Managing Acute Lower Extremity DVT

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• No Financial Disclosures
Objectives

• Discuss the diagnosis of an Acute Lower Extremity DVT
• Discuss the current evidence and indications on the drug therapy management of an Acute LE DVT
• Discuss current evidence and indications for surgical or endovascular intervention for an Acute LE DVT
• Discuss Venous Clinical Scenarios related to Venous Thrombosis
  – Post-Thrombotic Syndrome
  – Phlegmasia
  – May-Thurner Syndrome
DVT – “A National Crisis...”
U.S. Surgeon General, 2008

• > 600,000 Americans are diagnosed with VTE annually
• VTE is the leading cause of preventable hospital death
• DVT is the third most common cardiovascular disease
• 17.9% DVT patients will suffer recurrent VTE within 3 years
• As many as two thirds of all DVT patients will develop Post Thrombotic Syndrome (PTS)
• U.S. spends $2.4B to treat DVT annually
Diagnosis

CUS sensitivity of 100% for proximal DVT (95% CI, 95-100) and a mean specificity of 99% (95% CI, 97-100)

Less sensitive for calf vein DVT

**Wells Deep Vein Thrombosis Risk Score**

<table>
<thead>
<tr>
<th>Clinical Characteristic</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active Cancer</td>
<td>1</td>
</tr>
<tr>
<td>Paralysis, recent immobilization of the lower extremities</td>
<td>1</td>
</tr>
<tr>
<td>Recently bedridden for $\geq 3$ days, or major surgery within the previous 12 weeks</td>
<td>1</td>
</tr>
<tr>
<td>Localized tenderness along the distribution of the deep venous system</td>
<td>1</td>
</tr>
<tr>
<td>Calf swelling at least 3 cm larger than contralateral side</td>
<td>1</td>
</tr>
<tr>
<td>Pitting edema of symptomatic leg</td>
<td>1</td>
</tr>
<tr>
<td>Collateral superficial veins</td>
<td>1</td>
</tr>
<tr>
<td>History of DVT</td>
<td>1</td>
</tr>
<tr>
<td>Alternate diagnosis at least as likely as DVT</td>
<td>-2</td>
</tr>
</tbody>
</table>

*Lancet 1997;350(9094):1795*
D-dimer

- D-dimer is a degradation product of crosslinked fibrin, marker of endogenous fibrinolysis
- When combined with a clinical probability score, D-Dimer measurements in outpatients have been shown to significantly reduce the use of ultrasound, from a mean of 1.34 tests per patient to 0.78 (P=0.008)
- 218 pts (39%) in the D-dimer group did not require US imaging

Conclusion:
- DVT can be ruled out in a patient who is judged clinically unlikely and who has a negative D-dimer without the use of ultrasound

Hospitalized Patients

- Well’s clinical model is not as sensitive in hospitalized patients
- 70 elderly inpatients with clinically suspected DVT
  - Frequency of DVT was not statistically different in 3 clinical categories
    - High: 60.6%  Moderate: 54.5%  Low: 54.5%
- Sensitivity of D-dimer assay 90.5% specificity 64.2% (85%), NPV 81% (98%)

*Thromb Res 1998;91 (Suppl 1):S54-55*
CTV

- US has decreased accuracy for pelvic veins
- Retrospective study of patients who received CTA and CTV were reviewed for the dx of PE and DVT
  - 10/642 patients pelvic DVT without PE
  - 5 had DVT leg on US
  - Isolated Pelvic DVT = 0.7%
  - All 10 patients + PE
  - Isolated pelvic DVT without PE was 0%
  - Mean XRT dose was higher CTV than CTA

_Eur J Rad 2011;80:50-53_
Drug Therapy for DVT

American College of Chest Physicians Recommendations:

• In acute DVT, we recommend:
  – initial treatment with LMWH, UFH or fondaparinux for at least 5 days and until the INR is ≥ 2 for 24 h
  – initial treatment with LMWH SC once or twice daily as an outpatient if possible or as an inpatient if necessary rather than the treatment with IV UFH
  – the use of compression stockings 30-40 mmHg

• In acute DVT
  – and RENAL FAILURE we suggest UFH over LMWH
  – And CANCER we recommend LMWH for the first 3 to 6 months of long-term therapy
    Subsequent therapy with VKA or LMWH indefinitely or until the cancer is resolved
Advances in Drug Therapy

