Venous thromboembolism in 2018
Best evidence and Best practices

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May 4th, 2018
Presenter Disclosure

• Faculty / Speaker’s name: Vi Dao

• Relationships with commercial interests:
  – Grants/Research Support: none
  – Speakers Bureau/Honoraria: Celgene, Pfizer, Jansen
  – Consulting Fees: none
Mitigating Potential Bias

• All honoraria received had been forwarded to professional development fund or CancerCare Manitoba Foundation

• No off label use of drugs will be discussed in this talk
Learning Objectives

1. Recognize the different subgroups of venous thromboembolism
   – Proximal versus distal clot
   – Unprovoked versus provoked by various risk factors

2. Select the appropriate choice of anticoagulants as well as the appropriate duration for anticoagulation for the various VTE subgroups
Referral to Hematology

Question to Consultant
Please provide specific clinical question for consult below

See attachments:  
- History  
- Labs  
- Diagnostic Imaging  
- Other

The patient recently had a PE is shortly after being taken off the respirator. The patient has been feverish, shortness of breath, and chest pain.
Why do we treat VTE?

- Untreated PE can be fatal
  - historical estimate risk of death is 26% (Barritt et al, Lancet 1960)
  - Even with treatment, 2% die at 30 days and 9% at 1 year
    3 patients needed to be treated to prevent 1 death
- Mortality rate from VTE in the modern era is lower compared to historical cohort

Kelly et al, J Int Med 2003
Risk of treating VTE: bleeding

- Anticoagulation increases the risk of bleeding
  - Major bleed in the first 3 month with LMWH/warfarin: 2.1%
  - 0.4% result in death (4 per 1000 patient)
- Clinicians need to ensure that the risk of untreated VTE is higher than the risk of treating the VTE

Linkins et al, Ann Int Med 2003
Impact of clot location & clot burden

• Location of clot matters (PE vs DVT)
  – Mortality is 2-3x higher for PE when compared to DVT
  – Despite having the same risk of recurrence (~20%), patients with PE is more likely to recur with PE (10% vs 3%)

• Size of clot matters (proximal vs distal)
  – Smaller clot burden such as distal DVT or PE in subsegmental vessels (SSPE) has no impact on mortality

Baglin et al, J Thromb Haem 2010
Case 1

- A 30 year old man presents with moderate calf pain and swelling for 5 days after he was kicked playing soccer. Ultrasound shows DVT in the posterior tibial vein. Does he need anticoagulation?
  - Yes
  - No
Distal DVT

- Leg US have lower sensitivity and specificity to detect clot in smaller vessels
- Difficult to know if the reported “DVT” is a new clot or residual thrombosis (scarring)
- Indirect evidence suggests treating distal DVT does not further reduce the 3 month VTE risk → 0.3% rec VTE
- Therefore, selected patients may not benefit from anticoagulation

Righini et al, Curr Opin Pulm Med 2008
Subsegmental PE (SSPE)

- Is a common incidental finding (5-10% of all PE)
- Can be false positive (low inter-observer agreement)
- Some patients may not need to be treated (0% recurrent at 3 month)
Which patients do not require anticoagulation?

1. Patients with **small** clot burden (distal DVT or SSPE with no DVT)
2. Adequate cardiopulmonary reserve (absent of: syncope, tachyarrhythmias, abnormal spirometry, hypoxia, SBP<90)
3. A major risk factor for VTE that is no longer present
4. Compliant and trustworthy patient who would return for serial noninvasive leg imaging
Approach to the patient with small clot burden

Subsegmental PE (SSPE) or Distal DVT

Anticoagulation IF
» Very symptomatic
» Multiple SSPE
» Ongoing risk for thrombus extension (active malignancy, immobilization, etc)

Observation with serial imaging IF
» Isolated SSPE AND bilateral leg US is negative for DVT
» Distal DVT needs q5-7 days leg US for 2 weeks (or until symptom resolution)
Initial management of VTE

1. Start *empiric* anticoagulation while waiting for imaging
2. Review history/exam including vitals, weight
3. Review medications
4. Baseline investigations
   1. CBC, reticulocytes (?platelet, myeloproliferative d/o, cancer)
   2. Creatinine (to estimate GFR)
   3. Liver enzymes, INR (to help estimate bleeding risk)
   4. Urinalysis (to rule out hematuria) and urine albumin/creatinine (rule out nephrotic syndrome)
Simplified Pulmonary Embolus Severity

1. Age >80
2. History of cancer
3. COPD
4. HR >110
5. SBP <100mmHg
6. O₂ saturation <90% on room air

High risk if >1 point: **11% 30 day mortality**
Low risk if ≤1: **1% 30 day mortality**

