
- 10x fold increase in significant/complete lysis
- < 50% have good-outcomes
- 3x fold increase risk of bleeding

**Intra-thrombus delivery CDT**

- Clot dissolution by activation of fibrin-bound plasminogen
- Delivery of plasminogen activator into the thrombus activates plasminogen to form plasmin
- Intrathrombus delivery
  - Protects the plasminogen activator from neutralization by circulating plasminogen activator inhibitors
  - Protects the resulting plasmin from neutralization by circulating alpha-2-antiplasmins

**3 large series - CDT**

<table>
<thead>
<tr>
<th>Efficacy (%)</th>
<th>Bjarnason et al.</th>
<th>Mewissen et al. (NVR)</th>
<th>Comerota et al.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial Success</td>
<td>79%</td>
<td>83%</td>
<td>84%</td>
</tr>
<tr>
<td>Primary Patency at 1 year</td>
<td>63%</td>
<td>64%</td>
<td>78%</td>
</tr>
<tr>
<td>Iliac stent patency at 1 year</td>
<td>54%</td>
<td>74%</td>
<td>89%</td>
</tr>
<tr>
<td>Complications (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major bleed</td>
<td>5</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Intra-cranial bleed</td>
<td>0</td>
<td>&lt;1</td>
<td>0</td>
</tr>
<tr>
<td>PE</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Fatal PE</td>
<td>0</td>
<td>0.2</td>
<td>0</td>
</tr>
<tr>
<td>Death 2yr to lysis</td>
<td>0</td>
<td>0.4</td>
<td>0 (2)</td>
</tr>
</tbody>
</table>

**1-year results: National Venous Registry**

<table>
<thead>
<tr>
<th>Initial Lytic Response</th>
<th>&lt;50%</th>
<th>50-99%</th>
<th>100%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Residual thrombus (%)</td>
<td>73</td>
<td>45</td>
<td>16</td>
</tr>
<tr>
<td>Reflux (%)</td>
<td>89</td>
<td>48</td>
<td>39</td>
</tr>
<tr>
<td>Asymptomatic (%)</td>
<td>36</td>
<td>68</td>
<td>84</td>
</tr>
</tbody>
</table>

Bjarnason et al., JVR 1997; Mewissen et al., Radiol 1999; Comerota & Kagan, Phlebology 2000
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:
- Iliofemoral patency in 72% of lysis patients versus 12% of those anticoagulated (p=.001)
- Valvular function normal in 89% of lysis patients versus 50% of those randomized to anticoagulation alone (P=.04).
- Complications minimal


CaVenT Trial (Catheter-directed venous thrombolysis)
- Randomized, multi-center trial
- Ilio-femoral DVT < 21 days
- Upper half of thigh, common iliac vein or combined iliolumbar segment
- N=103
- Alteplase, 0.01mg/kg/hr (max dose 20mg in 24 hours)
- Recruitment ongoing to 200 patients

Results:
- At 6-month follow-up, iliolumbar patency was 64% in the CDT group versus 36% in the controls (P=.004)
- Hemodynamic venous obstruction was found in 20% of the CDT group versus 49% of the anticoagulation group (P=.004).
- Valve function at 6 months did not differ between groups.
- Major complications: 1) compartment syndrome, 2) nerve injury


Percutaneous Mechanical Thrombectomy

A Systematic Review of Percutaneous Mechanical Thrombectomy in the Treatment of Deep Venous Thrombosis


Results: 16 retrospective case series have reported the use of rheolytic, rotational, or ultrasound-assisted PMT in a total of 481 patients. No randomized trials were available. Technical success of 82–100% was reported with Grade II or III lysis in 83–100% of patients. The different devices all appeared to be safe, with no reported procedure-related deaths or strokes and < 1% incidence of symptomatic PE. Bleeding complications were reported in 6/16 studies, in which 4–14% of patients required transfusion (global incidence 11/146 patients, 7.3%).