- Rapid in onset
- Easy to administer
- Do not interact with other medications/food
- Have limited side effects
- Administered in a fixed dose
• Oral DTI compared in a double-blind randomized noninferiority trial to coumadin for patients with acute VTE
• Randomized after a mean of 9d of parenteral anticoagulation therapy
• Primary outcome: 6-mo incidence recurrent VTE / related deaths
• Safety endpoints: bleeding events
• VTE:
  – Dabigatran 30/1274 (2.4%)
  – Warfarin 27/1265 (2.1%)
Dabigatran vs. Warfarin for VTE

- No difference in Major bleeding
  - Dabigatran 1.6%: Warfarin 1.9% P=0.38

- Dabigatran had significantly less “any bleeding” than Warfarin
  - Dabigatran 16.1%: Warfarin 21.9% P<0.001

- Study limitation: dabigatran initiated after parental anticoagulation

- For VTE a fixed dose of dabigatran is as effective as warfarin and has a safety profile that is similar without lab monitoring.

• Rivaroxaban: oral factor Xa inhibitor was compared with sc enoxaparin followed by VKA in patients with acute DVT in a randomized, non-inferiority study
• In parallel, another double-blind, randomized superiority study comparing Rivaroxaban with placebo for an additional 6 to 12 mo in patients who had completed 6 to 12 mos of treatment for DVT
• Primary outcome: recurrent VTE
• Principle safety outcome: major bleeding
• 3449 patients: 1731: Rivaroxaban, 1718: Enoxaparin + VKA

Rivaroxaban was non-inferior to enoxaparin + VKA for recurrent VTE (36 events [2.1%] VS. 51 events [3%] with enoxaparin) (HR, 0.68:95% CI 0.44 to 1.04; P<0.001)

Principle safety outcome occurred in 8.1% of the patients in each group
Rivaroxaban

- In the continued treatment study; rivaroxaban had superior efficacy (8 events [1.3%] vs. 42 events with placebo [7.1%]) (HR 0.18; 95% CI 0.09 to 0.39; P<0.001)
- 4 patients in the Rivaroxaban group had nonfatal major bleeding (0.7%) vs. none in the placebo group P=0.11
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Post Thrombotic Syndrome

- 30%- 80% patients PTS after DVT
- Persistent edema
- Pain, heaviness
- Purpura
- hyperpigmentation
- Itchiness
- Cellulitis
- Ulceration
Post DVT

Residual Thrombus leads to Valvular Damage

Chronic Obstruction

Venous insufficiency, and Reflux contribute to stasis and Ambulatory Venous Hypertension

Post Thrombotic Syndrome Develops

Impairs a patient’s ADL, Work Performance and QOL
Post Thrombotic Syndrome

- Prospective multicenter cohort study of 387 patients acute DVT
- Patients were assessed PTS Severity score
  - PTS developed in 50% within 2 years after DVT
  - 3% had severe disease: leg ulcers
- Significant Predictors of higher PTS severity score
  - Proximal clot (iliac, CFV)
  - Previous ipsilateral venous thrombosis
  - Higher BMI /Older age/Female sex

Annals of Internal Medicine 2008;149:698
Post Thrombotic Syndrome

- patients with chronic venous obstruction have the most severe PTS
- Multi-segment venous involvement and iliofemoral obstruction result in the most profound morbidity

_J Vasc Surg_ 2007;46:1065
Iliofemoral DVT: Anticoagulation Alone

- 67% required recurrent hospitalizations (≥ 5)
- 81% experienced loss of financial productivity
- 95% patients had ambulatory venous HTN
- 90% developed CVI
- 15% developed ulceration within 5 years
- 15-40% experienced venous claudication

Iliofemoral DVT: Anticoagulation Alone

- Recurrent DVT is an important risk factor for PTS
- Patients with IVDVT treated with anticoagulation alone: have a 2.6 fold higher risk of recurrence than patients with less extensive DVT
- How do we reduce the risk of recurrence and thus the risk of PTS?
  - Patients who are free from residual intraluminal venous pathology are at low risk for recurrent DVT

  *J Vasc Surg 1995;22 (5):558-67*

- Canine models of acute DVT demonstrate that thrombolysis preserves endothelial function and vein valve competence compared with leaving the thrombus in place

  *J Vasc Surg 2000; 31 (6):1193*
Evolution of DVT Treatment Options

- **1950**: Anticoagulation Therapy
- **1980**: Venous Thrombectomy
- **1990**: Systemic Thrombolysis
- **2000**: Catheter Directed Thrombolysis
- **TODAY**: Isolated Pharmaco-mechanical Thrombolysis
Venous Thrombectomy

– Phlegmasia

– PMT fails:
  • Technical: catheter access can not be achieved
  • Thrombus removal is unsuccessful
  • Lytic infusion is contraindicated
Venous Thrombectomy Pearls

