Updates on Anticoagulation and venous Thrombolysis

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The Cardiovascular Care Group
DISCLOSURES

NONE
Risk Factors for VTE

- Recent surgery
- Lower extremity trauma
- Use of oral contraceptives or HRT
- Inflammatory states
- Inherited Hypercoagulable conditions
- Immobilization or prolonged bed rest
- Previous VTE

- Malignancy
- Obesity
- Pregnancy or postpartum Status
- Congestive Heart Failure
- Varicose Veins
- Drugs which can induce antiphospholipid antibodies
Who should be worked up for Familial Hypercoagulable Disorders?

• 1st degree relative with VTE before age 45
• Young patient with VTE ( <45) ?
• Patient With Recurrent Un Provoked DVT
• Thrombosis of Multiple Venous sites or unusual vascular beds
Hypercoagulable work up – Inherited Thrombophilias

- Protein C deficiency
- Protein S deficiency
- Antithrombin deficiency
- Factor V mutation
- Prothrombin mutation
- APS
### Natural History DVT

- **Predictors of recurrent DVT**
  - Unprovoked DVT
  - Thrombophilia
  - Primary DVT
  - Shorter anticoagulation
  - Age

### Table: VTE Incidence Over Time

<table>
<thead>
<tr>
<th>Months</th>
<th>Idiopathic VTE (N)</th>
<th>Idiopathic Cum Incid</th>
<th>Secondary VTE (N)</th>
<th>Secondary Cum Incid</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>85</td>
<td>10%</td>
<td>32</td>
<td>4.2%</td>
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<td>12</td>
<td>39</td>
<td>15%</td>
<td>17</td>
<td>6.6%</td>
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<td>60</td>
<td>130</td>
<td>40.8%</td>
<td>48</td>
<td>22.5%</td>
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<td>120</td>
<td>14</td>
<td>52.6%</td>
<td>8</td>
<td>16.1%</td>
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</tbody>
</table>

*Prandoni et al, Hematologica 2007*
Goals of DVT Therapy

• Prevent recurrent VTE
• Prevent thrombus extension
• Prevent death from PE
• Prevent PTS
• PTS will develop in as many as 70% of patients with VTE after their first episode of DVT\(^1\)
  • 20-50% of DVT patients are treated with appropriate anticoagulation
  • 8-10% develop severe PTS including ulcers
• Annual cost of developing PTS is 32% higher compared to DVT/PE patients without PTS\(^2\)

• 355 consecutive patients with first DVT
• 1º Outcome - Villalta score
• Cumulative incidence of PTS
  • All - 28% at 5 years
  • Severe - 9.3% at 5 years

Treatment options for DVT

- Anticoagulation
- Compression
- IVC filters
- Pharmaco-mechanical thrombectomy
- Surgery
Pharmacologic therapy

• Anticoagulation
  • Mainstay in management of DVT
  • Except patients with high risk of bleeding
  • Critical to obtain therapeutic level in first 24hrs

• Heparin/LMWH
• Coumadin – INR 2-3
• NOACs
Anticoagulation

• Maintain therapeutic level throughout the treatment period

• Incidence recurrent VTE 5-7% with adequate anticoagulation regiment vs. 25% with sub-therapeutic treatment.

• Complications: bleeding, osteoporosis, thrombocytopenia, HIT.
Outpatient Management of DVT

• Hospital admissions not required unless ...
  • ESRD
  • Severely Symptomatic VTE
  • High Bleeding Risk

Relieves pressure on hospital beds & Decrease Cost
• Xa inhibitors:
  - Xarelto
  - Elaquis

• IIa inhibitors:
  - Pradaxa
  - Savaysa
NOACS - Pro

- No need for bridging
- Fast onset of action
- Oral administration
- No need for monitoring
- Limited drug interactions
**NOACS Con**

- No Xa reversal agents
  - Coming soon: prt4445
- Contraindication ESRD pt:
- Elaquis 2.5mg dose?

