Duration of Anticoagulation for VTE

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Objectives:

- Restate indications for time-limited anticoagulation therapy following venous thromboembolism.
- Restate the indications for indefinite anticoagulation following venous thromboembolism.
- Discuss and outline a process by which shared decision-making can take place with patients when selecting a duration of anticoagulation following venous thromboembolism.
Thrombosis Guidelines 2016 – Updates that Change Practice

Duration of Anticoagulation for VTE

David A. Kaplan, M.D.
April 22\textsuperscript{nd}, 2016
Learning objectives

• Indications for time-limited anticoagulation for VTE

• Indications for indefinite anticoagulation following VTE

• Review a process of shared decision making with patients to help determine the length of anticoagulation
Definitions

Phases of anticoagulation

<table>
<thead>
<tr>
<th>Initial</th>
<th>Long-term</th>
<th>Extended</th>
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<tbody>
<tr>
<td>(0 to ~7 days)</td>
<td>(~7 days to ~3 months)</td>
<td>(~3 months to indefinite)</td>
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</table>

- Parenteral*: Heparin, LMWH, fondaparinux
- Vitamin K antagonist or other agent†: Includes LMWH, dabigatran, rivaroxaban

* Heparin, LMWH, fondaparinux; † Includes LMWH, dabigatran, rivaroxaban

Figure 1. Phases of anticoagulation. LMWH = low-molecular-weight heparin.

Fig. 1 The different phases of treatment and traditional therapies in venous thromboembolism
Definitions

- Other terms:
  - Indefinite
  - Chronic
  - Time-limited

- DOACs

- In most cases 3 months vs. indefinite

(0-10 days)  3 months  > 3 months

Dx
Optimal duration of anticoagulation

VTE Recurrence: consequences
- Post-thrombotic syndrome (↑6x)
- CTEPH (~3%)
- Fatal pulmonary embolism (3.6%)

Bleeding from extended AC
- Major bleeding (↑2.6x @1 year)
- Intracranial bleeding
- Fatal bleeding

Patient preferences
- Fear of VTE vs. fear of bleeding
- Sense of well being
- Monitoring
- Cost

References:
Optimal duration of anticoagulation

- As long as anticoagulation is not contraindicated...
  - Virtually always beneficial for 3 months
  - Benefit after 3 months depends on recurrence risk, bleeding risk

- 0-3 months: benefit > risk
  - For every 1000 VTE patients treated for less than 3-6 months:
    - 53 more VTE recurrences
    - 5 fewer major bleeds (CI: 0.22-1.32)
    - 2 fewer deaths (CI: 0.68-1.38)

- >3 months: two possible scenarios
  - VTE risk reduction > risk of bleeding
  - Risk of bleeding > VTE risk reduction
Why 3 months of therapy (minimum)?

- Symptomatic distal DVT – warfarin vs. no treatment
  - Symptomatic extension
  - 0% vs. 29% at 3 months

- Proximal DVT – warfarin vs. low dose UFH
  - Recurrent VTE
  - 0% vs. 47% at 3 months

- VTE – warfarin for 4 weeks vs. 3 months
  - Recurrent VTE
  - 2-10x rate of recurrence with shorter duration

Lancet 1985; 2:515
NEJM 1979; 301:855
Lancet 1992; 10;340
Thromb Haemost. 995;74(2)
Why not 6 months (or 9 or 12 or...)?

- Pooled analysis from 7 randomized trials
- n=2925 VTE patients

“...three months of anticoagulant treatment resulted in a similar risk of recurrence after treatment was stopped to a longer duration of treatment...”

BMJ 2011;342:d3036
Why not 6 months (or 9 or 12 or...)?

- PADIS-PE RCT
- 2015: n=371
Why indefinite therapy?

- Unprovoked VTE – recurrence
  - 10% at 1 year
  - 30% at 5 years
- Recurrent unprovoked VTE – recurrence

Haematologica 2015; 100(2)
Why indefinite therapy?

- Recurrent VTE reduction
  - Warfarin INR 2-3: ~90%
  - Warfarin INR 1.5-2: ~60% (with no reduction in bleeding risk)
  - Aspirin: ~30%

- DOACs
  - Dabigatran vs. warfarin
  - Dabigatran vs. placebo
  - Rivaroxaban vs. placebo
  - Apixaban vs. placebo
  - >80% recurrent VTE reduction
VTE risk recurrence

• Low risk
  • Surgery
  • 1% at 1 year
  • 5% at 5 years

• Intermediate risk
  • Non-surgical transient risk factor
  • 5% at 1 year
  • 15% at 5 years

• High risk
  • Unprovoked, cancer
  • 10% at 1 year
  • 30% at 5 years
  • Perhaps much higher if recurrent, cancer-associated
Duration: 3 months OR indefinite

- **Low and intermediate VTE recurrence risk: 3 months**
  - Treatment of VTE
  - ↓ Short term recurrence risk
  - Provoked VTE
  - First unprovoked distal DVT
  - Patients with a high bleeding risk

- **High VTE recurrence risk: Indefinite**
  - ↓ Long term recurrence risk
  - Unprovoked VTE
  - Cancer-associated VTE
VTE risk factor: surgery

- Surgery: RR 9.6-70 during the first 6 postoperative weeks
- Risk persists for months
- Variable risk according to type of surgery and other risk factors
  - Age
  - History of VTE
  - Malignancy
  - Medical comorbidities
  - Thrombophilia
  - Time in surgery
  - Time under anesthesia
  - Duration of immobilization
VTE risk factor: surgery

- 91 day incidence of VTE among patients without cancer
  - Neurosurgery: 0.5-2.3%
  - Head and neck: 0.1-0.2%
  - Cardiothoracic: 0.4-1.4%
  - Vascular: 0.2-2.8%
  - Gastrointestinal: 0.2-1.6%
  - Urologic: 0.3-1%
  - Gynecologic: 0.3%
  - Orthopedic: 0.2-2.4%
  - Other (wound debridement): 0.9%

- Higher among cancer patients

- 56% VTE occurred after hospital discharge

Thromb Haemost 2003; 90:446
VTE risk factors: non-surgical transient

- Major trauma
- Plaster cast
- Minor injury (3-5x ↑)
- IV drug use (femoral vein)
- Pregnancy, postpartum (>4x ↑)
- Estrogen – OCPs, HRT (2-4x ↑)
- Immobilization -- ≥3 days
- Extended travel – eg, flight ≥8 hours (2-4x ↑)
- Medical illness
- Obesity
- Other Rx: testosterone, tamoxifen, glucocorticoids, bevacizumab

Arch Intern Med. 2008;168(1):21
Br J Haematol. 2001;112(3):641
BMJ. 2009;339:b2921
Ann Intern Med. 2005;143(10):697
JAMA. 2004;292(13):1573
Arch Intern Med. 2010;170(19):1710-1716
VTE risk factor: cancer

- High risk of recurrence: ~15% per year
  - Active: treated in the past 6 months, persistent, progressive
  - Other factors
    - Chemotherapy
    - Metastases
    - CVC
    - Higher risk cancers

- High total mortality and VTE mortality

- High bleeding risk independent of anticoagulation

Blood. 2002;100(10):3484
Predicting bleeding risk

• Several models developed

• **No validated bleeding prediction tool**

• Risk factors:
  • Age >65
  • Age >75
  • Previous bleeding
  • Cancer
  • Metastatic cancer
  • Renal failure
  • Thrombocytopenia
  • Previous stroke
  • Diabetes
  • Anemia
  • Antiplatelet therapy
  • Poor anticoagulant control
  • Comorbidity and reduced functional capacity
  • Recent surgery
  • Frequent falls
  • Alcohol abuse
## Predicting bleeding risk

<table>
<thead>
<tr>
<th></th>
<th>Low risk (0 RFs)</th>
<th>Moderate risk (1 RF)</th>
<th>High risk (≥2 RFs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticoagulation after first 3 months</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</td>
</tr>
<tr>
<td><strong>Total risk (%/y)</strong></td>
<td><strong>0.8</strong></td>
<td><strong>1.6</strong></td>
<td><strong>≥6.5</strong></td>
</tr>
</tbody>
</table>