Jimenez et al, Arch Int Med 2010
Initial VTE management in first 3 months

- In patients with DVT or PE without active cancer
  - NOAC are preferred over warfarin (Grade 2B)
- Common themes with NOAC
  - All are given in fixed doses
  - None has significant dietary interactions (though rivaroxaban should be taken with food)
  - Drug interactions with CYP 3A4 and P-glycoprotein modulators
  - Contraindicated in patients with poor renal function (CrCl <30ml/min)

Kearon et al, CHEST Guideline, Chest 2016
# NOAC versus warfarin

<table>
<thead>
<tr>
<th>Trials</th>
<th>EINSTEIN DVT/PE</th>
<th>AMPLIFY</th>
<th>RECOVER I/II</th>
<th>HOKUSAI VTE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regimen</td>
<td>Rivaroxaban 15 mg BID x 21 days then 20 mg OD</td>
<td>Apixaban 10mg BID x 7 days then 5 mg BID</td>
<td>LMWH/UFH x 5 days then dabigatran 150 mg BID</td>
<td>LMWH/UFH x 5-12 days then edoxaban 60 mg OD</td>
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<tr>
<td>Efficacy</td>
<td>Non-inferior</td>
<td>Non-inferior</td>
<td>Non-inferior</td>
<td>Non-inferior</td>
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<tr>
<td>Major Bleed</td>
<td>Less</td>
<td>Less</td>
<td>Non-inferior (or less)</td>
<td>Non-inferior</td>
</tr>
<tr>
<td>*CRNMB</td>
<td>Non-inferior</td>
<td>Less</td>
<td>Less</td>
<td>Less</td>
</tr>
<tr>
<td>*clinically relevant non major bleed</td>
<td></td>
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</tbody>
</table>
Initial choice of anticoagulation (for the first 3 months)

### Warfarin (with UFH/LMWH for at least 5 days, target INR 2-3) IF
- GFR < 30 mL/min
- Financial concern
- Patient is at low bleeding risk
- Patient has stable diet
- Patient has no major drug interaction
- Patient is reliable for INR monitoring

### Non Vitamin K antagonist oral anticoagulant (NOAC)
- GFR > 30 mL/min
- Weight is between 40-120 kg
- Good oral intake
- Not on dual P-glycoprotein and CYP3A4 inhibitors
- Avoid use in patients with upper GI cancer due to bleeding risk
- Avoid use if dose adjustment for thrombocytopenia is anticipated
Case 2

- 68 M with stage 4 NHL on chemotherapy, now with a symptomatic PE

How should he be treated?

A. LMWH x 6 month
B. NOAC x 6 month
C. LMWH and transition to warfarin x 6 month
Initial VTE management in the patient \textit{with cancer}

- NOAC is an \textit{option} in patients with cancer associated thrombosis
- Similar rate of recurrent VTE compared to dalteparin
- Higher rate of clinically relevant bleeding
  - Particularly in patients with GI malignancy
- Other limitations of NOACs
  - Oral route (poor oral intake, absorption issues)
  - Drug interactions with modulators of P-glycoprotein and CYP3A4 function
Cancer associated VTE

**Initial choice of anticoagulation (for the first 3 months)**

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- Weight is between 40-120 kg
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- Avoid use in patients with upper Gl cancer due to bleeding risk
- Avoid use if dose adjustment for thrombocytopenia is anticipated

**Low Molecular Weigh Heparin (LMWH) IF**
- GFR > 30 mL/min
- Advanced cancer (especially upper Gl cancer)
- Poor oral intake
- Active chemotherapy with anticipated need for dose adjustment for thrombocytopenia
  - Platelet > 50 – 100% dose
  - Platelet 30-50 – 50% dose
  - Platelet 20-30 – Prophylaxis dose
  - Platelet < 20 – Hold
Case 2 continued

• 68 M with stage 4 NHL and cancer associated PE. He was treated with 6 months of NOAC.
• He is completed chemotherapy and is in remission. When can he stop the NOAC?
Deciding when to stop anticoagulation?

• All patients should be treated for a minimum of 6 months
• Who are good candidates to stop?
  1. If cured or in remission from their cancer and is not receiving active treatment → risk of rec VTE 3.2 per 100 patient year (most had recurrent of their cancer)
  2. High bleeding risk that is not controlled
  3. Reaching the end of the cancer journey

Van der Hulle et al, Chest 2016
Case 3

• 30F with unprovoked PE. Treated for 3 months with NOAC and recovering well. She asks if she can stop her NOAC and what is her risk of recurrent clot?
  ❑ She needs to complete 6 months of anticoagulation and stop
  ❑ High risk (>10%) and no, she should not stop
  ❑ Risk unclear. She needs a thrombophilia work up to determine risk of recurrent
Duration of anticoagulation

- All patients should be treated for a minimum of 3 months
- Factors to consider when deciding on the duration of treatment:
  1. What is the risk of VTE recurrence after stopping treatment?
  2. What is the risk of bleeding when treatment is continued?
  3. What is the patients’ values and preferences?
1. “Weak” thrombophilia status did NOT influence risk of VTE recurrence

2. The protective benefit is lost when a patient stops anticoagulation

Baglin et al, Lancet 2003
Who should stop anticoagulation?

