Thrombosis

Pantep Angchaisuksiri, M.D.
Division of Hematology
Ramathibodi Hospital
35 y.o. female with right leg swelling for 2 wks
History of OC use for 2 months; No FH of VTE

Which test would you do?

1. Protein S, protein C, antithrombin
2. Lupus anticoagulant
3. Cancer screening
4. None
35 y.o. female with right leg swelling for 2 wks
History of OC use for 2 months; No FH of VTE

How do you treat this patient?

1. LMWH
2. LMWH/Warfarin
3. NOAC
4. LMWH/NOAC
35 y.o. female with right leg swelling for 2 wks
History of OC use for 2 months; No FH of VTE

How long will you treat this patient?

1. 3 months
2. 6 months
3. 12 months
4. Indefinite
Venous Thromboembolism (VTE)

• Clinically important problem:
  – death from pulmonary embolism
  – morbidity resulting from
    • acute event
    • recurrent VTE events
    • post-thrombotic syndrome
    • pulmonary hypertension
# Risk Factors for Venous Thrombosis

<table>
<thead>
<tr>
<th>Inherited</th>
<th>Acquired</th>
<th>Mixed/Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antithrombin deficiency</td>
<td>Cancer</td>
<td>Hyperhomocysteinemia</td>
</tr>
<tr>
<td>Protein C deficiency</td>
<td>Major surgery</td>
<td>High levels of factor VIII</td>
</tr>
<tr>
<td>Protein S deficiency</td>
<td>Acute medical illness</td>
<td>High levels of factor IX</td>
</tr>
<tr>
<td>Factor V Leiden (FVL)</td>
<td>Immobilization</td>
<td>High levels of factor XI</td>
</tr>
<tr>
<td>Prothrombin 20210A</td>
<td>Pregnancy</td>
<td>APCR in the absence of FVL</td>
</tr>
<tr>
<td></td>
<td>Oral contraceptive use</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hormonal replacement therapy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Antiphospholipid syndrome (APS)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Myeloproliferative neoplasms (MPN)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Paroxysmal nocturnal hemoglobinuria (PNH)</td>
<td></td>
</tr>
</tbody>
</table>

APCR, activated protein C resistance
Clinical Characteristics Suggestive of Thrombophilia in Patients with VTE

Thrombosis at a young age (<50yr), especially in association with weak provoking factors (minor surgery, or immobility) or unprovoked VTE

Strong family history of VTE (first-degree family members affected at a young age)

Recurrent VTE events, especially at a young age*

VTE in unusual sites such as splanchnic or cerebral veins†

*The antiphospholipid syndrome must also be considered, but it is not inherited.
†Patients with splanchnic vein VTE should be assessed for MPN and PNH.
Risk Categorization of Patients with VTE

- UNPROVOKED
- PROVOKED by a permanent risk factor (e.g. cancer)
- PROVOKED by a transient, surgical risk factor
- PROVOKED by a transient, non-surgical factor (e.g. immobilization, acute medical illness, pregnancy, hormonal therapy)
Risk of Recurrence Depends on Type of VTE Event

Provoked VTE
*Transient risk factors*
- e.g. surgery, trauma, significant immobility, pregnancy

Unprovoked VTE
- No previous risk factor for VTE

Provoked VTE
*Persistent risk factors*
- e.g. active cancer, antiphospholipid syndrome

Provoked vs. Unprovoked: Risk of Recurrence

Selecting Patients with a First VTE for Thrombophilia Testing

First VTE

- **Provoked by strong triggers**
  - No role for testing

- **Provoked by weak triggers in a young patient with strong family history**
  - Determine role of testing
  - Consider testing for protein S, protein C, antithrombin
  - Consider APA testing in the case of extensive DVT or PE

- **Unprovoked**
  - Determine role of testing
  - Consider APA testing, especially in the case of arterial or recurrent events
  - If patient is young and has a strong family history consider testing for protein S, protein C, and antithrombin

- **Unusual site**
  - Cerebral vein
  - Splanchnic vein
  - Test for protein S, protein C, antithrombin, and APA
  - Test for inherited thrombophilia, APA, MPN, and PNH

APA, antiphospholipid antibody
Reasons for Thrombophilia Testing

- Influence on duration of anticoagulation therapy
- Possible explanation (for patient and physician) why thrombosis occurred
Reasons against Thrombophilia Testing

• Lack of therapeutic consequences even if test positive
• Suboptimal performance of tests (false-positive/negative results)
• Anxiety, if test is positive
• False sense of security that thrombosis risk is low, if test result negative
• Cost of testing
• Lack of impact for asymptomatic first-degree relatives (possible exception is women contemplating estrogen use or pregnancy)
• Impact on ability to obtain life or health insurance
Antiphospholipid Syndrome (APS)

• autoimmune disease
• thrombosis
• pregnancy morbidity
• antiphospholipid antibodies (APA)
Lupus anticoagulants, anti-cardiolipin antibodies and \( \beta_2 \)-glycoprotein I antibodies are antibodies with overlapping specificity but they are not identical antibodies.
SYDNEY, 2006

A preconference workshop, preceding the Eleventh International Congress on antiphospholipid antibodies (aPL), Sydney consensus conference

One clinical criteria (thrombosis or pregnancy loss)  

+  

One laboratory criteria: anticardiolipin antibodies (no longer required the aCL ELISA to be β2GPI-dependent), lupus anticoagulant, AND anti β2-GPI antibodies  

[Positive 12 weeks apart]
CLASSIFICATION CRITERIA

Concept of subclassification: Two different categories of APA

I: More than one Laboratory criteria present (any combination)

IIa: Lupus Anticoagulant present alone

IIb: Anti-cardiolipin antibody present alone

IIc: Anti-β2 glycoprotein-I antibody present alone

Classification criteria are often mistaken for diagnostic criteria

Thus APS is diagnosed in the presence of a single positive test*

Patients fulfilling classification criteria are put together in clinical studies

* The other two tests either negative or not performed
Definite thrombotic and/or obstetric APS

• **Triple positive** patients (LAC positive, IgG or IgM aCL> 99th percentile, IgG or IgM ab2GPI> 99th percentile) and proven venous/arterial thrombosis and/or pregnancy loss as of 2006 International consensus statement.
Laboratory diagnosis of the APS

- Perform all three assays: LAC, aCL, β2GPI AB

- Antibody profiles
  - LAC, aCL, β2GPI antibodies

- Medium/high titers
  - IgG > IgM > IgA

- Persistent antibodies (> 12 weeks)
35 y.o. female with right leg swelling for 2 wks
History of OC use for 2 months; No FH of VTE

Which test would you do?

1. Protein S, protein C, antithrombin
2. Lupus anticoagulant
3. Cancer screening
4. None
Cancer Screening in Patients with VTE

• Optimal occult cancer screening strategy remains unclear
  – Limited screening (History, PE, basic blood work and CXR), and age & gender-specific screening?

• Unknown if detecting these malignancies reduces morbidity, ameliorates quality of life, is cost effective or improves survival

• Clinicians should maintain a low-threshold of suspicion for cancer
Phases of treatment for VTE

1. Kearon et al. Chest 2012;141(2suppl):e419s–e494s;

VKA or other agent†

Initial¹ (0–~7 days) Long-term (~7 days – ~3 months) Extended (~3 months – indefinite)

Parenteral* VKA or other agent†

Risk of recurrent VTE

Treatment Secondary prevention

Time since starting treatment

Start of treatment and secondary prevention²

Completion of active treatment

*Heparin, LMWH, fondaparinux, thrombolysis. Initial therapy may be with oral rivaroxaban or apixaban.
†Includes LMWH and NOACs.

1. Kearon et al. Chest 2012;141(2suppl):e419s–e494s;
## VTE requires acute treatment and prevention of recurrence

<table>
<thead>
<tr>
<th>Initial management</th>
<th>Secondary prophylaxis (3 months)</th>
<th>Extended prophylaxis (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parenteral AC* ≥5 days¹</td>
<td>Dabigatran 150 mg BID†²</td>
<td>Rivaroxaban 10 mg OD</td>
</tr>
<tr>
<td>Parenteral AC* ≥5 days¹</td>
<td>Edoxaban 60 mg OD‡³</td>
<td>Rivaroxaban 10 mg OD</td>
</tr>
<tr>
<td>Rivaroxaban 15 mg BID 21 days⁴</td>
<td>Rivaroxaban 20 mg OD</td>
<td>Rivaroxaban 10 mg OD</td>
</tr>
<tr>
<td>Apixaban 10 mg BID 7 days⁵</td>
<td>Apixaban 5 mg BID 6 months</td>
<td>Apixaban 2.5 mg BID</td>
</tr>
</tbody>
</table>

*LMWH, fondaparinux or UFH; †Dabigatran 110 mg BID for aged ≥80 years, concomitant verapamil, or based on individual assessment of thromboembolic/bleeding risk; ‡Edoxaban 30 mg OD for CrCl 15–50 mL/min, weight ≤60 kg, certain concomitant P-gp inhibitors

When to Provide Extended Therapy

- Recurrent VTE
- Unprovoked VTE if bleeding risk is not high
- VTE provoked by major persistent risk factors
Which patients can have their dose reduced

All patients except

- Recurrent VTE on lower dose
- Active cancer
- High risk thrombophilia
- Concomitant atherothrombosis
No NOACs for:

- Severe renal failure
- Mechanical heart valves
- Triple positive antiphospholipid syndrome
- Concomitant strong inducers/inhibitors of P-glycoprotein or CYP3A4
  - >50% decrease/increase in exposure (?)
- (Extreme body weight, poor compliance)
35 y.o. female with right leg swelling for 2 wks
History of OC use for 2 months; No FH of VTE

How do you treat this patient?

1. LMWH
2. LMWH/Warfarin
3. NOAC
4. LMWH/NOAC
Need for Extended Anticoagulation Depends on Balance between Risk of Recurrence off Treatment and Risk of Bleeding on Treatment

Risk of VTE recurrence

Risk of bleeding
Extending Anticoagulant Beyond 3 Months in Patients with VTE: Key Elements

**Recurrence risk**
- Idiopathic, history of VTE, location, gender
- D-dimer, residual vein thrombosis

**Alternatives**
- New oral anticoagulant
- Aspirin

**Consider**

**Bleeding risk**
- Patient characteristics
- Stability of anticoagulation

**Patient preferences and values**
## Risk of Recurrence – Prediction Scores

<table>
<thead>
<tr>
<th>Vienna Prediction Model</th>
<th>DASH Score</th>
<th>HERDOO2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Variables</strong></td>
<td>Male sex</td>
<td>Male sex</td>
</tr>
<tr>
<td></td>
<td>D-dimer (off AC)</td>
<td>(off AC)</td>
</tr>
<tr>
<td></td>
<td>PE &gt; prox DVT</td>
<td>(2 pt)</td>
</tr>
<tr>
<td></td>
<td>&gt; distal DVT</td>
<td>Age ≥ 65</td>
</tr>
<tr>
<td><strong>Total score</strong></td>
<td>0 to 350</td>
<td>-2 to 4</td>
</tr>
<tr>
<td><strong>Annual risk of recurrence</strong></td>
<td>2% - 15% (nomogram)</td>
<td>≤1: 1.3%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2: 6.4%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥3: 12.3%</td>
</tr>
</tbody>
</table>

Eichinger Circulation 2010; Tosetto, JTH 2012; Rodger CMAJ 2008
## Risk Factors for Bleeding with Anticoagulant and Estimated Risk of Major Bleeding in Low-, Moderate-, and High-risk Categories

### Risk Factors
- age >65 y
- age >75 y
- previous bleeding
- cancer
- metastatic cancer
- renal failure
- liver failure
- thrombocytopenia
- previous stroke
- diabetes
- anemia
- antiplatelet therapy
- poor anticoagulant control
- Comorbidity & reduced functional capacity
- recent surgery
- frequent falls
- alcohol abuse
- nonsteroidal anti-inflammatory drug

### Categorization of Risk of Bleeding

<table>
<thead>
<tr>
<th>Estimated Absolute Risk of Major Bleeding</th>
<th>low Risk (0 Risk Factors)</th>
<th>moderate Risk (1 Risk Factor)</th>
<th>high Risk (≥2 Risk Factors)</th>
</tr>
</thead>
<tbody>
<tr>
<td>anticoagulation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-3 mo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>baseline risk (%)</td>
<td>0.6</td>
<td>1.2</td>
<td>4.8</td>
</tr>
<tr>
<td>increased risk (%)</td>
<td>1.0</td>
<td>2.0</td>
<td>8.0</td>
</tr>
<tr>
<td>total risk (%)</td>
<td><strong>1.6</strong></td>
<td><strong>3.2</strong></td>
<td><strong>12.8</strong></td>
</tr>
<tr>
<td>anticoagulation after first 3 mo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>baseline risk (%/y)</td>
<td>0.3</td>
<td>0.6</td>
<td>≥2.5</td>
</tr>
<tr>
<td>increased risk (%/y)</td>
<td>0.5</td>
<td>1.0</td>
<td>≥4.0</td>
</tr>
<tr>
<td>total risk (%/y)</td>
<td><strong>0.8</strong></td>
<td><strong>1.6</strong></td>
<td><strong>≥6.5</strong></td>
</tr>
</tbody>
</table>

Bleeding Risk Factors

- Age
- Prior bleeding
- Drug interactions
- Co-morbidities (kidney, liver, cancer, anemia, thrombocytopenia)
35 y.o. female with right leg swelling for 2 wks
History of OC use for 2 months; No FH of VTE

How long will you treat this patient?