- Estimates only
- Precision limited by variable severity of factors
- Temporal relationships
- Variable definitions
Predicting VTE recurrence risk

- Several models developed
- No validated recurrence prediction tool

1%*/y  
Low risk  
Surgically provoked

5%*/y  
Unprovoked

15%*/y  
High risk  
Cancer

Non-surgically provoked

Recurrent unprovoked

Can we further risk stratify patients here?
VTE risk factors: persistent

• Male sex, RR ~1.6
• aPL, RR ~2
• Hereditary thrombophilia, RR ~1.5
  • “high risk” thrombophilia
  • protein S, protein C, antithrombin III deficiency, homozygous factor V Leiden and homozygous prothrombin gene mutations
• Asian ethnicity, RR ~0.8
• Residual thrombus in proximal veins, RR ~1.5
• Post-thrombotic syndrome, RR ~2.6

“Prothrombotic abnormalities do not appear to play an important role in the risk of a recurrent thrombotic event. Testing for prothrombotic defects has little consequence with respect to prophylactic strategies. Clinical factors are probably more important than laboratory abnormalities in determining the duration of anticoagulation therapy.”

JAMA. 1998;279(21):1679-1681
Predicting VTE recurrence: D-dimer

- Predictive value
  - Patient-level meta-analysis, 7 studies, n=1818
  - D-dimer measurement after stopping anticoagulation
  - D-dimer + : HR 2.59 (3.7 vs. 8.8 per 100 patient-years)

Ann Intern Med. 2010;153(8):523-531
Predicting VTE recurrence: D-dimer

- Two major studies since AT9
  - DULCIS
  - Serial D-dimer
  - No M:F difference
  - Negative: 3%/year

- Kearon C, Spencer FA, O'Keeffe D et al
- Annualized VTE recurrence

<table>
<thead>
<tr>
<th></th>
<th>D-dimer (-)</th>
<th>D-dimer (+)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>8%</td>
<td>16%</td>
</tr>
<tr>
<td>Women</td>
<td>5%</td>
<td>10%</td>
</tr>
</tbody>
</table>

*No recurrences among women who were on estrogen*
Predicting VTE recurrence: D-dimer

- Recurrence risk stratification: possibly helpful in select patients
- Data conflicting
- Possibly not useful in men, women with estrogen provocation
- ACCP, ISTH: 5% annualized risk threshold:
  - Would result of D-dimer influence patient decision?
  - Consider testing in women with unprovoked VTE who were not taking estrogen to further risk stratify?
    - D-dimer negative -> reclassified as intermediate risk -> stop anticoagulation?
    - D-dimer positive -> remains in high risk group -> resume anticoagulation?
VTE recurrence vs. bleeding

- After 3 months of anticoagulation
  - If AC stopped: VTE recurrence -> Fatal PE, CTEPH, PTS
  - If AC continued: bleeding -> major bleeding, fatal bleeding

- Case fatality rate
  - VTE
    - During first 6 months of AC: 11.3%
    - After discontinuation of AC: 3.6%
  - Bleeding
    - During first 6 months of AC: 11.3%
    - Beyond 6 months: ???

Ann Intern Med. 2010;152(9):578-589
Bleeding case fatality rate

- **11.3%** used as estimate in guidelines
- Possibly lower?
  - **RE-COVER**
    - dabigatran: 5%
    - VKA: 4.2%
  - **EINSTEIN-PE**
    - rivaroxaban: 7.7%
    - VKA: 5.8%
  - **AMPLIFY**
    - apixaban: 6.7%
    - VKA: 4.1%
  - **Hokusai-VTE**
    - edoxaban: 3.6%
    - VKA: 15%

Indications for 3 months AC

- VTE provoked by surgery
  - Bleeding risk not considered
  - Low recurrence risk
  - Indefinite AC -> increase in major bleeding without benefit
  - Strong recommendation against indefinite AC