- Patients with low risk (<5%) for VTE recurrence
  - Patients with small clot burden (distal DVT or SSPE without DVT)
  - Patients with VTE provoked by major risk factors that are no longer present
- These patients should receive VTE prophylaxis when they encounter VTE risk period in the future

Kearon et al, Blood 2005
Unprovoked VTE: higher VTE recurrence

• About ½ of all patients will fall into this group
• Risk of VTE recurrence is comparable to other high risk thrombophilias (antiphospholipid syndrome, antithrombin, protein C or S deficiency or compound defects)
• Risk of VTE recurrence estimate varies widely (~5-10% recurrence in the first year)

Kearon et al, Blood 2005
Can we identify a “low” risk patient?

• All men are considered high risk
• For women: 4 risk factors
  1. Hyperpigmentation, Edema, or Redness in either leg (“HER”)
  2. D-dimer ≥250 µg/L during treatment
  3. Obesity (BMI ≥30)
  4. Older age (Age ≥65)
    ➢ Low risk: 0 or 1 risk factor
    ➢ High risk: 2 or more risk factors

Rodger et al, BMJ 2017
HERDOO2 can identify a “low” risk women

• Women at low risk
  – Can stop anticoagulation after 6 months with acceptable risk of VTE recurrence (3% at 1 year)

• For the remainder high risk patients
  – If anticoagulation is discontinued → higher risk of VTE recurrence (8% at 1 year)
  – If anticoagulation is continued → treatment is effective with 2% VTE recurrence

Rodger et al, BMJ 2017
Extended anticoagulation

• Patients who continue active treatment (compared to observation or placebo) has less VTE during the treatment phase (3% vs 10%, p<0.001)

• The case fatality for recurrent VTE AND bleeding is in favour of NOAC for extended treatment

Marik et al, Plos ONE 2015
Can we lower the dose of NOAC?

- Apixaban or rivaroxaban at prophylactic dose is effective at reducing risk of VTE recurrence without increase in major bleeding

- Unclear if we can apply this to all patients
  - Higher risk patients may not have been included (those with anticoagulation failure, severe thrombophilies)
Take home messages

1. Not all clots require anticoagulation ➔ review imaging to confirm the clot location/burden to decide if anticoagulation is required

2. If treatment is required ➔ treat for a minimum of 3 months

3. At 3 months, assess the risk of VTE recurrence, risk of bleeding as well as patient’s preference to determine if extended prophylaxis is warranted

➔ Re-evaluate this decision annually (for bleeding risk, CBC, renal function) to decide if extended prophylaxis is still appropriate
Venous Thromboembolism

Venous thrombosis

Proximal clot
- Hospitalization
  - Hematology consult to consider IVC filter
    - Absolute contraindication to anticoagulation:
      - Uncontrolled bleeding
      - Thrombocytopenia (platelet <20-30)
- Safe to treat as outpatient?
- Safe to Anticoagulate?

Distal clot
- Safe to treat as outpatient?
- Safe to Anticoagulate?

Subsegmental PE (SSPE) or Distal DVT
- Anticoagulation IF
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- Observation with serial imaging IF
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Continued...
Venous Thromboembolism

Duration of anticoagulation (after the initial 3 months)

Proven VTE IF occurred within 12 weeks of major risk factors
- Surgery
- Hospitalization
- Cast/severe immobilization >3 days
  Risk of recurrent VTE without anticoagulation = 1-3%

Proven VTE by minor risk factors
- Leg trauma without immobilization
- Mild immobilization (plane rides >6 hour)
- Estrogen associated (OCP/HRT or pregnancy)
  Risk of recurrent VTE without anticoagulation = 5-10%

Unprovoked VTE (idiopathic)
- Risk of recurrent VTE without anticoagulation:
  - at 12 month = 10%
  - at 5 year = 30%
  - and at 10 year = 50%

Refer to Hematology

Is there additional high risk features for recurrence VTE?
- Male gender OR
- Female with 2 of the following factors: post thrombotic syndrome, D Dimer, BMI >30, Age >65
- High risk thrombophilia defects (antithrombin, protein C or S deficiency)
- High consequences of recurrent VTE (i.e. massive PE)
- Patient preference to continue anticoagulation

STOP after completion of 3 months

Are the VTE risk factors reversible and risk of recurrence acceptable to patient?

YES

STOP after completion of 3 months

NO

Continue anticoagulation and reassess annually (bleeding risk, CBC + GFR)
Thank you

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