Current guidelines
- Extensive venous thrombosis is associated with long-term post-thrombotic morbidity
- CHEST 2008:
  - Evidence supports the use of venous thrombectomy (grade 2B) and catheter-directed thrombolysis (grade 2B)
- AHA 2011:
  - CDT or PCDT should be given to patients with IFDVT associated with limb-threatening circulatory compromise (ie, phlegmasia cerulea dolens) (Class Ia; Level of Evidence C).
  - CDT or PCDT is reasonable as first-line treatment of patients with acute IFDVT to prevent PTS in selected patients at low risk of bleeding complications (Class IIa; Level of Evidence B).
Aims

- Review:
  - Morbidity of the post-thrombotic syndrome (PTS)
    - HIGH MORBIDITY, IFDVT > FPDVT
  - Medical therapies for proximal DVT
    - COMPRESSION THERAPY: 30-40mm Hg
    - ANTICOAGULATION as per guidelines
    - IVC Filters… Let’s wait to see what Dr. Kerlan has to say…

- Examine the evidence for:
  - Thrombolysis in IFDVT
    - SIGNIFICANT BENEFITS IN GOOD RISK PATIENTS
  - Thrombolysis for femoropopliteal DVT

What about patients with femoropopliteal DVT?

Why only treating IFDVT with thrombolysis?

- Patients iliofemoral DVT will have severe postthrombotic morbidity if treated with anticoagulation alone, whereas postthrombotic morbidity is much less severe in patients with femoropopliteal DVT.
  - Higher recurrence of DVT in IFDVT compared to femoropopliteal DVT
    - ? Higher thrombus burden
    - ? Underlying occult malignancy

Thrombolysis in patients with femoropopliteal DVT

Acute Venous Thrombosis: Thrombus Removal with Adjunctive Catheter-Directed Thrombolysis (ATTRACT)

- Funded by NIH
- PI: Dr. Suresh Vedantham
- Plan to recruit 692 patients
- Phase 3, open-label, multicenter randomized controlled trial


Aims

- Review:
  - Morbidity of the post-thrombotic syndrome (PTS)
    - HIGH MORBIDITY, IFDVT > FPDVT
  - Medical therapies for proximal DVT
    - COMPRESSION THERAPY: 30-40mm Hg
    - ANTICOAGULATION as per guidelines
    - IVC Filters… Let’s wait to see what Dr. Kerlan has to say…

- Examine the evidence for:
  - Thrombolysis in IFDVT
    - SIGNIFICANT BENEFITS IN GOOD RISK PATIENTS
  - Thrombolysis for femoro-popliteal DVT
    - EVIDENCE IS LACKING – TRIALS UNDERGOING

Summary

- Treatment with thrombolysis can be an important measure to decrease the morbidity of the post-thrombotic syndrome in patients with femoral DVT

- Iliofemoral DVT
  - Offer to patients who:
    - Good risk
    - Likely to benefit
    - Have no contraindications

- Femoropopliteal DVT
  - No evidence-based indication
  - Would consider offering in cases of:
    - Young, good risk patients
    - No contraindications
    - Very symptomatic from DVT

Acknowledgements

- Dr. Darren Schneider
- Dr. Jade Hiramoto
- Dr. Christopher Owens
Recommendations for Percutaneous Transluminal Venous Angioplasty and Stenting

1. Stent placement in the iliac vein to treat obstructive lesions after CDT, PCDT, or surgical venous thrombectomy is reasonable (Class IIa; Level of Evidence C).
2. For isolated obstructive lesions in the common femoral vein, a trial of percutaneous transluminal angioplasty without stenting is reasonable (Class IIa; Level of Evidence C).
3. The placement of iliac vein stents to reduce PTS symptoms and heal venous ulcers in patients with advanced PTS and iliac vein obstruction is reasonable (Class IIa; Level of Evidence C).
4. After venous stent placement, the use of therapeutic anticoagulation with similar dosing, monitoring, and duration as for IFDVT patients without stents is reasonable (Class IIa; Level of Evidence C).
5. After venous stent placement, the use of antiplatelet therapy with concomitant anticoagulation in patients perceived to be at high risk of rethrombosis may be considered (Class IIb; Level of Evidence C).

Recommendations for Endovascular Thrombolysis and Surgical Venous Thrombectomy

1. CDT or PCDT should be given to patients with IFDVT associated with limb-threatening circulatory compromise (ie, phlegmasia cerulea dolens) (Class I; Level of Evidence C).
2. Patients with IFDVT at centers that lack endovascular thrombolysis should be considered for transfer to a center with this expertise if indications for endovascular thrombolysis are present (Class I; Level of Evidence C).
3. CDT or PCDT is reasonable for patients with IFDVT associated with rapid thrombus extension despite anticoagulation (Class IIa; Level of Evidence C) and/or symptomatic deterioration from the IFDVT despite anticoagulation (Class IIa; Level of Evidence B).
4. CDT or PCDT is reasonable as first-line treatment of patients with acute IFDVT to prevent PTS in select patients at low risk of bleeding complications (Class IIa; Level of Evidence B).
5. Surgical venous thrombectomy by experienced surgeons may be considered in patients with IFDVT (Class IIb; Level of Evidence B).
6. Systemic fibrinolysis should not be given routinely to patients with IFDVT (Class III; Level of Evidence A).
7. CDT or PCDT should not be given to most patients with chronic DVT symptoms (>21 days) or patients who are at high risk for bleeding complications (Class III; Level of Evidence B).