- VTE provoked by non-surgical factor/unprovoked distal DVT
  - Higher recurrence risk
  - Indefinite AC -> increase in major bleeding without benefit
  - Strength of recommendation against indefinite AC weaker for patients with low or moderate bleeding risk
  - Strong recommendation against indefinite AC for high risk
Indications for indefinite AC

• First unprovoked proximal DVT or PE
  • High recurrence risk, reduced by indefinite AC
  • Low or moderate bleeding risk: weak recommendation in favor of indefinite AC
  • High bleeding risk: strong recommendation against indefinite AC

• Second unprovoked VTE
  • Very high recurrence risk, large reduction in risk by indefinite AC
  • Low bleeding risk: strong recommendation in favor of indefinite AC
  • Moderate bleeding risk: weak recommendation in favor of indefinite AC
  • High bleeding risk: weak recommendation against indefinite AC
Indications for indefinite AC

- VTE and active cancer
  - Very high recurrence risk, reduced by indefinite AC
  - Low or moderate bleeding risk: strong recommendation for indefinite
  - High bleeding risk: weak recommendation for indefinite
### Provoked VTE
- Stop after 3 months

### Unprovoked VTE
- First VTE
  - **Distal DVT**
    - Stop after 3 months
  - **Proximal DVT and/or PE**
    - High bleeding risk
      - Stop after 3 months
  - Recurrent VTE
    - Low or moderate bleeding risk
      - Indefinite therapy
    - High bleeding risk
      - Stop after 3 months

### Cancer-associated VTE
- Indefinite or until cancer “not active”

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VTE: Venous Thromboembolism
DVT: Deep Vein Thrombosis
PE: Pulmonary Embolism
Shared decision making

- Consider strength of evidence
  - Surgically provoked: 3 months
  - Cancer: indefinite
  - First unprovoked VTE with high bleeding risk: 3 months
  - Second unprovoked VTE with low bleeding risk: indefinite
  - All other situations: gray areas remain, personalize treatment

- DVT vs. PE
- Recurrent provoked
- Persistent risk factors
- Fears
- Hobbies
- Burdens of therapy
- VKA vs. DOAC

CTEPH

- Chronic Thromboembolic Pulmonary Hypertension
  - No RCTs
  - High quality indirect evidence

- Recurrence risk high

- Severe consequences of recurrence

- Recommendation: indefinite anticoagulation (1B)
Superficial vein thrombosis

- Risk factors similar to DVT, PE
- Small studies: NSAIDs, UFH, LMWH, VKA
- CALISTO
  - n=3000
  - placebo vs. fondaparinux 2.5mg/d for 45 days
  - Lower extremity SVT ≥5cm
  - 85% RRR in composite outcome
  - One patient with major bleeding in each group

- Recommendation: prophylactic dose of LMWH or fondaparinux for 45 days (2B)
Upper extremity DVT

- No RCTs
  - Observational studies
  - Recurrent VTE and PTS: lower extremity > upper extremity

- Risk factors generally similar to LE DVT
  - CVC
  - Cancer
Upper extremity DVT

- Recommendations

  - UEDVT of axillary vein or more proximal: 3 months (2B)

  - UEDVT with CVC: 3 months over longer duration
    - Without cancer (1B)
    - With cancer (2C)

  - UEDVT with CVC: AC as long as CVC in place over 3 months
    - Without cancer (2C)
    - With cancer (1C)

  - UEDVT not associated with cancer/CVC: 3 months over longer duration (1B)
Splanchnic vein thrombosis

- No RCTs
- Incidental
  - Anticoagulation vs. no treatment
  - Extent of thrombosis
  - Progression
  - Cancer
  - Chemotherapy
  - Duration?
- Provoked versus unprovoked
  - Surgical or medical factors: 3 months?
  - Unprovoked, persistent risk factor, myeloproliferative disorder: indefinite?
Hepatic vein thrombosis

- No RCTs
- Incidental
  - Anticoagulation vs. no treatment
  - Extent of thrombosis
  - Progression
  - Cancer
  - Chemotherapy
  - Duration?

- Provoked versus unprovoked
  - Surgical or medical factors (eg, estrogen): 3 months?
  - Unprovoked, persistent risk factor: indefinite?
Questions