- Longitudinal groin incision/ venotomy common femoral
- Proximal thrombectomy
  - under fluoroscopic guidance using a contrast inflated balloon (IVC filter)
  - PEEP should be applied during the iliocaval thrombectomy to avoid PE
- AVF should be created between the GSV and SFA
  - Increases blood flow in the thrombectomized iliac segment preventing rethrombosis
  - Allows healing of the endothelium
  - Promotes development of collateral vessels in case of incomplete clearance
  - ligated at 6 weeks/ Percutaneous coiling
Systemic Thrombolysis

12 studies randomized patients IFDVT to anticoagulation alone vs systemic thrombolysis: summary analysis of lytic outcomes in these trials

**Table 3 Phlebographic Results of Randomized Trials (n = 12) of Systemic Lytic Therapy versus Anticoagulation**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>None/Worse (%)</th>
<th>Partial (%)</th>
<th>Significant/Complete (%)</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>

- Complete clot resolution 5% vs 45% lytic group
- 3 fold increased risk of bleeding complications in the lytic group

*Semin Vasc Surg 2010;23:192*
Catheter –Directed Thrombolysis

• Advantages over systemic infusion
  – Protects against neutralization from PAI and antiplasmins
  – Decreases the necessary dose and duration of infusion

• Technique
  – US used to access popliteal/PT vein
  – Infusion catheter is advanced antegrade
National Venous Registry

- 287 patients treated in 63 academic/comm hospitals: DVT
- 71% IFDVT: CDT
- 65% IFDVT had complete clot resolution
- 60% Thrombus free at 1 year
- Significant correlation between effect of initial therapy and thrombus-free survival
- At 1 year
  - Vein Patency
    - 78% in patients who had complete clot resolution
    - 37% in patients who achieved < 50% clot resolution
  - Normal Valvular Function:
    - 72% in complete clot resolution patients (P<0.02)
    - 38% of in patients with <50% clot resolution

Radiology 1999;211:39-49
National Venous Registry: QOL Questionnaire

• Given to patients with IFDVT treated with CDT vs anticoagulation at 16 and 22 mo after treatment

• CDT
  – Significantly better QOL
  – Results were directly related to initial success CDT
  – Better clot resolution correlating with:
    • Better physical functioning status/ Less health distress
    • Fewer symptoms of PTS/ Less stigmata of CVI
  – Patients in whom CDT failed had outcomes similar to those treated with anticoagulation alone

*J Vasc Surg 2000;32:130-7*
Egypt Trial

• First RCT of CDT vs. anticoagulation alone for acute IFDVT
• 35 patients were randomized to CDT + anticoagulation or anticoagulation alone
• pulse spray technique/low dose infusion with repeat phlebography at 12 hr intervals
• 6 month Iliofemoral patency (P < 0.001)
  – Lytic group: 72%
  – Anticoagulation: 12%
• Normal Valvular Function (P =0.04)
  – Lytic group: 89%
  – Anticoagulation group: 59%
• No major bleeding events

J Vasc Endovas Surg 2002;24:209-214
CaVenT Study

- Multicenter RCT: 209 patients with acute iliofemoral DVT randomized to anticoagulation or CDT + anticoagulation
- Mean duration DCT 2.4 days
- 2 Primary End Points
  - Iliofemoral patency at 6 months
  - Frequency of PTS at 24 months

<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></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>
</tr>
</tbody>
</table>

Post-thrombotic syndrome defined as Villalta score of 5 points or higher. *x^2* test. †Co-primary outcomes. ‡Five patients had inconclusive patency assessments and one was lost to follow-up at 6 months. §Secondary outcome.

Table 2: Short-term and long-term outcomes

*Lancet 2012; 379:31*
The absolute RR of developing PTS at 2 year follow up in the patients treated with CDT compared with the control group was 14.4% and the number needed to treat was 7.

20 bleeding complications

- 3 were major: 1 abd wall hematoma, 1 calf compartment syndrome, inguinal puncture site hematoma
- No deaths, PE or cerebral hemorrhages

_Lancet_ 2012; 379:31
Pharmacomechanical Thrombolysis

• Advantages
  – Significantly shortens the duration and dose of lytic therapy
  – Removes more of the thrombus and restores patency
  – Shorten hospital stay, reduces bleeding risk

• Disadvantages
  – Possible damage to venous endothelium and vein valves
  – Fragmentation of thrombus with pulmonary embolism
  – Increased procedure time (compared to CDT)
ANGIOJET
(Posis Medical, Minneapolis, MN)

