Duration of Anticoagulation for Venous Thromboembolism

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Disclosures

Consultant - Portola Pharmaceuticals
Consultant - Boehringer Ingelheim
Consultant - Daiichi Sankyo
Research - Siemens
Venous Thromboembolism

(Includes DVT and PE)

- Common, lethal, multicausal disease
- Considerable morbidity and mortality
- 3rd most common cardiovascular disease after MI and stroke

References:
- Blood 2012;120(8):1562-1569
- CHEST 2012;141(2 Suppl):195S-226S
- BMJ 1991;302:709-711
Burden of Venous Thromboembolism

- Pulmonary hypertension
- Pulmonary embolism
- Post-thrombotic syndrome
- Symptomatic DVT
- Asymptomatic DVT
# Key Risk Factors for VTE

<table>
<thead>
<tr>
<th>Acute illness</th>
<th>Clinical</th>
<th>Genetic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute MI</td>
<td>Age &gt;60 y</td>
<td>Antithrombin deficiency</td>
</tr>
<tr>
<td>Acute heart failure</td>
<td>History of VTE</td>
<td>Protein C deficiency</td>
</tr>
<tr>
<td>Acute infectious disease</td>
<td>History of malignancy and cancer therapy</td>
<td>Protein S deficiency</td>
</tr>
<tr>
<td>Acute respiratory disease</td>
<td>Known thrombophilia (Antiphospholipid syndrome)</td>
<td>Hyperhomocysteinemia</td>
</tr>
<tr>
<td>Acute rheumatic disease</td>
<td>Extreme limitation in mobility, Surgery, Trauma, Fractures</td>
<td>Raised prothrombin levels (G20210A)</td>
</tr>
<tr>
<td>Autoimmune disease</td>
<td>Estrogen therapy or pregnancy</td>
<td>Factor V Leiden</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>Obesity</td>
<td>Raised factor VIII levels</td>
</tr>
<tr>
<td></td>
<td>Myeloproliferative Disorders</td>
<td>Hyperfibrinogenemia</td>
</tr>
<tr>
<td></td>
<td>CKD or nephrotic syndrome</td>
<td></td>
</tr>
</tbody>
</table>
Phases of anticoagulation

**Initial** (0 to ~7 days)

**Long-term** (~7 days to ~3 months)

**Extended** (~3 months to indefinite)

- Initial: Parenteral*
- Long-term: Vitamin K antagonist or other agent†

* Heparin, LMWH, fondaparinux;
† Includes LMWH, dabigatran, rivaroxaban
Duration of Anticoagulation -

*Was the VTE Event Provoked or Unprovoked?*
Duration of Anticoagulation

Provoked (Transient or Reversible) Risk Factors

**Major Factors:**
- Surgery
- Trauma
- Hospitalization
- Plaster cast
- Immobilization

“All within 1 month of a diagnosis of VTE”

**Minor Factors:**
- Estrogen therapy
- Pregnancy
- Prolonged travel (>8 hours)
- Any general anesthesia
- Minor injury causing a limp
- Bed-bound for a day or chair-bound for 3 days

“Or the previously noted major factors when they have occurred 1 to 3 months before diagnosis of VTE”
Minor Risks Factors that may Contribute to A Provoked VTE

- Age
- Inflammatory bowel disease
- Infectious diseases (UTI, pneumonia, HIV)

- Smoking
- Endocrine disorders
- Mild thrombophilia
- ANCA-associated vasculitis
Minor Risks Factors that may Contribute to Provoked VTE

- Cigarette smoking
- Hypertension
- Diabetes mellitus
- Obesity
- Hyperlipidemia
- Nutritional
- Stress

An Association between Atherosclerosis and Venous Thrombosis

Paolo Prandoni, M.D., Ph.D., Franca Bilora, M.D., Antonio Marchiori, M.D., Enrico Bernardi, M.D., Francesco Petrobelli, M.D., Anthonie W.A. Lensing, M.D., Ph.D., Martin H. Prins, M.D., Ph.D., and Antonio Girolami, M.D.

JACC 2010; 56: 1-7
Circulation 2010; 121: 1896-1903
NEJM 2003; 348: 1435-1441
Treatment of DVT or PE - Provoked

5. In patients with a proximal DVT of the leg or PE provoked by surgery, we recommend treatment with anticoagulation for 3 months over (i) treatment of a shorter period (Grade 1B), (ii) treatment of a longer time-limited period (eg, 6, 12, or 24 months).

6. In patients with a proximal DVT of the leg or PE provoked by a nonsurgical transient risk factor, we recommend treatment with anticoagulation for 3 months over (i) treatment of a shorter period.
Duration of Anticoagulation for the Unprovoked or Idiopathic Event

“Extended or Indefinite Therapy”
Duration of Anticoagulation

• Extended or Indefinite treatment with a VKA reduces recurrent VTE by ~80% to 90%
• Direct and indirect comparisons using the NOACs have found similar reductions in VTE with extended or indefinite anticoagulation and also LMWH in cancer patients
• But, anticoagulation with a VKA is associated with a 2.6 fold increase in major bleeding

Blood 2014;123(12):1794-1891
Hematology 2013;471-477
Duration of Anticoagulation

Who is a Candidate for Extended or Indefinite Therapy?

- Unprovoked or idiopathic VTE
- Recurrent VTE
- Patients with more extensive thrombosis who do not have reversible provoking factors
- Patients with unprovoked proximal DVT or PE
- Cancer-related VTE
- Select Thrombophilia’s
## Clinical Features Associated with a High Risk of Recurrent Venous Thrombosis

<table>
<thead>
<tr>
<th>Feature</th>
<th>Evidence</th>
<th>Clinical relevance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absence of a temporary risk condition</td>
<td>Strong</td>
<td>High ★</td>
</tr>
<tr>
<td>Pulmonary embolism or proximal DVT</td>
<td>Strong</td>
<td>High ★</td>
</tr>
<tr>
<td>More than two thrombotic events</td>
<td>Strong</td>
<td>Restricted, consider bleeding risk during prolonged anticoagulation ★</td>
</tr>
<tr>
<td>Male sex</td>
<td>Strong</td>
<td>High ★</td>
</tr>
<tr>
<td>Residual vein thrombosis</td>
<td>Strong</td>
<td>Low</td>
</tr>
<tr>
<td>Vena cava filter</td>
<td>Strong</td>
<td>High ★</td>
</tr>
<tr>
<td>Continued estrogen use</td>
<td>Strong</td>
<td>High ★</td>
</tr>
<tr>
<td>Cancer</td>
<td>Strong</td>
<td>High ★</td>
</tr>
<tr>
<td>Post thrombotic syndrome</td>
<td>Moderate</td>
<td>Moderate</td>
</tr>
<tr>
<td>Overweight</td>
<td>Weak</td>
<td>Low</td>
</tr>
</tbody>
</table>

*Lancet 2010;376:2032-2039*
Additional Risk Factors for Recurrent VTE

- Immobilization
- Chronic obstructive lung disease
- Family history
- Thrombophilia (antithrombin, protein C, S deficiencies)
- Elevated D-dimer after stopping anticoagulation
## Predictors of Late Recurrence after VTE

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Hazard Ratio</th>
<th>95% C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient age&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.17</td>
<td>1.11, 1.24</td>
</tr>
<tr>
<td>Body mass index&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.24</td>
<td>1.04, 1.47</td>
</tr>
<tr>
<td>Neurologic disease with leg paresis</td>
<td>1.87</td>
<td>1.28, 2.73</td>
</tr>
<tr>
<td>Active cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer with chemotherapy</td>
<td>4.32</td>
<td>2.58, 6.95</td>
</tr>
<tr>
<td>Cancer without chemotherapy</td>
<td>2.21</td>
<td>1.60, 3.06</td>
</tr>
</tbody>
</table>

<sup>a</sup> Per decade increase in age  
<sup>b</sup> Per 10 kg/m² increase in body mass index
Risk of Recurrent VTE after Discontinuing Anticoagulation

• 1626 consecutive patients followed after stopping anticoagulation following a proximal DVT and/or PE

• Cumulative incidence of recurrent VTE was
  – 11.0% after 1 year
  – 19.6% after 3 years
  – 29.1% after 5 years
  – 39.9% after 10 years
Predictor of Late Recurrence of VTE

Cumulative incidence of first venous thromboembolism recurrence (—), and the hazard of first recurrence per 1,000 person-days (---).