**COST**
What is The Recommended Duration of Treatment?
Clinical Case
VTE and Cancer

• 72 year old male with prostate cancer receiving chemotherapy. Presents with 1 week history of left leg pain and swelling.

• Exam – Left leg swelling

• DU – Left femoral-popliteal DVT

VTE management?
ACCP guidelines 2016
Choice of Long-Term (First 3 Months) and Extended Anticoagulant

• In patients with DVT of the leg or PE and no cancer
  • dabigatran, rivaroxaban, apixaban, or edoxaban over vitamin K antagonist (VKA) therapy

• In patients with DVT of the leg or PE and cancer
  • we suggest LMWH over VKA therapy, dabigatran, rivaroxaban, apixaban, or edoxaban.

• In patients with DVT of the leg or PE who receive extended therapy, we suggest that there is no need to change the choice of anticoagulant after the first 3 months
Clinical Case
VTE and Cancer

- 72 year old male with prostate cancer receiving chemotherapy. Presents with 1 week history of left leg pain and swelling.
- Exam – Left leg swelling
- DU – Left femoral-popliteal DVT

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VTE management?
Clinical Case

Post-op DVT

• 36 year old female underwent laparoscopic cholecystectomy. Developed right leg swelling post-op day 3 & SOB

• No PMH or FH of VTE

• DU – Left popliteal DVT

• Started on Lovenox/Coumadin

Duration of treatment?
ACCP guidelines 2016
Duration of Anticoagulant Therapy

• In patients with a proximal DVT of the leg or PE provoked by surgery or nonsurgical transient risk factor:
  
  • anticoagulation for 3 months over
    (i) treatment of a shorter period (Grade 1B)
    (ii) treatment of a longer time-limited period (eg, 6, 12, or 24 months) (Grade 1B)
    (iii) extended therapy.
Clinical Case
Post-op DVT

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• No PMH or FH of VTE

• DU – Left popliteal DVT

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Duration of treatment?

anticoagulation for 3 months
Clinical Case
Unprovoked DVT

• 25 year old female presents with 2 week history of left leg swelling.
• No identifiable VTE risk factors.
• No family history of VTE
• DU – Left CFV DVT

What do you do now?
• In patients with an unprovoked DVT of the leg (isolated distal or proximal) or PE

• anticoagulation for at least 3 months over treatment of a shorter duration

• After 3 months of treatment, patients with unprovoked DVT of the leg or PE should be evaluated for the risk-benefit ratio of extended therapy
In patients with a first VTE that is an unprovoked proximal DVT of the leg or PE and who have a:

- **low or moderate bleeding risk**, we suggest **extended** anticoagulant therapy (no scheduled stop date) **over** 3 months of therapy (Grade 2B)

- **high bleeding risk**, we recommend **3 months** of anticoagulant therapy **over** extended therapy (no scheduled stop date) (Grade 1B)
Clinical Case
Unprovoked DVT

• 25 year old female presents with 2 week history of left leg swelling.
• No identifiable VTE risk factors.
• No family history of VTE
• DU – Left CFV DVT

What do you do now?

anticoagulation for at least 3 months
Clinical Case

Recurrent DVT

• 72 year old with history of left leg popliteal vein thrombosis. Treated with Coumadin for 9 months. Develops left calf pain 3 years after stopping anticoagulation.

• PMH – Parkinson, frequent falls

• DU – Left peroneal DVT

VTE management?
In patients with a second unprovoked VTE and who have a

- **low bleeding risk**, recommend extended anticoagulant therapy over 3 months (Grade 1B)
- **moderate bleeding risk**, suggest extended anticoagulant therapy over 3 months of therapy (Grade 2B)
- **high bleeding risk**, suggest 3 months of anticoagulant therapy over extended therapy (no scheduled stop date) (Grade 2B).
Clinical Case

Recurrent DVT

- 72 year old with history of left leg popliteal vein thrombosis. Treated with Coumadin for 9 months. Develops left calf pain 3 years after stopping anticoagulation.
- PMH – Parkinson, frequent falls
- DU – Left peroneal DVT

anticoagulation for at least 3 months

VTE management?
Clinical Case

Recurrent DVT

• 72 year old with history of left leg popliteal vein thrombosis. Treated with Coumadin for 9 months. Develops left calf pain 3 years after stopping anticoagulation.

• PMH – Parkinson

• DU – Left calf pain

VTE management?
Clinical Case

Distal vein thrombosis

• 65 year old female with recent subdural hematoma evacuation.
• Doing well post-op, ambulating.
• Prior to discharge, on screening duplex ultrasound found to have calf vein thrombosis.
• On exam – no pain or swelling

VTE management?
• In patients with acute isolated distal DVT of the leg and
  
  • without severe symptoms or risk factors for extension, suggest serial imaging of the deep veins for 2 weeks over anticoagulation (Grade 2C)
  
  • with severe symptoms or risk factors for extension, suggest anticoagulation over serial imaging of the deep veins (Grade 2C).
Clinical Case
Distal vein thrombosis

- 65 year old female with recent subdural hematoma evacuation.
- Doing well post-op, ambulating.
- Prior to discharge, on screening duplex ultrasound found to have calf vein thrombosis.
- On exam – no pain or swelling.

VTE management?
Clinical Case
Distal vein thrombosis with serial imaging

• 45 year old male seen 1 week after varicose vein procedure.

• Ultrasound was done to evaluate for DVT. Patient had no clinical symptoms. DU with single peroneal vein thrombosis.

• Managed with serial DU.

• At week 2 - DU shows both peroneal veins thrombosed.

VTE management?
In patients with acute isolated distal DVT of the leg who are managed with serial imaging

• If the thrombus does not extend recommend no anticoagulation (Grade 1B)

• if the thrombus extends but remains confined to the distal veins suggest anticoagulation (Grade 2C)

• if the thrombus extends into the proximal veins recommend anticoagulation (Grade 1B)
Clinical Case

Distal vein thrombosis with serial imaging

• 45 year old male seen 1 week after varicose vein procedure.

• Ultrasound was done to evaluate for DVT. Patient had no clinical symptoms. DU with single peroneal vein thrombosis.

• Managed with serial DU.

• At week 2 - DU shows both peroneal veins thrombosed.

**VTE management?**

anticoagulation for 3 months
• In patients with an unprovoked proximal DVT or PE who are stopping anticoagulant therapy and do not have a contraindication to aspirin, suggest aspirin over no aspirin to prevent recurrent VTE
In patients with acute DVT of the leg, we suggest not using compression stockings routinely to prevent PTS (Grade 2B).

Remarks: This recommendation focuses on prevention of the chronic complication of PTS and not on the treatment of symptoms. For patients with acute or chronic symptoms, a trial of graduated compression stockings is often justified.
The SOX Trial
Kahn SR, Lancet 2014

• 806 patients (24 North American Centers)
  • 30 – 40 mm Hg stockings
  • Placebo (5 mm Hg) stockings

• Cumulative incidence of PTS at 2 yrs
  • 1º - Ginsberg criteria
    • Pain & swelling > 1 month
    • Less sensitive to mild to moderate PTS
  • 2º - Villalta score

• No differences in
  • Quality of life (SF-36, VEINES)
  • Recurrent VTE
  • Popliteal venous reflux

• 69.1% compliance at 24 months
Prevention of PTS: Compression
Kakkos et al, Thromb Haemost 2006

- Metanalysis – 4 randomized trials
  - Belcaro 1993 (n = 116)
  - Brandjes 1997 (n = 194)
  - Ginsberg 2001 (n = 47)
  - Prandoni 2004 (n = 180)
- Recurrent DVT – non-significant reduction
  - RR 0.79 (0.5 – 1.26)
  - NNT – 34
- Post-thrombotic syndrome – 50% reduction
  - RR 0.47 (0.36 – 0.95)
  - NNT - 4
Superficial Thrombophlebitis (SVT)

• Generally “Benign”:
• when associated with IV
• Varicose Veins ( >50% cases)

• Consider in DDX:
• Hypercoagulable state
• cancer
SVT- Not always benign

Prospective study: 844 consecutive patients with acute SVT of >5cm long

At initial presentation 210 had a VTE

- 4% of them had symptomatic PE
- Routine ultrasound detected
  - Proximal DVT in 10% and
  - Calf DVT in an additional 13% of patients

At follow up 90.5% patients without VTE at presentation were treated with either prophylactic/therapeutic anticoagulation

- 3.1% developed symptomatic VTE
  - (0.4% PE, 1.2% proximal DVT, 1.4% distal DVT)
- 1.9% had recurrent SVT at a different location
- 3.3% had an extension of SVT in the same location at 3 months

Management of patient with suspected superficial vein thrombosis, adapted from ACCP guidelines

- Surgical options:
  - < 1cm from junction → ligation +/- excision
  - Recurrent phlebitis → excision / phlebectomy
  - Post Ablation → microthrombectomy
  - Significant pain → microthrombectomy

Catheter Associated DVT
Catheter Associated DVT

- Treat with anticoagulation while catheter in place
- Treat as provoked DVT:
  - 3 months AC
Inferior Vena Cava Filter

- Recommended: (1B)
  - VTE + Contraindication to AC

Not Recommended: (1B)
- VTE + AC+ PE
  *** unless large PE with instability ***

Not Recommended:
- AC failure → Filter placement
  *** considered last resort ***

ACCP guidelines 2016
Mechanico-chemical Treatment of Iliocaval Thrombosis

- AngioVac
- Cleaner XT
- Angiojet
- Penumbra
- Jet i
- Catheter Directed Lysis
Catheter Directed Lysis

**Pros**
- Quick initial intervention
- Effective for large thrombus burdens
- No need for special devices
- Infusion Catheter is fairly cheap
  - McNamara, uni-fuse

**Cons**
- Require knowledgeable staff & attentive post operative care
- ICU = not cheap
- Multiple interventions / more intervention days
Catheter Directed Lysis

• Multiple fr sizes depending on treatment vessel

• Infusion
  • .5mg-1mg per hour via catheter
  • .01mg/kg/hr

• Monitor in ICU setting
  • Risk of access site complications
  • Intracranial bleeding
    • High risk: elderly female
Contraindications for Lysis

• Ischemic CVA within 3 months
• Hemorrhagic CVA
• Structural CNS pathology or tumors
• Major Surgery within 2-4 weeks
• Age >75
• Recent TBI
Angiojet Zelante - Thrombectomy Catheter

- 8 Fr sheath
- Power pulse capability
  - For TPA infusion (10mg/50-100ml sterile water)
  - Rotatable catheter tip for circumferential infusion
- Treatment length 15mm
- Vessel Diameter ≥ 6mm
- Requires separate generator
Penumbra Thrombectomy system

Continuous Aspiration Mechanical Thrombectomy

• CAT8 –catheter for venous mechanical thrombectomy

• Recommend pre thrombectomy TPA infusion with ~30 min dwell time
Penumbra Thrombectomy system

Continuous Aspiration Mechanical Thrombectomy
• CAT8 – catheter for venous mechanical thrombectomy
  • - Be very cautious of blood loss
Cleaner XT

- Rotational Thrombectomy System
- 8 & 6 fr catheter options
- 8 fr catheter: 15 mm sinusoidal wave
- ** Recommend Pre Thrombectomy TPA**
AngioVAC -

- Utilized 26 fr sheath (Dry seal)
- 22F coil reinforced Cannula
  - Straight 20 deg. Angled tip
  - Inflatable funnel Tip
- Requires some element of flow lumen to function
- Can function with any off the shelf extracorporeal pump set up
AngioVAC-
EkoSonic™ Endovascular System