• high pressure saline jets are created from the tip directed backward, this generates a vacuum force which macerates the thrombus and aspirates it into the catheter.
Review of 52 patients PMT (Angiojet) compared the clinical outcome with a group of 46 patients who were treated with CDT

No difference:
  - thrombus removal: PMT 75% vs. CDT 70%
  - improvement in clinical symptoms
  - patency rates at 1 year

PMT had less procedural time, ICU stay and overall LOS
  - CDT (2.4 and 8.4 days)
  - PMT (0.6 and 4.6 days)

Resulting in a significantly reduced hospital cost with PMT vs. CDT

*Am J Surg 2006;192 (6)782-8*
Trellis Catheter
(Bacchus Vascular Santa Clara, CA)

- Catheter delivered over a guidewire through thrombus
- Isolation achieved with two occluding balloons, lytic agent infused
- Catheter forms a sinewave configuration that oscillates at 1500 rpms
- Thrombus is dissolved and aspirated
- Review of patients with IFDVT
  - 27 patients treated with CDT
  - 22 ISPMT± CDT
- ISPMT
  - Thrombus resolution was increased:
    - 80% vs. 60% P =0.0016
  - Treatment Time was decreased:
    - CDT : 55.4 hrs vs ISPMT: 23.4 hrs  P <0.0001
  - TPA Dose was decreased:
    - 59.3 vs 33.4 mg  P=0.0009
  - No difference in complications, ICU/LOS

EKOS Catheter

- **Ekosonic catheter**: (Corp, Bothell, WA) ultrasound-accelerated thrombolytic system, combining high frequency, US with simultaneous CDT accelerating clot dissolution.
  - disassociates the fibrin mesh to increase the thrombus SA available to the thrombolytic agent
  - the US waves drives the TPA deep into the loosened clot
- US energy penetrates venous valves and dissolves thrombi behind the valves
### Baylor’s Prospective Database:

#### Acute IFDVT

<table>
<thead>
<tr>
<th>Variable</th>
<th>Angiojet</th>
<th>Trellis</th>
<th>EKOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>% pts DVT</td>
<td>40%</td>
<td>33%</td>
<td>28%</td>
</tr>
<tr>
<td>Complete Treatment Success</td>
<td>83%</td>
<td>82%</td>
<td>88%</td>
</tr>
<tr>
<td>Partial Success</td>
<td>17%</td>
<td>18%</td>
<td>12%</td>
</tr>
<tr>
<td>PTA/Stenting</td>
<td>87%</td>
<td>82%</td>
<td>84%</td>
</tr>
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</table>

*Perspect Vasc Surg and Endovasc Ther* 2010;22 (3)152
# Chronic DVT

<table>
<thead>
<tr>
<th>Variable</th>
<th>Angiojet</th>
<th>Trellis</th>
<th>EKOS</th>
<th>Trellis + EKOS</th>
<th>Angiojet + EKOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>% pts Chronic DVT</td>
<td>29%</td>
<td>5%</td>
<td>23%</td>
<td>19%</td>
<td>24%</td>
</tr>
<tr>
<td>Mean Days</td>
<td>27</td>
<td>32</td>
<td>34</td>
<td>42</td>
<td>37</td>
</tr>
<tr>
<td>Complete Treatment Success</td>
<td>39%</td>
<td>0%</td>
<td>64%</td>
<td>75%</td>
<td>73%</td>
</tr>
<tr>
<td>Partial Success</td>
<td>61%</td>
<td>100%</td>
<td>36%</td>
<td>25%</td>
<td>37%</td>
</tr>
</tbody>
</table>

Future advances are in chronic DVT and the potential combination of PMT with US enhanced thrombolysis

*Perspect Vasc Surg and Endovasc Ther* 2010; 22 (3) 152
Outcome Measures after IFDVT Lysis

42 patients underwent CDT ± PMT. Patients were divided into 2 groups based upon % lysis
Mean f/u 14 mo

Group 1 (n=33)
> 50% Lysis

- CEAP Score: 0.85
- Villalta Scale: 2.38

Group 2 (n=9)
≤ 50%

- CEAP Score: 3.13
- Villalta Scale: 6.25

> Clot lysis = less PTS and better QOL
ATTRACT TRIAL
Acute Venous Thrombosis:
Thrombus Removal with Adjunctive Catheter-Directed Thrombolysis

• NIH funded multicenter RCT: 55 US centers, enrollment began 2010
  – CDT ± pharmacomechanical techniques
  – Plus anticoagulation vs. anticoagulation alone
• Compare the efficacy of pharmacomechanical techniques to drip infusion of plasminogen activators
• Cost effectiveness of treatment
• Risk-to-benefit ratio of Catheter based techniques vs. anticoagulation alone
• Frequency of PTS at 24 months
ACCP Recommendations IFDVT