Recurrence at 1, 2, 5 and 10 years: 13, 17, 23 and 30%

Hazard of VTE recurrence is highest within first 6 months, but hazard never returns to baseline (patients with incident VTE are always at risk of recurrence)

Am J Hematol 2012;87:S63-S67
Arch Intern Med 2008;168:425-430
Arch Intern Med 2000;160:761-768
Risk of recurrence was 25% in patients with an unprovoked VTE 5 years after the incident event and increased with time.
Duration of Anticoagulation - Unprovoked

Recurrence Risk
D-dimer, ultrasound, thrombophilia results

What should we Consider?

Alternatives
Low-intensity warfarin
NOACs

Bleeding Risk
Patient characteristics, stability of anticoagulation

Patient Preferences and Values
(Includes lifestyle and occupation)
D-dimer Testing to Determine the Duration of Anticoagulation Therapy

- Elevated D-dimer after discontinuing warfarin
- Patients with an abnormal D-dimer one month after discontinuing anticoagulation have a significant incidence of recurrent VTE, which is reduced by resuming anticoagulation
- The rate is doubled one month after stopping warfarin

D-Dimer and Recurrence After Unprovoked VTE

Cumulative Incidence of Outcomes

Abnormal D-dimer level without anticoagulation

Normal D-dimer level

Abnormal D-dimer level with anticoagulation

Days

HR=2.49
P=0.003

HR=5.36
P=0.007

HR=2.17
P=0.21

Cleveland Clinic

Risk of recurrence in patients with a first unprovoked VTE who have negative D-dimer results is **not low enough** to justify stopping anticoagulation therapy in men but **may be** low enough to justify stopping in women.
Persistent Residual Vein Thrombosis to Determine the Duration of Anticoagulation

- **Persistent residual vein thrombosis**
  - Controversial

- Prospective cohort study, patients with persistent residual vein thrombosis had a 2-fold higher risk of recurrent VTE compared with patients with early vein recanalization

- 538 consecutive patients randomized to fixed duration anticoagulation versus ultrasonography-guided duration of anticoagulation
  - 17.2% of patients allocated to fixed duration had recurrent VTE
  - 11.9% of patients allocated to flexible ultrasound-guided duration had recurrent VTE
At present the data on RVO suggest that it does not reliably identify patients with a higher risk of recurrence of thrombosis after discontinuation of an initial period of anticoagulation following a first unprovoked VTE.

There is little clinical value in assessing RVO and it should not be part of the standard clinical practice.
Thrombophilia Screening

• Routine screening for a single thrombophilic risk factor not recommended for the following reasons:
  – Trials that have assessed the benefits of testing for thrombophilia are absent
  – Testing may lead to over-treatment
  – Testing may cause unnecessary concern
  – One third of patients with a recurrent unprovoked VTE have a normal test result and a negative finding may result in a false sense of safety
• Presence of most risk factors including factor V Leiden are at best only weak predictors of recurrence
• Thus knowledge of the thrombophilia status of affected patients fails to substantially help clinicians in practice to prevent recurrence of VTE in those patients

Patient Preference and Values

Lifestyle & Occupation

- Chris Bosh
- Serena Williams
- Brian Vickers
- Tomas Vokoun
What about the Bleeding Risk?
Bleeding Risk

The clinical impact of anticoagulant-related major bleeding in patients with VTE is considerable and clinicians should take this into account when deciding whether to continue long-term anticoagulant therapy in an individual patient.

About 1 in 7 bleeding episodes are fatal or intracranial.

Table 3. Clinical Effect of Anticoagulant-Related Bleeding

<table>
<thead>
<tr>
<th>Time Period of Anticoagulant Therapy</th>
<th>Case-Fatality Rate of Major Bleeding (95% CI), %</th>
<th>Rate of Intracranial Bleeding (95% CI) per 100 patient-years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entire period of anticoagulant therapy</td>
<td>13.4 (9.4–17.4)</td>
<td>1.15 (1.14–1.16) per 100 patient-years</td>
</tr>
<tr>
<td>Initial 3 mo of anticoagulant therapy</td>
<td>9.3 (3.1–20.3)</td>
<td>1.48% (1.40%–1.56%)</td>
</tr>
<tr>
<td>After initial 3 mo of anticoagulant therapy</td>
<td>9.1 (2.5–21.7)</td>
<td>0.65 (0.63–0.68) per 100 patient-years</td>
</tr>
</tbody>
</table>
**Risk of Bleeding**

**TABLE 11** Risk Factors for Bleeding with Anticoagulant Therapy and Estimated Risk of Major Bleeding in Low-, Moderate-, and High-Risk categories

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Estimated Absolute Risk of Major Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;65 y</td>
<td></td>
</tr>
<tr>
<td>Age &gt;75 y</td>
<td></td>
</tr>
<tr>
<td>Previous bleeding</td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td></td>
</tr>
<tr>
<td>Metastatic cancer</td>
<td></td>
</tr>
<tr>
<td>Renal failure</td>
<td></td>
</tr>
<tr>
<td>Liver failure</td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td></td>
</tr>
<tr>
<td>Previous stroke</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
</tr>
<tr>
<td>Anaemia</td>
<td></td>
</tr>
<tr>
<td>Antiplatelet therapy</td>
<td></td>
</tr>
<tr>
<td>Poor anticoagulant control</td>
<td></td>
</tr>
<tr>
<td>Comorbidity and reduced functional capacity</td>
<td></td>
</tr>
<tr>
<td>Recent surgery</td>
<td></td>
</tr>
<tr>
<td>Frequent falls</td>
<td></td>
</tr>
<tr>
<td>Alcohol abuse</td>
<td></td>
</tr>
<tr>
<td>Nonsteroidal anti-inflammatory drug</td>
<td></td>
</tr>
</tbody>
</table>

Compared with low-risk patients, moderate-risk patients are assumed to have a twofold risk and high-risk patients are assumed to have an eightfold risk of major bleeding.
Risk of Major Bleeding in Individual Patients if Anticoagulants are Continued

- Older age >65 and especially >75 years
- Previous bleeding
- Cancer (especially metastatic)
- Renal insufficiency
- Liver failure
- Diabetes
- Previous stroke
- Thrombocytopenia

- Anemia
- Concomitant antiplatelet therapy
- Recent surgery
- Frequent falls
- Alcohol abuse
- Comorbidities and reduced functional capacity
- Poor control of VKA
Predictive Variables for Major Bleeding Events in Patients with VTE

Findings from the RIETE Registry

<table>
<thead>
<tr>
<th>Variable</th>
<th>β</th>
<th>Odds ratio (95% CI)</th>
<th>P-value</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recent major bleeding</td>
<td>0.996</td>
<td>2.7 (1.6–4.6)</td>
<td>&lt;0.001</td>
<td>2</td>
</tr>
<tr>
<td>Creatinine levels &gt;1.2 mg/dl</td>
<td>0.761</td>
<td>2.1 (1.7–2.8)</td>
<td>&lt;0.001</td>
<td>1.5</td>
</tr>
<tr>
<td>Anemia</td>
<td>0.739</td>
<td>2.1 (1.7–2.7)</td>
<td>&lt;0.001</td>
<td>1.5</td>
</tr>
<tr>
<td>Cancer</td>
<td>0.553</td>
<td>1.7 (1.4–2.2)</td>
<td>&lt;0.001</td>
<td>1</td>
</tr>
<tr>
<td>Clinically overt PE</td>
<td>0.545</td>
<td>1.7 (1.4–2.2)</td>
<td>&lt;0.001</td>
<td>1</td>
</tr>
<tr>
<td>Age &gt;75 years</td>
<td>0.504</td>
<td>1.7 (1.3–2.1)</td>
<td>&lt;0.001</td>
<td>1</td>
</tr>
</tbody>
</table>

PE, pulmonary embolism; CI, confidence intervals.

Six variables independently associated with an increased risk for bleeding—
1). Patients with a risk score of 0 had a 0.3% incidence of major bleeding.
2). Patients with a risk score of 1-4 had a 2.6% incidence of major bleeding.
3). Patients with a risk score of >4 had a 7.3% risk of major bleeding.

Use to identify patients at low, medium or high risk for major bleeding during the first 3 months of anticoagulation.
Fatal bleeding was more frequent than fatal recurrent PE in all subgroups.
<table>
<thead>
<tr>
<th>Bleeding Risk Score</th>
<th>Definition of Major Bleeding</th>
<th>Score variables (Points)</th>
<th>Risk of Major Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outpatient Bleeding Risk Index</td>
<td>&gt; 2 units in &lt;7 days or otherwise life threatening bleeding, intracranial hemorrhage</td>
<td>Age $\geq$ 65 years (+1) History of GI bleeding, stroke, recent MI and/or HCT $&lt;30%$, and/or diabetes and/or creatinine $&gt;1.5$ mg/dL (all +1)</td>
<td>Low = 0 points Intermediate = 1-2 points High = $\geq$ 3 points</td>
</tr>
<tr>
<td>Kuijer Score</td>
<td>Overt bleeding with a decline in hemoglobin $&gt;20$ g L, transfusion of more than 2 units, retroperitoneal, intracranial bleeding or permanent discontinuation of treatment</td>
<td>Age &gt; 60 years (+1.6) Female gender (+1.3) Malignancy (+2.2)</td>
<td>Low = 0 points Intermediate = 1-3 points High = $\geq$ 3 points</td>
</tr>
<tr>
<td>Kearon Score</td>
<td>Overt bleeding $&gt;20$ g L or transfusion of $&gt;2$ units, retroperitoneal or intracranial hemorrhage</td>
<td>Age $\geq$ 65 years (+1) Previous stroke (+1) Peptic ulcer disease (+1) GI bleeding (+1) Renal impairment (+1) Anemia (+1) Thrombocytopenia (+1) Liver disease (+1) Diabetes (+1) Antiplatelet Rx (+1)</td>
<td>Low = 0-1 point Intermediate = 2-3 points High = $\geq$ 4 points</td>
</tr>
<tr>
<td>RIETE</td>
<td>Overt bleeding that required $&gt;2$ units, retroperitoneal, intracranial hemorrhage or fatal bleeding event</td>
<td>Recent major bleed (+2) Creatinine $&gt;1.2$mg.dL (+1.5) Anemia (+1.5) Cancer (+1.5) Clinically overt PE (+1) Age $&gt;75$ years (+1)</td>
<td>Low = 0 points Intermediate = 1-4 points High = $\geq$ 4 points</td>
</tr>
</tbody>
</table>

*J Thromb Haemost 2012;11:435-443*
Stratifying Patients for Risk of Bleeding

- Young healthy patients (<65 years) with good VKA control will have a risk of (<1% per pt.-year)
- Patients with less severe risk factors will have an intermediate risk for bleeding
- Elderly patient with severe or multiple risk factors are at high risk for major bleeding (>4% per patient-year)

Blood 2014;123(12):1794-1801
Chest 2012:141(Suppl 2):e419-e494s
Arch Intern Med 2003:163(8):917;920
## Models to Predict Recurrence Risk of VTE

<table>
<thead>
<tr>
<th>Author</th>
<th>Number of patients</th>
<th>Predictive variables</th>
<th>Recurrence risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rodger et al</td>
<td>646</td>
<td>Men: <strong>None</strong> Women: Age ≥ 60 yrs. (+1 point) Signs of PTS (+1 point) BMI ≥ 30 kg/m² (+1 point) D-Dimer &gt; 250 ug/l during anticoagulation (+1 point)</td>
<td>≤1 point (1.6%)</td>
</tr>
<tr>
<td>Eichinger et al</td>
<td>929</td>
<td>Sex Location of first VTE D-Dimer after anticoagulation</td>
<td>&lt;180 points (according to nomogram) &lt;4.4%</td>
</tr>
<tr>
<td>Tossetto et al</td>
<td>1818</td>
<td>- Abnormal D-Dimer after stopping anticoagulation (+2 points) - Age &lt; 50 years (+1 point) - Male sex (+1 point) Hormonal therapy (-2 points)</td>
<td>≤1 point 3.1%</td>
</tr>
</tbody>
</table>

CMAJ 2008;179:417-424  
Circulation 2010;121:1630-1636  
J Thromb Haemost 2010;10:1019-1025
The Men Continue and HERDOO2*
Clinical Decision Rule to Identify Patients at Low Risk of Recurrent VTE after 5-7 Months of Oral Anticoagulation for a First Unprovoked VTE

<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 &gt;2</td>
</tr>
</tbody>
</table>

Predictive risk factors for women

<table>
<thead>
<tr>
<th>Predictive risk factors for women</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postthrombotic signs (hyperpigmentation, edema or redness in either leg)</td>
<td>1</td>
</tr>
<tr>
<td>D-dimer level ≥ 250 ug/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>

Followed for ~18 months:
Women with ≤ 1 had an annual recurrence risk of 1.6%
Women with 2 or more risk factors had annual recurrence risk of 14.1%

*HERDOO2, hyperpigmentation, edema, redness, D-Dimer, obesity, older age, 2 scores

CMAJ 2008;179:417-426
The Vienna Prediction Model

*Clinical Decision Rule to Identify Patients at Low Risk of Recurrent VTE*

<table>
<thead>
<tr>
<th>Predictive Values</th>
<th>Points (According to Nomogram)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
</tr>
<tr>
<td>MALES</td>
<td>60</td>
</tr>
<tr>
<td>Females</td>
<td>0</td>
</tr>
<tr>
<td><strong>Site of VTE</strong></td>
<td></td>
</tr>
<tr>
<td>Distal DVT</td>
<td>0</td>
</tr>
<tr>
<td>Proximal DVT</td>
<td>70</td>
</tr>
<tr>
<td>PE</td>
<td>90</td>
</tr>
<tr>
<td><strong>D-DIMER LEVELS (after stopping anticoagulants)</strong></td>
<td></td>
</tr>
<tr>
<td>Continuous</td>
<td>0 -100</td>
</tr>
</tbody>
</table>

Patients at low risk rate of recurrence of 4.4% when points [according to nomogram] are \(<180\)

Web-based risk calculator available [www.meduniwien.ac.at/user/georg.heinze/zipfile/](http://www.meduniwien.ac.at/user/georg.heinze/zipfile/)
The DASH Score

Clinical Decision Rule to Identify Patients at Low Risk of Recurrent VTE

<table>
<thead>
<tr>
<th>Predictive Factors</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated D-Dimer levels 1 month after stopping vitamin K antagonists</td>
<td>2</td>
</tr>
<tr>
<td>Age &lt; 50 years</td>
<td>1</td>
</tr>
<tr>
<td>Male sex</td>
<td>1</td>
</tr>
<tr>
<td>Women taking oral contraceptives</td>
<td>-2</td>
</tr>
</tbody>
</table>

Low risk of recurrence when the score is less than 1

Annualized recurrence risk:
- 3.1% in patient score ≤1
- 6.4% in patients score 2
- 12.3% in patients score ≥3
Patients with recurrent or unprovoked IFDVT should have at least 6 months of anticoagulation and be considered for indefinite anticoagulation with periodic reassessment of the risks and benefits of continued anticoagulation (Class I; Level of Evidence A).
Duration of Anticoagulant Therapy after a First Episode of an Unprovoked PE or DVT

Guidance from the SCC of the ISTH

• It is **not possible** to give a definite guidance statement as to which patient should or should not receive long-term anticoagulant therapy after an episode of an unprovoked PE or DVT.
2014 ESC Guidelines on the diagnosis and management of acute pulmonary embolism

The Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC)

Extended oral anticoagulation should be considered for patients with a first episode of unprovoked PE and low bleeding risk.

IIa  B  375
9. In patients with a first VTE that is an unprovoked proximal DVT of the leg or PE and who have a (i) low or moderate bleeding risk (see text), we suggest extended anticoagulant therapy (no scheduled stop date) over 3 months of therapy (Grade 2B), and (ii) high bleeding risk (see text), we recommend 3 months of anticoagulant therapy over extended therapy (no scheduled stop date) (Grade 1B).

Remarks: Patient sex and D-dimer level measured a month after stopping anticoagulant therapy may influence the decision to stop or extend anticoagulant therapy.
Duration of Anticoagulation - First episode of VTE treated with 3 months OAC

VTE associated with temporary risk factors
- Surgery
- Non-surgical risk factor
  - Stop anticoagulation

Cancer-associated VTE
- Complete 6 months of treatment
  - Is cancer cured? Is anti-cancer therapy completed?
    - Yes
    - No
      - Continue anticoagulation for additional 6 months

Unprovoked VTE
- Stop anticoagulation
- Risk Stratification for Recurrent VTE
  - Low recurrence risk OR high bleeding risk
  - High recurrence risk AND low bleeding risk
    - Complete 12 months of treatment

Risk Stratification for Recurrent VTE
- Estimate bleeding risk
  - Is cancer cured?
  - Is anti-cancer therapy completed?
    - Yes
    - No
      - Stop anticoagulation
Duration of Anticoagulation - Treat for 3 months and Reassess

- **Isolated DVT**
  - Stop at 3 months

- **Reversible provoking factor**
  - Stop at 3 months

- **Unprovoked proximal DVT or PE**
  - Indefinite therapy or until cancer inactive

- **Cancer**
  - Indefinite therapy

- **High bleeding risk OR prefer 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 negative**
  - Indefinite therapy

- **Second VTE**
  - Indefinite therapy

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

- **Positive D-dimer**
  - Restart therapy (Indefinite therapy)

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1. Male would stop even if recurrence risk 16% in first year
2. Female would stop even if recurrence risk 10% in first year
3. Male would stay on if recurrence risk 8% in first year
4. Female would stay on even if recurrence risk 5% in first year

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Who Should Not Receive Extended or Indefinite Therapy?

- Lower than average risk of recurrence
- High risk of bleeding
- Patient preference
Three Months of Anticoagulation is Sufficient

• Proponents of long-term anticoagulant therapy are assuming that every person who has had an idiopathic DVT or PE will have an ongoing thrombophilic tendency and therefore is highly likely to develop recurrent events once anticoagulation is discontinued.

• This is unlikely to be the case as the etiology of idiopathic VTE is likely to be diverse and the risk of recurrence is also likely to be variable.

• Indiscriminate long-term anticoagulation treatment in every such person is clearly not a logical option.
Three Months of Anticoagulation is Sufficient

- Recurrent VTE event such as a massive PE can be fatal, however, hemorrhagic complications of anticoagulation can be equally dangerous.
- A decision to continue anticoagulation therapy beyond three months should not be taken lightly.
- Long-term treatment should not be considered universally for all patients with idiopathic VTE.
Secondary Prevention of VTE
One Regimen May Not Fit All!

- Whether to consider an extended phase of anticoagulation in individual patients has become a major challenge for care providers but logically depends on the risk of VTE recurrence and bleeding.
- This decision can be further refined by patient preferences, a theoretically highly desirable criterion that, however, is often difficult to assess objectively, and by the efficacy/safety balance of available therapies.