Duration of Therapy for Venous Thromboembolism

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VTE Duration of Therapy Principles

• Optimal duration of therapy balances the risk of harm from recurrent VTE and AC-associated bleeding

• VTE recurrence risk is highest in the first 3 months after the event and declines thereafter

• Bleeding risk is highest in the first 3 months and declines and stabilizes thereafter
Transient risk factors influence recurrence risk

- Metaanalysis of 15 RCT or observational studies
- Follow up 12-24 months
- Recurrent VTE
  - Provoked 3.3% per pt.-yr
  - Unprovoked 7.4% per pt-yr
- Duration of therapy does not influence recurrence rate in provoked VTE
  (Boutitie F et al BMJ 2011)

Iorio A et al Arch Intern Med 2010
VTE location influences recurrence risk

- Pooled analysis of 7 RCT including 2925 patients
- Follow up – 4023 pt-years (mean 1.4 years)
- Compared with proximal DVT, distal DVT at lower risk of recurrence (HR 0.49 [95%CI 0.34 to 0.71])

Boutitie F et al BMJ 2011
Duration of therapy influences recurrence risk

- Pooled analysis of 7 RCT including 2925 patients
- Follow up – 4023 pt-years (mean 1.4 years)
- Compared with longer durations, 1-1.5 months of therapy associated with higher risk of recurrence (HR 1.52 [95% CI 1.14 to 2.02])

Boutitie F et al BMJ 2011
Cancer patients are at high risk for recurrent VTE

Hazard Ratio 3.2

Hormonal therapy-associated VTE poses a lower recurrence risk

- Prospective cohort of 630 women followed for 69 months
- Cumulative recurrent VTE after 1, 2, and 5 years: 1%, 1%, and 6%
- Recurrent VTE lower in estrogen OCP (RR 0.4) and HRT (RR 0.7)

Men are at two-fold higher risk for recurrent VTE

- Kyrle P et al. – Prospective cohort of 826 patients with unprovoked VTE
  - Recurrent VTE- Relative Risk (RR) 3.6 (2.3-5.5)
- McRae S et al.- study level meta-analysis of 5416 patients
  - Recurrent VTE- RR 1.6 (1.2-2)
- Douketis J et al.- patient-level meta-analysis of 2554 patients
  - Unprovoked VTE Hazard Ratio (HR) 2.2 (1.7-2.8)
  - Provoked VTE HR 1.2 (0.6-2.4)

Pregnancy-associated VTE increases risk with future pregnancies

• Pregnancy increases risk of VTE by 4-5 fold
  – Risk highest in 3rd trimester and post-partum
  – Elevated risk extends to 12 weeks post-partum

• White R et al. Administrative database analysis
  – Recurrence risk less with pregnancy-associated VTE than unprovoked VTE within 5 years (5.8% v. 10.4% HR 0.6 [0.4-0.9])
  – Pregnancy-associated VTE has a higher recurrence risk higher during subsequent pregnancy than unprovoked (5.7% v. 3.5% RR 1.7 [1.0-2.8])

• Anticoagulant prophylaxis is essential during subsequent pregnancies

Inherited thrombophilia is not a potent risk factor for recurrent VTE

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Follow up (mos.)</th>
<th>Recurrent VTE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baglin T 2003</td>
<td>570 1st VTE</td>
<td>24</td>
<td>15% vs. 10% (HR 1.5 [0.8-2.8])</td>
</tr>
<tr>
<td>Christiansen S 2005</td>
<td>474 1st DVT</td>
<td>87</td>
<td>28 vs. 22 per 1000 pt.-yrs (HR 1.4 [0.9-2.2])</td>
</tr>
<tr>
<td>Prandoni P 2007</td>
<td>1626 1st VTE</td>
<td>50</td>
<td>HR 2.02 [1.52-2.69]</td>
</tr>
<tr>
<td>Santamaria M 2005</td>
<td>267 1st DVT</td>
<td>47</td>
<td>HR 1.78 [1.0-3.14]</td>
</tr>
<tr>
<td>Ribierio D 2012</td>
<td>378 1st VTE</td>
<td>43</td>
<td>IRR 1.6 [0.5-5.5]</td>
</tr>
<tr>
<td>Tosetto A 2012</td>
<td>1785 1st idiopathic VTE</td>
<td>22</td>
<td>23.4% vs. 20.9%, p=0.4</td>
</tr>
</tbody>
</table>

Limited evidence supports APS as a risk factor for recurrent VTE

- Systematic review of 6 RCT and 2 OS
- Relative Risk of recurrent VTE 1.41 (0.99-2.36)
- Weaknesses - varied APL testing, timing of testing
- Conclusion - More research needed
Adverse outcomes during VTE treatment

Lecumberri R et al Thromb Haemost 2013
Fatal events during VTE therapy

Lecumberri R et al Thromb Haemost 2013
Case Fatality rates during VTE therapy

N=41,826

Lecumberri R et al Thromb Haemost 2013
The Natural History of VTE

- Observational cohort of consecutive patients after 1st VTE
- Duration of AC ≤ 6 mos. in 83%
- Median follow up – 50 mos. (2-120 mos.)
- Conclusion - Not all patients with unprovoked VTE recur

D Dimer alone does not identify low risk patients

- Prospective management study of 410 1\textsuperscript{st} VTE
- D Dimer at 0 and 30 days
- Negative D dimer associated with low risk in women with estrogen-associated VTE

How can we identify low and high risk patient with idiopathic VTE?

Enrolled at 4 centers between July 1992 and August 2008 prior to DC of warfarin after at least 3 months of therapy

Information on laboratory and clinical variables associated with VTE were collected at time of discontinuation of AC

Multivariate analysis used to develop clinical prediction rule for recurrent VTE

<table>
<thead>
<tr>
<th>Results</th>
<th>Risk Factors for Recurrent VTE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary embolism vs. distal DVT</td>
<td>HR 2.8 (1.4-6.2)</td>
</tr>
<tr>
<td>Male gender</td>
<td>HR 2.0 (1.3-3.2)</td>
</tr>
<tr>
<td>Peak thrombin generation</td>
<td>HR 1.4 (1.2-1.7)</td>
</tr>
<tr>
<td>D dimer</td>
<td>HR 1.3 (1.1-1.7)</td>
</tr>
</tbody>
</table>

Median F/U -43.3 months (14.7-78.5 mos.)

Risk Stratification for Recurrent VTE: The Vienna Risk Prediction Model

Risk Stratification for Recurrent VTE: The Vienna Risk Prediction Model

Cumulative Recurrence Rate

- 1 year: 8.2%
- 5 year: 27.9%

Sex: male
Location: pulm
DDimer: 850

Months after discontinuation of anticoagulation

How do we identify the low risk patient with idiopathic VTE?

Prospective cohort study of 665 patients with idiopathic VTE

Enrolled at 12 centers, 4 countries prior to DC of warfarin after 5-7 months of therapy

Information of 76 laboratory and clinical variables associated with VTE collected

Multivariate analysis used to develop clinical prediction rule for recurrent VTE

Results

<table>
<thead>
<tr>
<th>Results</th>
<th>Recurrent VTE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annual Risk</td>
<td>9.3% (7.7-11.3%)</td>
</tr>
<tr>
<td>- Men</td>
<td>13.7% (10.8-17%)</td>
</tr>
<tr>
<td>- Women</td>
<td>5.5% (3.7-7.8%)</td>
</tr>
</tbody>
</table>

- F/U population 600/665 (90%)
- Mean F/U -18 months (1-47 mos)

Rodger MA, et al. CMAJ. 2008
## Clinical Prediction Rule for Recurrent VTE in Women

<table>
<thead>
<tr>
<th>Model</th>
<th>Variable</th>
<th>Annual Risk of Recurrent VTE</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>NPV</th>
<th>Low-risk</th>
<th>High-risk</th>
<th>% Low-risk by Model</th>
</tr>
</thead>
</table>
| 1     | • Hyperpigmentation, edema and redness  
       • Body mass index > 30 kg/m²  
       • Age > 65 years | 0.89 | 0.37 | 0.97 | 1.6% | 7.9% | 34.7% |
| 2     | • Hyperpigmentation, edema and redness  
       • D-Dimer > 250 µg/L  
       • Body mass index > 30 kg/m² | 0.88 | 0.38 | 0.97 | 2.3% | 10.4% | 35.5% |
| 3     | • Hyperpigmentation, edema and redness  
       • D-Dimer > 250 µg/L  
       • Body mass index > 30 kg/m²  
       • Age > 65 years | 0.88 | 0.57 | 0.98 | 1.6% | 14.1% | 52.2% |
| 4     | • Hyperpigmentation, edema and redness  
       • D-Dimer > 250 µg/L  
       • Body mass index > 30 kg/m²  
       • Previous secondary VTE | 0.76 | 0.65 | 0.96 | 2.9% | 14.8% | 38.7% |
| 5     | • Hyperpigmentation, edema and redness  
       • D-Dimer > 250 µg/L  
       • Body mass index > 30 kg/m²  
       • Previous secondary VTE  
       • Age > 65 years | 0.88 | 0.56 | 0.98 | 1.7% | 13.8% | 51.4% |

Model 3 final - due to smallest annual risk of recurrent VTE in low-risk group, highest NVP, >10% risk recurrence in high-risk group, highest low-risk excluded proportion; most parsimonious and easy to remember and apply in clinical setting.

NVP = negative predictive value

Rodger MA, et al. CMAJ. 2008
Validation of the HERDOO2 Rule

- Prospective Cohort study of 2785 pts.
- Intervention - Low risk - discontinue AC, High risk - clinician discretion
- Outcome - sx VTE
- Conclusion - The HERDOO2 rule can identify women at low risk for recurrence

Rodger M et al BMJ 2017
Bleeding risk scores

• Designed to predict bleeding risk of anticoagulation

• Limitations
  – Developed in Afib pts (HEMORR2HAGES, HAS-BLED, ATRIA) or mixed populations (mOBRI)
  – Expert opinion based (ACCP)
  – Validation studies found modest predictive value (AUC 0.49-0.66)

• Further investigation needed before routine use

Schoeb M and Fang M J Thromb Thrombolysis 2013;
AMPLICIFY-EXT: Apixaban versus Placebo for extended treatment of VTE

Recurrent VTE (%)

- Placebo 8.8%
- Apixaban 2.5 mg 1.7%
  (RR 0.19; 0.11-0.33)

AMPLIFY-EXT: Low dose apixaban associated with similar bleeding risk compared with placebo

Placebo (N=823)
Apixaban 2.5 mg (N=840)
Apixaban 5 mg (N=811)

Placebo 2.7%
Apix 2.5 mg 3.2%
(RR 1.2; 0.69-2.1)

Low-dose rivaroxaban for extended treatment of VTE

- DB-RCT of riva (10 mg or 20 mg) v. aspirin for extended treatment after 6-12 mos. Of AC
- Median Follow up 351 days
- Rivaroxaban is associated with fewer recurrent VTE and similar bleeding compared with aspirin

![Graph showing outcomes of rivaroxaban and aspirin](image)

VTE and bleeding are low during extended therapy with DOAC

- Placebo (N=3640)
- Aspirin (N=616)
- Warfarin (N=1920)
- DOAC (N=4366)

Wu C et al. Thromb Res 2015
Duration of Therapy for VTE

• Surgical/major trauma associated VTE- at least 3-6 months
  • Extended prophylaxis for subsequent surgery
    • Ambulatory surgery 10-14 days
    • Inpatient surgery- 1-3 months
• Estrogen-associated VTE- 3-6 months
  • Thromboprophylaxis for pregnancy
• Pregnancy-associated VTE- 3-6 months and beyond the post-partum period (6-12 weeks)
  • Thromboprophylaxis for subsequent pregnancies
Duration of Therapy for VTE

• Cancer-associated VTE
  • At least 3-6 months and until cancer in remission and therapy is completed

• Medical-illness VTE
  • At least 3-6 months

• Unprovoked VTE
  • Consider indefinite therapy
  • Consider VTE risk stratification
Summary

• The appropriate duration of therapy depends upon the constellation of VTE risk factors and bleeding risk factors confronting the individual patient.

• Multicomponent VTE risk assessment models show promise in identifying patients at elevated risk for recurrence.

• Research to identify a bleeding risk assessment tool for VTE patients with acceptable performance characteristics is ongoing.

• Low-dose DOAC regimens for extended treatment offer the promise of low risks for VTE and bleeding.
Questions ?