Hypercoagulable States

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DISCLOSURES

Off-Label Usage
  • None

Interests
  • Bristol-Myers Squibb
  • Bayer
  • Instrumentation Laboratory
  • Janssen Pharmaceuticals
  • Pfizer
Agenda

- Risk Factors and Pathophysiology
- Initial Rx and Prognosis of VTE
- Acquired and inherited thrombophilias
- Duration of anticoagulation/Risk Stratification
Risk Factors for VTE

- **Transient/Provoked**
  - Surgery
  - Trauma (major trauma or lower-extremity injury)
  - Acute medical illness
  - Immobilization
  - Estrogen-containing contraceptives or hormone replacement therapy
  - Pregnancy/puerperium
  - Central venous catheters
  - Prolonged air travel (operationally manage as idiopathic)

- **Persistent**
  - Obesity
  - Chronic Medical Illnesses
    - Cancer and its therapy
    - Inflammatory bowel disease
    - Nephrotic syndrome
    - Myeloproliferative neoplasms/PNH
  - Paralysis

- **Idiopathic/Unprovoked**
VTE Risk Factor Model

Genes

- Anticoagulant deficiencies
  - Antithrombin 20-fold $\uparrow$ RR
  - Protein S 10-fold $\uparrow$
  - Protein C 10-fold $\uparrow$
- Prothrombin 3-fold $\uparrow$
- Factor V Leiden 3-8 fold $\uparrow$

Acquired Risk Factors

- Age
- Previous VTE
- Cancer
- Obesity

Intrinsic Thrombosis Risk

Triggering Factors

- Estrogens
- Pregnancy
- Surgery
- Immobilization

Prophylaxis

Thrombosis Threshold

VTE

Adapted from Folsom A
Activated Protein C
Mechanism of Action

Thrombomodulin  EPCR  APC

Thrombin  PC

PS  Va  VIIIa  PAR-1

Anticoagulant  Anti-inflammatory

Adapted from Weiler H

Factor V Leiden (Arg506Gln)

→  Va resistant to inactivation by APC
Prothrombin Gene Mutation
G $\rightarrow$ A Mutation at Position 20210 in 3´- UT Region

<table>
<thead>
<tr>
<th>GENOTYPE</th>
<th>PROTHROMBIN</th>
<th>RANGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>20210 AG</td>
<td>132%</td>
<td>95-178</td>
</tr>
<tr>
<td>20210 GG</td>
<td>105%</td>
<td>55-156</td>
</tr>
</tbody>
</table>

From Poort et al, Blood 1996

Mutation leads to increased efficiency of prothrombin mRNA 3´-end formation and increased prothrombin biosynthesis without affecting the rate of transcription.
Agenda

- Risk Factors and Pathophysiology
- Initial Rx and Prognosis of VTE
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Initial Treatment of DVT/PE

- Two drug approach
  - Unfractionated (IV with PTT monitoring) or Low Molecular Weight Heparin or Fondaparinux (SC without coagulation monitoring) overlapping with warfarin for at least 5 days until INR >2 for 1-2 days

- Warfarin
  - Start on day 1 to achieve INR of 2-3, treat for 3-6 months
  - Clinical utility of pharmacogenomic testing for 2Cy9 and VKORC1 polymorphisms not established

- Dabigatran (no laboratory monitoring required)

- Oral factor Xa inhibition (“one drug approach”)
  - No laboratory monitoring required

- Dabigatran and rivaroxaban not indicated for VTE treatment if creatinine clearance <30 mL/ min (different from a fib)
Approaches to VTE treatment

**‘SINGLE DRUG APPROACH’**
DOSE INTENSIFICATION DURING “INITIAL RX”
3 WEEKS OF “INITIAL RX” WITH RIVAROXABAN

* Or UFH or Fondaparinux
** Not FDA Approved
Question: Now that NOACS are approved for the treatment of VTE, when should we use them? Wouldn’t use (or be cautious) in:

- Cancer-associated VTE or pregnancy-associated VTE
- Massive PE (hemodynamically unstable) or DVT (phlegmasia cerulea dolens) where thrombolysis is a consideration
- Obese or very obese patients (? weight > 250 or 300 lbs)
- Very frail patients (? weight < 110 lbs)
- Renal dysfunction (creatinine clearance <30 mL/min and use caution if creatinine clearance 30-40 mL/min)
- Don’t use in patients on medications with major interactions
- Be cautious in "difficult" patients (recurrent DVT or PE on established therapies such as warfarin or LMWH)

➤ Important to ensure that patients will comply with therapy and can acquire medication (reimbursement issues)
Risk of recurrent VTE after discontinuing anticoagulation in a cohort of 1626 patients

Prandoni P et al, Haematologica 2007

10% per year

3% per year

Idiopathic

Secondary
VTE rates after different durations of anticoagulation for unprovoked VTE

![Graph showing recurrence of VTE per year (%) against months of anticoagulation. The graph includes data from various studies such as BTS, DURAC 1, LAFIT, Pin, Prandoni, WODIT 1, WODIT 2, and DOTAVK. The x-axis represents months of anticoagulation, while the y-axis shows recurrence of VTE per year (%).]
Duration of anticoagulant treatment

Summary

- 3 months is equivalent to 6 months
- Extending anticoagulant treatment is highly effective (>90% relative risk reduction), but only as long as treatment is continued and is associated with more bleeds.
- Recurrence risk is highest during the two first years.
- Unprovoked DVT/PE is associated with a significantly higher risk of recurrence after discontinuation of anticoagulants.
Agenda

- Risk Factors and Pathophysiology
- Initial Rx and Prognosis of VTE
- **Acquired and inherited thrombophilias**
- Duration of anticoagulation/Risk Stratification
Lowering homocysteine levels with B-vitamins does not lower risk of recurrent thrombosis

- **Arterial Thrombosis**
  - NORVIT Trial (N Eng J Med 2006)
    - 3,479 patients with acute MI
    - Trend toward increased risk with combined B vitamin treatment
  - HOPE 2 Investigators (N Eng J Med 2006)
    - 5,522 patients > age 55 with vascular disease or diabetes

- **Venous Thrombosis**
  - HOPE 2 Investigators (Ann Int Med 2007)
  - VITRO Study (Blood 2007)
    - Patients ages 20-80 with unprovoked proximal DVT or PE
    - Recurrences: 43/348 vitamins, 50/353 placebo

⇒ No reason to measure homocysteine levels
⇒ Never test for MTHFR polymorphisms (C677T, A1298C)
Antiphospholipid Antibody Syndrome (APLS) Criteria

Updated Sapporo Criteria for APS (2006):

• Clinical criteria:
  – Vascular thrombosis
  – Pregnancy morbidity
  – Clinical manifestations include immune thrombocytopenia and livedo reticularis

• Laboratory criteria*:
  – Lupus Anticoagulant
  – Elevated cardiolipin antibody levels (IgG or IgM) (high titer: >40 GPL/MPL or >99th percentile)
  – $\beta_2$-glycoprotein I antibodies (IgG or IgM) (>99th percentile)

*2 or more occasions, >12 wks apart.

Antiphospholipid antibody Syndrome

APLS is associated with SLE, cancer, infections, drugs; often idiopathic
Antiphospholipid Antibody Syndrome (APLS)

- LA result from the presence of immunoglobulins which bind to phospholipids and plasma proteins ($\beta_2$-glycoprotein 1, prothrombin) in vitro and prolong clotting times (critically dependent on the amount of phospholipid in assay). LA do not cause bleeding.

- 1st unprovoked venous/arterial thrombotic event in association with persistent LA $\Rightarrow$ high risk for recurrent thrombosis $\Rightarrow$ long-term anticoagulation indicated

- Two randomized trials have shown that an INR of 2-3 is adequate in patients with venous thrombosis and APLS.
Venous Thromboembolism in Cancer

- Common (~20% of all patients with VTE)
- Increased risk of recurrent VTE
  - Can occur with an adequate INR (“warfarin failure”)
- Increased risk of bleeding during anticoagulant therapy
- Rx: Consider chronic low molecular weight heparin in lieu of warfarin
CLOT in Cancer Trial

- Multicenter, randomized, open-label study

Initial Rx 6 months

Cancer patients with proximal DVT, PE or both

R
dalteparin — OAC
dalteparin — dalteparin

Lee A. New Eng J Med 2003
Recurrent VTE

Risk reduction = 52%
p-value = 0.0017

Days Post Randomization

Probability of Recurrent VTE, %

OAC
dalteparin

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Rivaroxaban</th>
<th>Enoxaparin/VKA</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>%</td>
<td>n/N</td>
</tr>
<tr>
<td>Recurrent VTE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>16/316</td>
<td>5.1</td>
<td>20/281</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No cancer</td>
<td>70/3834</td>
<td>1.8</td>
<td>75/3850</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major bleeding</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>9/316</td>
<td>2.8</td>
<td>14/278</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No cancer</td>
<td>31/3820</td>
<td>0.8</td>
<td>58/3832</td>
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Different cancer population than the CLOT Trial
(~2-fold higher recurrence rate on warfarin)
Available data do not support an extensive search for occult malignancy; it is however important to pursue symptoms or signs which suggest an underlying malignancy and to ensure that age-appropriate screening tests have been performed.
# Sites of Thrombosis

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Arterial</th>
<th>Venous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor V Leiden</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Prothrombin 20210A</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>AT Deficiency</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Protein C Deficiency</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Protein S Deficiency</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Lupus Anticoagulant</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>
Prevalence of Defects in Caucasian Patients with Venous Thrombosis

Factor V Leiden (FVL)  
40%  

Prothrombin Gene Mutation (PGM)  
6-18%  

Deficiencies of AT, Protein C, Protein S  
5-15%  

Antiphospholipid Antibody Syndrome  
~5%  

Unknown  
20-70%  

Several new variants have been found by candidate and genome-wide screens - all common and weak (OR < 1.5) (Smith NL, JAMA 2007; Bezemer ID, JAMA 2008; Li Y, JTH 2009)

Genetic risk score based on 5 most strongly associated SNPs (FVL, PGM, ABO blood group, 1 SNP in fibrinogen γ gene and 1 in factor XI gene) performed similarly to one based on 31 SNPs (de Haan, Blood 2012)
Hereditary Thrombophilia and Obstetric Complications

- Significantly increased risk for second and third trimester fetal loss (~3-fold ↑)
- No association with preeclampsia, IUGR
- ? Role of LMWH to prevent recurrent fetal loss
  - One positive trial in thrombophilic women
  - Two negative trials in women with recurrent losses before 20 weeks (Kaandorp SP, N Eng J Med 2010; Clark P, Blood 2010)
The “Hypercoagulable Workup”

- Genetic test for Factor V Leiden mutation
- Genetic test for Prothrombin G20210A mutation
- Functional assay of Antithrombin
- Functional assay of Protein C
- Functional assay of Protein S
  - Free Protein S Antigen
  - Total Protein S Antigen

- Tests for Antiphospholipid Antibody Syndrome
  - Lupus anticoagulant
  - Cardiolipin/β2-glycoprotein I antibodies
<table>
<thead>
<tr>
<th>TYPE</th>
<th>ANTIGEN</th>
<th>ACTIVITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>II</td>
<td>Normal</td>
<td>Low</td>
</tr>
</tbody>
</table>

Protein S levels and the risk of venous thrombosis: results from the Mega Study - a population-based case-control study (Blood 2013)

N=5,317, protein S deficient if protein S level < 2.5 th percentile of controls

- