Duration of Anticoagulant Therapy

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September 17, 2016
Conflicts of Interest

- No conflicts of interest to report
Objectives

At the end of the program participants will be able to:

- Design an evidence-based plan for duration of anticoagulation therapy
- Assess various prediction models for recurrence of VTE
- Evaluate the utility of testing for hypercoagulability and residual vein thrombosis
- Discuss the role of aspirin in secondary VTE prophylaxis
FIRST EPISODE OF VTE

Provoked VTE

3 Months of Anticoagulation
Clinical follow Up, No Lab or Imaging Required

Cancer Associated VTE

Upper Extremity DVT?
Yes
At least 3 months then until catheter pulled

No
At least 6 months or until cancer in remission (cured)

Unprovoked VTE

Shared Decision Making (Consider Bleeding Risk and Male Sex)

Patient With a Strong Preference for Duration
Yes
Follow Patient Preference

No

D-dimer on Therapy or Prediction Model
Positive or High Risk
Continue Anticoagulation

Negative or Low Risk
Stop Anticoagulation, D-dimer Check in One Month

Positive
Consider Secondary Prophylaxis

Negative
5-year rate of recurrence
- 3% if provoked by surgery
- 15% for non-surgically provoked
Provoked by Surgery

• Surgery within 3 months prior to VTE
• Risk of recurrence in 5 years is about 3%.
• 3 months of anticoagulation is recommended

Kearon Chest 2016
Kearon JTH 2016
Ageno Thromb Res 2015
Streiff J Thromb Thrombolysis 2016
Non-Surgical Transient Risk Factor

In general, 3 month of anticoagulation therapy is recommended

<table>
<thead>
<tr>
<th>Estrogen therapy associated</th>
<th>Pregnancy associated</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Treat for at least 3 months after therapy is stopped</td>
<td>• Treat for least 3 months</td>
</tr>
<tr>
<td></td>
<td>• for the duration of pregnancy and up to 12 weeks post partum</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Medical illness associated</th>
<th>Travel associated</th>
</tr>
</thead>
<tbody>
<tr>
<td>• At least 3 months or until illness is resolved</td>
<td>• Length of travel most important risk factor rather than the mode of travel</td>
</tr>
<tr>
<td>• Whichever is longer</td>
<td>• Chest 2016 specifies flights of more than 8 hours</td>
</tr>
<tr>
<td></td>
<td>• 3 months of anticoagulation is recommended</td>
</tr>
</tbody>
</table>

Kearon Chest 2016
Ageno Thromb Res 2015
Streiff J Thromb Thrombolysis 2016
Annualized rate of recurrence
• 15% per year

FIRST EPISODE OF VTE

Cancer Associated VTE

Upper Extremity DVT?

Yes
At least 3 months then until catheter pulled

No
At least 6 months or until cancer in remission (cured)
Cancer Associated DVT of Leg or PE

- Extended treatment is recommended regardless of bleeding risks.
- Until active cancer is resolved.

Kearon Chest 2016
van der Hulle Chest 2016
Cancer Associated DVT Of Leg or PE

Figure 1 – Treatment of cancer-associated venous thromboembolism in the total cohort (N = 358) is shown.

van der Hulle Chest 2016
Figure 2 – Shown is the cumulative incidence rate of recurrent VTE in patients who stopped anticoagulation therapy after being cured of cancer (solid line) and after stopping anticoagulation for reasons other than major hemorrhage despite active cancer (dotted line).
Cancer Associated Upper Extremity DVT

- The guidance statement from the International Society of Thrombosis and Haemostasis recommends treating for at least 3 months and then continue until the cancer is in remission
  - They acknowledge that this recommendation is extrapolated from those for lower extremity DVT
- ASCO says duration is unclear
  - 3 to 6 months seems reasonable
  - It is possible (even likely) that the duration can be shorter if the catheter has been removed.
- NCCN recommends at least 3 months or as long as the catheter is in place
5-year rate of recurrence
• 30% composite
First Unprovoked Proximal or Distal DVT Of Leg or PE

- Treatment with anticoagulation for 3 months is recommended over treatment of a shorter period
- With low to moderate bleeding risk, extended (no stop date) therapy is suggested
- With high bleeding risk, 3 months is suggested
For all patients who receive extended anticoagulant therapy, the continued treatment should be reassessed periodically.

- Usually done annually, but should be done any time the patient’s condition changes.
# Bleeding Risks

## Risk Factors

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Age &gt; 65 years</th>
<th>Age &gt; 75 years</th>
<th>Previous bleeding</th>
<th>Cancer</th>
<th>Metastatic Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 65 years</td>
<td>Thrombocytopenia</td>
<td>Renal Failure</td>
<td>Frequent Falls</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &gt; 75 years</td>
<td>Previous Stroke</td>
<td>Liver Failure</td>
<td>Alcohol Abuse</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous bleeding</td>
<td>Diabetes</td>
<td>Poor Anticoag Control</td>
<td></td>
<td>Anemia</td>
<td>Antiplatelet Therapy</td>
</tr>
<tr>
<td>Cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Recent Surgery</td>
</tr>
<tr>
<td>Metastatic Cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## Estimated Absolute Risk of Major Bleeding, %

<table>
<thead>
<tr>
<th>Categorization of Risk of Bleeding</th>
<th>Anticoagulation 0-3 months</th>
<th>Anticoagulation after 1st 3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low Risk (0 Risk Factors)</td>
<td>Moderate Risk (1 Risk Factor)</td>
</tr>
<tr>
<td>Baseline Risk (%)</td>
<td>0.6</td>
<td>1.2</td>
</tr>
<tr>
<td>Increased Risk (%)</td>
<td>1.0</td>
<td>2.0</td>
</tr>
<tr>
<td>Total Risk (%)</td>
<td>1.6</td>
<td>3.2</td>
</tr>
<tr>
<td>Baseline Risk (%)</td>
<td>0.3</td>
<td>0.6</td>
</tr>
<tr>
<td>Increased Risk (%)</td>
<td>0.5</td>
<td>1.0</td>
</tr>
<tr>
<td>Total Risk (%)</td>
<td>0.8</td>
<td>1.6</td>
</tr>
</tbody>
</table>
Estrogen women are those on estrogen therapy at the time of the clot
Prediction Models
FIRST EPISODE OF VTE

Unprovoked VTE

Shared Decision Making
(Consider Bleeding Risk and Male Sex)

Patient With a Strong Preference for Duration

Yes

Follow Patient Preference

No

D-dimer on Therapy or Prediction Model

Positive or High Risk

Continue Anticoagulation

Negative or Low Risk

Stop Anticoagulation, D-dimer Check in One Month

Positive

Consider Secondary Prophylaxis

Negative
# Prediction Models

<table>
<thead>
<tr>
<th>Study design</th>
<th>Men continue and HER D002 (44)</th>
<th>Vienna Prediction Model (45)</th>
<th>DASH-score (46)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients</strong></td>
<td>646</td>
<td>929</td>
<td>1818</td>
</tr>
<tr>
<td>Predictive variables</td>
<td>Men: none</td>
<td>Sex</td>
<td>Abnormal D-dimer after anticoagulation</td>
</tr>
<tr>
<td></td>
<td>Women:</td>
<td>Location of first VTE</td>
<td>Age &lt; 50 years</td>
</tr>
<tr>
<td></td>
<td>- age ≥ 60 years</td>
<td>D-dimer after anticoagulation</td>
<td>Male sex</td>
</tr>
<tr>
<td></td>
<td>- signs of PTS</td>
<td></td>
<td>Hormonal therapy</td>
</tr>
<tr>
<td></td>
<td>- BMI ≥ 30 kg/m²</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- D-dimer &gt; 250 µg/l during</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>anticoagulation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased risk of</td>
<td>&gt;1 point</td>
<td>&gt; 180 points (according to a</td>
<td>&gt; 1 point</td>
</tr>
<tr>
<td>recurrent VTE</td>
<td></td>
<td>nomogram)</td>
<td></td>
</tr>
</tbody>
</table>
Table 1. The 'Men continue and HERDOO2'

Clinical decision rule to identify patients at low risk (*) of recurrent venous thromboembolism after 5–7 months of oral anticoagulant therapy

<table>
<thead>
<tr>
<th>Men</th>
<th>Always long-term anticoagulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td>Long-term anticoagulation if score ≥2</td>
</tr>
<tr>
<td>Predictive risk factors for women</td>
<td>Score</td>
</tr>
<tr>
<td>Postthrombotic signs (hyperpigmentation, edema or redness in either leg)</td>
<td>1</td>
</tr>
<tr>
<td>D-Dimer level ≥250 mg/l (during anticoagulation)</td>
<td>1</td>
</tr>
<tr>
<td>Body mass index ≥30 kg/m²</td>
<td>1</td>
</tr>
<tr>
<td>Age ≥65 years</td>
<td>1</td>
</tr>
</tbody>
</table>

HERDOO2, hyperpigmentation, edema, redness, D-dimer, obesity, older age, 2 scores. Adapted with permission.[9]
Vienna Prediction Score

Sex
● male  ● female

Location
● distal DVT  ● proximal DVT  ● pulmonary embolism

D-Dimer (ug/l) (100 - 2000)
Blood sample taken 3 weeks after discontinuation of anticoagulation therapy
500

Disclaimer
✓ I confirm that I have read the disclaimer carefully, that I understand it, and that I accept its contents.

[calculate] [reset]
<table>
<thead>
<tr>
<th></th>
<th>Cumulative Recurrence Rate</th>
<th>Risk Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>at 12 months</td>
<td>7.0</td>
<td>206</td>
</tr>
<tr>
<td></td>
<td>95% confidence interval</td>
<td>(4.8, 10.2)</td>
</tr>
<tr>
<td>at 60 months</td>
<td>24.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>95% confidence interval</td>
<td>(18.0, 32.4)</td>
</tr>
</tbody>
</table>

Cumulative Recurrence Rate

1 year: 7.0 %
5 year: 24.3 %

Sex: male
Location: pulm
DDimer: 500
Vienna Prediction Score

Sex
- male
- female

Location
- distal DVT
- proximal DVT
- pulmonary embolism

D-Dimer (µg/l) (100 - 2000)
Blood sample taken 3 weeks after discontinuation of anticoagulation therapy
- 100

Disclaimer
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[calculate]  [reset]
Vienna Prediction Score

<table>
<thead>
<tr>
<th>Cumulative Recurrence Rate</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>at 12 months</td>
<td>2.5</td>
</tr>
<tr>
<td></td>
<td>(1.4, 4.4)</td>
</tr>
<tr>
<td>at 60 months</td>
<td>9.2</td>
</tr>
<tr>
<td></td>
<td>(5.3, 15.6)</td>
</tr>
</tbody>
</table>

Risk Points: 91

Cumulative Recurrence Rate

- 1 year: 2.5%
- 5 year: 9.2%

Sex: female
Location: pulm
DDimer: 100

Months after discontinuation of anticoagulation
# DASH Prediction Score Derived From Cox Regression Analysis

<table>
<thead>
<tr>
<th>DASH Predictors</th>
<th>β coefficient</th>
<th>P-value</th>
<th>Recurrence score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. D-dimer abnormal, after stopping AC</td>
<td>0.96</td>
<td>&lt;0.0001</td>
<td>+2</td>
</tr>
<tr>
<td>2. Age &lt; 50 yr</td>
<td>0.43</td>
<td>0.002</td>
<td>+1</td>
</tr>
<tr>
<td>3. Sex - male</td>
<td>0.58</td>
<td>&lt;0.0001</td>
<td>+1</td>
</tr>
<tr>
<td>4. Hormone use at VTE onset</td>
<td>-1.05</td>
<td>0.002</td>
<td>-2</td>
</tr>
</tbody>
</table>

**DASH Prediction Rule**

<table>
<thead>
<tr>
<th>DASH Score</th>
<th>Annualized VTE Recurrence Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 1.0</td>
<td>3.1%</td>
</tr>
<tr>
<td>2.0</td>
<td>6.4%</td>
</tr>
<tr>
<td>≥ 3.0</td>
<td>12.3%</td>
</tr>
</tbody>
</table>

*Cox regression coefficients after backward elimination and optimism correction

Thrombophilia

- While thrombophilias are considered a risk factor for *initial* VTE, available evidence does not support the use of *inherited* thrombophilia testing to determine risk of *recurrent* VTE.

- Correctly diagnosed antiphospholipid antibody syndrome (APS), considered an acquired thrombophilia does seem to confer a high recurrence risk.
Residual Vein Obstruction

- A systematic review of studies of RVO as a predictor of occurrence in 2011 concluded RVO is not a strong predictor of recurrence of unprovoked clots.
- A recent randomized controlled trial by Prandoni concluded that an assessment of RVO after 3 months of therapy for an unprovoked clot can help guide treatment options.
  - They acknowledged that male sex, previous VTE, and extensive clots were better predictors of recurrence.
- Testing for RVO might be employed in combination with other risk factors if the risk for recurrence seems unclear.

Carrier JTH 2011
Prandoni Sem in Thromb Hemostasis 2015
Streiff J Thromb Thrombolysis 2015
FIRST EPISODE OF VTE

Unprovoked VTE

Shared Decision Making (Consider Bleeding Risk and Male Sex)

Patient With a Strong Preference for Duration

- Yes: Follow Patient Preference
- No:
  - D-dimer on Therapy or Prediction Model
    - Positive or High Risk: Continue Anticoagulation
    - Negative or Low Risk: Stop Anticoagulation, D-dimer Check in One Month

Positive: Consider Secondary Prophylaxis

Negative: Consider Secondary Prophylaxis
Second Unprovoked Proximal or Distal DVT Of Leg or PE

- Treat with extended anticoagulation with low to moderate bleeding risk
- With high bleeding risk, 3 months is suggested

Risk of recurrence is 50% higher than the risk following a first unprovoked VTE
Aspirin for Extended Treatment

In patients with an unprovoked proximal DVT or PE who are stopping anticoagulant therapy, and do not have a contraindication to aspirin, aspirin therapy is suggested to prevent recurrent VTE.

Kearon Chest 2012
Aspirin for Extended Treatment

• INSPIRE
  • A combined patient-level analysis of the WARFASA and ASPIRE trials
  • Enteric ASA 100mg daily vs placebo after 6-18 months (WARFASA) or 6 weeks to 2 years (Aspire) anticoagulation for unprovoked VTE
    • Planned and protocol for this project was developed before unblinding of the results of either trial
  • Of 1224 patients, 193 had recurrent VTE over 30.4 months’ median follow-up
  • After adjustment for treatment adherence, recurrent VTE was reduced by 42% in the ASA group
    • Similar rates of bleeding (0.4 to 0.5%)

Simes Circulation 2014
CASE STUDIES
Clark K. is a 28 year old man who developed an extensive proximal DVT after suffering multiple injuries falling off a building.

While in the hospital, Clark tested positive for protein C deficiency.

Due to his hypercoagulable state, the discharge summary suggests an indefinite duration of anticoagulant therapy.
After several months of treatment elsewhere, Clark has recently transferred to your service. He is now a 29 year old gentleman who has been on warfarin for one year due to an extensive LE DVT after multiple trauma. He was tested positive for protein C deficiency. He is requesting a home meter as monthly appointments to the clinic are difficult for him. He is always flying around to different places. What do you recommend?
Jiya

Jiya is a 30 year old school teacher from Pakistan. She suffered an unprovoked PE last year. This was the only clot she has ever had. Warfarin therapy is difficult for Jiya because she enjoys practicing martial arts.
What parameters should be considered when counseling Jiya?
FIRST EPISODE OF VTE

- Provoked VTE
  - 3 Months of Anticoagulation
    - Clinical follow Up, No Lab or Imaging Required
      - At least 3 months then until catheter pulled

- Cancer Associated VTE
  - Upper Extremity DVT?
    - Yes
      - At least 6 months or until cancer in remission (cured)
    - No

- Unprovoked VTE
  - Shared Decision Making (Consider Bleeding Risk and Male Sex)
    - Patient With a Strong Preference for Duration
      - Yes
        - Follow Patient Preference
      - No
        - D-dimer on Therapy or Prediction Model
          - Positive or High Risk
            - Continue Anticoagulation
          - Negative or Low Risk
            - Stop Anticoagulation, D-dimer Check in One Month
              - Positive
                - Consider Secondary Prophylaxis
Questions?
THANK YOU!


References


Rodger, M (2016, August) . HERDOO2 Rule to Guide Treatment Duration for Unprovoked Venous Thrombosis: The REVERSE II Study. Research presented at the European Society of Cardiology, Rome, Italy.


