New Drugs for Blood Clots: Implications for Myeloproliferative Neoplasms (MPN)

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Objectives

• Epidemiology of venous thromboembolism (VTE)
  • How common is it?
• What symptoms are typically associated with VTE and stroke?
• How is VTE diagnosed?
• What drugs are available to treat clots?
• What are the new drugs available to treat VTE?
• Do they have a role in managing VTE in patients with cancer?
• Implications for myeloproliferative neoplasms
Epidemiology of venous thromboembolism (how common is it)?

<table>
<thead>
<tr>
<th>Population</th>
<th>Thrombosis (venous/arterial)</th>
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</thead>
<tbody>
<tr>
<td>General</td>
<td>0.1 to 1% (venous)</td>
</tr>
<tr>
<td>Solid organ (pancreas, lung etc)</td>
<td>10 to 30%</td>
</tr>
<tr>
<td>Myeloproliferative Neoplasms</td>
<td></td>
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<tr>
<td>PV</td>
<td>12 to 39%</td>
</tr>
<tr>
<td>ET</td>
<td>10 to 29%</td>
</tr>
<tr>
<td>Myelofibrosis</td>
<td>13%</td>
</tr>
</tbody>
</table>
Contemporary treatment algorithm in essential thrombocythemia and polycythemia vera

- **No thrombosis history**
  - Age <60: JAK2/CVR
  - Age ≥60: Hydroxyurea + once-daily aspirin
    - Consider twice-daily aspirin
    - Once-daily aspirin
    - Observation

- **Arterial thrombosis history**
  - Any age: Hydroxyurea + once-daily aspirin
    - Consider twice-daily aspirin, in the presence of Age ≥60, CVR or JAK2V617F

- **Venous thrombosis history**
  - Any age: Hydroxyurea + systemic anticoagulation
    - Consider adding once-daily aspirin, in the presence of CVR or JAK2V617F

**In addition, all patients with PV require phlebotomy to keep hematocrit below 45%**

Tefferi AJH 2015
What symptoms are associated with venous thrombosis and stroke?
Weakness, Paralysis, visual changes

Blood clot lodges in the cerebral artery

Blood clot breaks off and travels to an artery in the brain

Diseased artery

Normal carotid artery
Deep vein thrombosis
Deep vein thrombosis

- External iliac vein
- Great saphenous vein
- Femoral vein
- Popliteal vein
- Anterior tibial vein
- Posterior tibial vein

Surrounding muscle squeezes vein, pushing blood up through valve.

When surrounding muscle relaxes, valve closes, stopping backflow of blood.
Swelling with or without pain

a. Normal blood flow in a deep vein

b. Deep vein thrombosis (DVT)
   A clot (thrombus) may block veins and prevent blood flow from nearby muscle.

c. Venous thromboembolism
   Part of the clot may dislodge and be carried to other areas of the body.
Pulmonary Embolism

Emboli travels up through inferior vena cava to heart and lungs.
How do blood clots form?
Virchow’s Triad

Circulatory Stasis

Thrombosis

Endothelial Injury

Hypercoagulable State
How is VTE and stroke diagnosed?
Duplex Ultrasound: deep vein thrombosis
CT Scan: pulmonary embolism
CT scan or MRI

Figure 6. Darker area on head CT scan shows brain tissue damaged by stroke.
What drugs are available to treat/prevent blood clots?

How do blood clots form?
Primary Hemostasis: platelet plug formation

1. Platelet Adhesion
2. Shape Change
3. Granule Release (ADP, TXA₂)
4. Recruitment
5. Aggregation (Hemostatic Plug)

Components:
- Endothelium
- Basement Membrane
- vWF
- Collagen
Secondary Hemostasis: clot formation

1. Tissue Factor
2. Phospholipid Complex Expression
3. Thrombin Activation
4. Fibrin Polymerization

Fibrin
Thrombus/Antithrombotic/Fibrinolytic Events: remodeling of clot

Release of:
- t-PA (fibrinolysis)
- thrombomodulin (blocks coagulation cascade)

ET: high platelets

PV: high red blood cells

Trapped Neutrophil
Trapped Red Blood Cells
Polymerized Fibrin
Thrombus/Antithrombotic/Fibrinolytic Events

Hydrea ± phlebotomy

Release of:
- t-PA (fibrinolysis)
- thrombomodulin (blocks coagulation cascade)

Anti-platelet agents:
Aspirin, clopidogrel (Plavix)

Anti-coagulants:
warfarin
What are the new drugs available to treat VTE?
The good news: currently, choosing anticoagulants is like buying jeans!

Then

Size?

Now

Cut, Fit, Style, Color, Wash, Finish?

Courtesy Dr McBane
Anti-thrombotics: Antiplatelet agents & Anticoagulants

- Injectable (IV or subcutaneous [SC])
  - Heparin (IV)
  - Low molecular weight heparin (SC)
    - Enoxaparin (Lovenox)
    - Dalteparin (Fragmin)
    - Tinzaparin

- Pills:
  - Warfarin (Coumadin, Jantoven)
    - Interfere with vitamin K
    - Reduces manufacture of vitamin K dependent clotting factor proteins
  - Newer anticoagulants:
    - Directly inhibit clotting factor proteins
Sites of action and [monitoring] of anti-thrombotic agents
What are the new drugs available to treat VTE? Direct acting anticoagulants

- Direct factor Xa inhibitors
  - Rivaroxaban
  - Apixaban
  - Edoxaban
- Direct thrombin (factor II) inhibitors
  - dabigatran
Do they have a role in managing VTE in patients with cancer?
FIGURE 2. Efficacy (A) and safety (B) of NOAC in patients with cancer.
Conclusion

• Preliminary results showed that NOAs are non-inferior to the current standard anticoagulant therapy.

• However, large scale randomized controlled trials specifically targeted cancer patients are needed.
How do they compare to standard treatment with warfarin?

• Atrial fibrillation trials
  • As safe and effective as warfarin for prevention of stroke

• Deep vein thrombosis treatment trials
  • As safe as and as effective as warfarin for treatment of deep vein thrombosis and pulmonary embolism

• What about treatment of stroke?
  • No clinical data
VTE treatment in solid organ malignancy

- Use of novel oral anticoagulants is not currently recommended for patients with malignancy and VTE (ASCO Guideline)
Implications for myeloproliferative neoplasms

• Currently no role in management of stroke associated with MPN
  • High risk patients: aspirin
  • Control of modifiable risk factors
    • Smoking, cholesterol, exercise

• Role in management of venous thrombosis is not defined
  • Follow standard approach to prevention and management
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In addition, all patients with PV require phlebotomy to keep hematocrit below 45%
When would I consider using a novel agent?

- Stroke: antiplatelet agents
- Venous thrombosis:
  - Initiate standard management for VTE
    - Heparin and warfarin
- If warfarin management is difficult or fails
  - Difficult to control INR
  - INR outside of therapeutic range more often
  - Recurrent thrombosis despite therapeutic INRs
Time in Therapeutic Range (INR target 2-3)
When would I consider using a novel agent?

- Tailor to specific situation (individualized approach)
  - Status of kidneys
  - Other medications that may interact
- Clinical trials in patients with MPN are needed
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Courtesy Dr McBane
Thank you for your attention

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