- 5.4 Fr catheter
- 106 and 135 cm working length
- 6, 12, 18, 24, 30, 40 and 50 cm treatment zones
Acoustic Pulse Thrombolysis™

Mechanism of action

**Fibrin Separation**
Ultrasound separates fibrin without fragmentation of emboli

**Active Drug Delivery**
Drug is actively driven into clot by “Acoustic Streaming”

EKOS™ Acoustic Pulse Thrombolysis™ treatment is a minimally invasive system for accelerating thrombus dissolution.

Mechanism of Action: Using ultrasonic energy to dissolve clots

- Ultrasonic energy causes fibrin strands to thin, exposing plasminogen receptor sites
- Thrombus permeability and lytic penetration are dramatically increased
- Ultrasound pressure waves force lytic agent deep into the clot and keep it there

Greater thrombus removal results in lower PTS rate

- Comerota et al. evaluated the correlation between residual thrombus and PTS in IFDVT patients (N=63) treated with CDT
- Blinded comparison of pre- and post-treatment phlebograms and CEAP/Villalta scores
- Direct correlation between PTS scores and thrombus clearance

When thrombus clearance is complete, PTS can be avoided (In Theory)

CDT reduces PTS compared to anticoagulation alone

- CaVenT Trial: RCT to determine benefit of CDT in acute IFVDT, N=209
- Treatment: anticoagulation vs anticoagulation + CDT with tPA
- CDT group had improved patient outcomes vs. anticoagulation
  - Lower rate of PTS at 24 months f/u
  - Higher patency at 6 months f/u

<table>
<thead>
<tr>
<th>Additional catheter-directed thrombolysis (n=90)</th>
<th>Standard treatment only (n=99)</th>
<th>p value*</th>
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<tbody>
<tr>
<td>n</td>
<td>% (95% CI)</td>
<td>n</td>
</tr>
<tr>
<td>Post-thrombotic syndrome at 24 months†</td>
<td>37 41.1% (31.5-51.4)</td>
<td>55</td>
</tr>
<tr>
<td>Iliofemoral patency at 6 months‡</td>
<td>58 65.9% (55.5-75.0)</td>
<td>45</td>
</tr>
<tr>
<td>Post-thrombotic syndrome at 6 months§</td>
<td>27 30.3% (21.8-40.5)</td>
<td>32</td>
</tr>
</tbody>
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CDT should be considered in patients with high proximal DVT and low risk of bleeding
CDT reduces PTS compared to anticoagulation alone

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- Treatment: anticoagulation vs anticoagulation + CDT with tPA
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  - Higher patency at 6 months f/u

CDT should be considered in patients with high proximal DVT and low risk of bleeding
**ATTRACT TRIAL**

- 692 patients
- 56 centers
- Randomized to
  - Best medical therapy
  - Pharmacomechanical lysis
    - Trellis 8
    - Angiojet powerpulse
- Iliofemoral & femoropopliteal DVT
- Clinically relevant endpoints
  - Objective PTS (Villalta)
  - Quality of life
ATTRACT TRIAL- Outcomes 24 Months

CDT
- 157/336 PTS 47%
- Moderate- Severe 18%
- 10 day major bleeding 1.7 %

AC
- 171/355 PTS 48%
- Moderate-Severe 24%
- 10 day major bleeding .3%
Among patients with acute proximal deep-vein thrombosis, the addition of pharmacomechanical catheter-directed thrombolysis to anticoagulation did not result in a lower risk of the post-thrombotic syndrome but did result in a higher risk of major bleeding. (Funded by the National Heart, Lung, and Blood Institute and others; ATTRACT ClinicalTrials.gov number, NCT00790335.)
Take Home Messages

• Novel agents make therapy easier for people
• We probably place too many filters
• CDT – the jury is still out, but we do it because it makes the patients(and us) feel better