• In patients with acute proximal DVT we suggest CDT to reduce acute symptoms and post-thrombotic morbidity
• We suggest the correction of underlying venous lesions using balloon angioplasty and stents
• PMT in preference to CDT alone to shorten treatment time
• CDT is preferable to operative venous thrombectomy

Chest 2008;133:454
Venous Clinical Scenarios

- Phlegmasia
- May-Thurner Syndrome
- Paget-Schroetter Syndrome
- Lower Extremity Superficial Thrombophlebitis
- Calf Muscle Thrombosis
- Calf DVT
Phlegmasia Cerulea Dolens

- Rare, severe consequence of extensive IFDVT
- Acute limb ischemia due to total or near total thrombosis of the venous outflow of an extremity
- IFDVT creates severe venous HTN leading to massive tissue edema followed by ischemia and ultimately venous gangrene
- Arterial insufficiency occurs as a result of small artery collapse
- 20-50% amputation rate
- 20-40% mortality
- Appear toxic, volume depleted, c/o unremitting pain, dopplers intact, Sensory and motor impairment = imminent gangrene!
Phlegmasia alba dolens

- PCD is distinct from Phlegmasia alba dolens (milk leg)
- Stage in the continuum prior to PCD
- Massive IFDVT with sparing of venous collaterals
- Alba doles does not result in limb ischemia
- Swollen, painful extremity that blanches
May-Thurner Syndrome

- 1957 Anatomical Variant of venous obstruction LCIV by RCIA and vertebral body
- Today: LLE venous HTN from compression by the Right Iliac Artery± IFDVT
- Prevalence is unknown: 24% population
- 2-3% lower extremity DVTs
- Young, multiparous women
- Dx: CTA, MRV, Venogram
- Treatment:
  - Clot removal
  - Stenting of iliac vein stenosis
- 2 year reported patency » 95%
Paget-Schroetter Syndrome
Primary axillosubclavian venous thrombosis

Effort Thrombosis
- sudden onset of non-pitting edema/pain
- prominence of superficial veins

Venous Compression
- 2-3% TOS cases
- junction of the clavicle and 1st rib

Etiology
- trauma, strenuous, repetitive activity (weight lifting) in a pt with some compressive elements
- Dominant arm 75%

Treatment
- Anticoagulation results in significant morbidity
- CDT combined with 1st rib resection
  - Transaxillary
  - Supraclavicular
  - Infraclavicular
  - Venography ± stenting/ PTA
Superficial Venous Thrombosis

- **POST Study**
  - Prospective Observational Superficial Thrombophlebitis
  - 844 patients with symptomatic SVT legs with $\geq 5$ cm on CUS
  - 24.9% had DVT or PE at Dx
  - At 3 mo follow up:
    - 10.2% developed VTE despite 90.5% having received anticoagulants
      - Majority LMWH median 11 days

*Ann Int Med* 2010;152:218
Fondaparinux for the Treatment of Superficial-Vein Thrombosis in the Legs

- Randomized, double blind trial 3002 patients:
  - Fondaparinux 2.5 mg sc q d
  - Placebo for 45 days
- Primary outcome: Sx PE/ DVT or SVT recurrence/extension
  - Fondaparinux vs placebo: 0.9% vs. 5.9%
  - RR reduction with Fondaparinux 85%; (95%CI, 74 to 92; P<0.001)
  - 88 patients would need to be treated to prevent one instance of PE or DVT
  - Major bleeding occurred in one patient in each group
  - No difference in SAE

ACCP Recommendations

- **SVT**
  - Prophylactic/intermediate doses LMWH for 4 wks
  - Or VKA INR 2.5 overlapped with 5 days of LMWH for 4 wks
  - When the affected venous segment is short in length and further from the SFJ anticoagulation is not required; oral or topical NSAIDs for symptom control

Calf Muscle Vein Thrombosis?

- Prospective randomized trial of 107 patients with symptomatic ICMVT in the soleal ± gastrocnemial muscle veins
  - LMWH 10 days therapeutic doses + compression therapy 3 months
  - Compression therapy alone
- Primary end points: DVT/PE
- DVT occurred in 2 patients in both groups (P=ns)
- No PE/death occurred
- Thrombus recanalization after 3 mo was not statistically different
- No major bleeding occurred in either group

J Vasc Surg 2010;52:1246-50
Review suggests that anticoagulation therapy for calf vein DVT may decrease the incidence of PE and thrombus propagation

*J Vasc Surg 2011 epub ahead of print*