Jaff et al, Circ 2011
Systemically and Locally Administered Thrombolytic Therapy for PE

- All PE patients should undergo rapid risk stratification (Grade 1C).
- For patients with evidence of hemodynamic compromise, we recommend use of thrombolytic therapy unless there are major contraindications owing to bleeding risk (Grade 1B).
- In selected high-risk patients without hypotension who are judged to have a low risk of bleeding, we suggest administration of thrombolytic therapy (Grade 2B).
- The decision to use thrombolytic therapy depends on the clinician’s assessment of PE severity, prognosis, and risk of bleeding. For the majority of patients with PE, we recommend against using thrombolytic therapy (Grade 1B).

AHI approach to IFDVT thrombolysis

- **Puncture**
  - Popliteal vein under U/S guidance
- **Catheter**
  - Unifuse 5Fr
- **Thrombolysis**
  - TNK 5mg bolus
  - TNK 0.5mg/hr x 5 hours, then 0.25 mg/hr for 12-24 hours
- **Repeat venogram next day**
  - In incomplete lysis, Angiojet

What are the contra-indications for thrombolysis in acute PE?

<table>
<thead>
<tr>
<th>Contra-indications to Thrombolytic Therapy for PE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recent (within 2 mo) cerebrovascular accident, or intracranial or intraspinal trauma or surgery</td>
</tr>
<tr>
<td>Active intracranial disease (aneurysms, vascular malformation, or tumors)</td>
</tr>
<tr>
<td>Major internal bleeding within the past 6 mo</td>
</tr>
<tr>
<td>Uncontrolled hypertension (systolic BP &gt; 180 mm Hg)</td>
</tr>
<tr>
<td>Severe, uncontrolled articular pain</td>
</tr>
<tr>
<td>Recent (&lt; 48 h) major surgery, puncture of a noncompressible vessel, organs biopsy, or obstetric delivery</td>
</tr>
<tr>
<td>Recent major and minor trauma, including cardiopulmonary resuscitation</td>
</tr>
<tr>
<td>Active sepsis</td>
</tr>
<tr>
<td>Active neoplastic disease</td>
</tr>
<tr>
<td>Pregnancy</td>
</tr>
<tr>
<td>Renal failure</td>
</tr>
<tr>
<td>Retinopathy</td>
</tr>
<tr>
<td>Pre-existing renal artery stenosis</td>
</tr>
<tr>
<td>Recent (&lt; 4 mo) myocardial infarction</td>
</tr>
<tr>
<td>Recent (&lt; 30 d) non-ST elevation myocardial infarction</td>
</tr>
</tbody>
</table>

IVC Filter Indications

- **Relative**
  - Free-floating thrombus
  - Venous thrombolysis/thromboembolectomy
  - Poor compliance with AC
  - Documented VTE and limited cardiopulmonary reserve
  - High risk for AC complications
  - Cancer, burn, pregnancy
  - Recurrent PE complicated by pulmonary hypertension
  - VTE prophylaxis
  - High-risk surgical patients
  - Trauma patients
  - High-risk medical condition
  - Renal cell CA with renal vein extension
Long-term results: systemic thrombolysis

<table>
<thead>
<tr>
<th>Rx</th>
<th>Pts</th>
<th>PTS Severe (%)</th>
<th>PTS Moderate (%)</th>
<th>Asymptomatic (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heparin</td>
<td>39</td>
<td>8 (21)</td>
<td>23 (59)</td>
<td>8 (21)</td>
</tr>
<tr>
<td>SK</td>
<td>39</td>
<td>2 (5)</td>
<td>12 (31)</td>
<td>25 (64)</td>
</tr>
</tbody>
</table>


Post-thrombotic syndrome

- Ginsberg measure
  - Daily leg pain + swelling x 1 month
  - 6 months or more after DVT
  - Worse with standing/walking
  - Relieved by rest/leg elevation

Villalta Scale

Subjective Symptoms:
- heaviness
- pain
- cramps
- pruritus
- paresthesia

Objective signs:
- pretibial edema
- induration
- hyperpigmentation
- new venous ectasia
- indness
- pain with calf compression

CaVenT Trial