1. 3 months
2. 6 months
3. 12 months
4. Indefinite
How long is long enough?

VTE recurrence after discontinuation of anticoagulant treatment

- 3 months of treatment
- 6 months of treatment
- 1 year of treatment

Event rate (%) over time in months.
# Summary of ACCP 2016 Guidelines: Acute treatment & secondary prevention of VTE

<table>
<thead>
<tr>
<th>Initial anticoagulation</th>
<th>ACCP recommendation</th>
<th>Grade of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute DVT or hemodynamically stable PE</td>
<td>NOAC preferred to LMWH/VKA</td>
<td>2B</td>
</tr>
<tr>
<td>PE with hypotension</td>
<td>Thrombolytic therapy (systemic rather than catheter-directed unless bleeding risk is high)</td>
<td>2B (2C)</td>
</tr>
</tbody>
</table>

## Duration of anticoagulant

| Proximal DVT or PE | 3 months recommended over shorter duration | 1B |
| First proximal DVT or PE provoked by surgery or other transient risk factor | 3 months | 1B (2B if low/moderate bleeding risk) |
| Unprovoked DVT or PE | Extended therapy if bleeding risk is low/moderate 3 months if bleeding risk is high | 2B 1B |

Duration of Anticoagulant Therapy

- Treat for 3 months and reassess

  - Isolated distal DVT
    - Stop at 3 Months
  - Reversible provoking factor
    - Stop at 3 Months
  - Unprovoked proximal DVT or PE
  - Cancer
    - Indefinite therapy or until cancer inactive

- High Bleeding Risk OR Prefers to stop (even if D-dimer was positive)
  - Stop at 3 Months

- Others
  - Stop and measure D-dimer after 1 month

- Not High Bleeding Risk AND Prefers to stay on (even if D-dimer was negative)
  - Indefinite therapy

- Second VTE
  - Indefinite therapy

- Negative D-dimer
  - Stay off therapy (Stop at 3 Months)

- Positive D-dimer
  - Restart therapy (Indefinite therapy)
What if the patient has cancer?
ACCP 2016 Guidelines

- LMWH is suggested over VKA (2B) and DOAC (2C)
- In those who do not have high risk of bleeding, extended therapy is recommended over 3 months (1B)
- In those who have a high bleeding risk, extended therapy is suggested over 3 months (2B)

NOACs for the Treatment of CAT

*Results reported are 6-month cumulative event rates.


- **select-d**
  - **HR=0.43**
  - 95% CI 0.19–0.99
  - Event rates: 11% for Dalteparin, 4% for Rivaroxaban
    - 7% in favour of Rivaroxaban
  - Event rates: 4% for Dalteparin, 6% for Rivaroxaban
    - 2% in favour of Dalteparin

*Results are 6-month cumulative event rates.*
NOACs for the Treatment of CAT

Hokusai-VTE-Cancer*

- **Recurrent VTE**: 3.4% in favour of edoxaban
- **Major bleeding**: 3.9% in favour of dalteparin

HR=0.71
95% CI 0.48–1.06;
p=0.09

HR=1.77
95% CI 1.03–3.04;
p=0.04

*Results reported are number and percentage of events at 12 months.

DOACs RCT in cancer patients

Bleeding issue:

- Significant increase in bleeding risk (HOKUSAI, SELECT-D and CASSINI)

- Incomplete absorption (topical anticoagulant effect)
- Direct caustic effect (e.g., tartaric acid in dabigatran)
- Inhibition of mucosal healing

GI tract

Systemic anticoagulant effect from NOAC

Mucosa

NOAC

Topical effect on the mucosa
Conclusions

• VTE is often a chronic condition
• DOACs are at least as effective as VKAs but produce less bleeding
• Availability of usual and lower dose DOAC regimens enable patient-specific choices
• DOACs were recently proved to be at least as effective as LMWH for VTE treatment in cancer patients but were associated with more bleeding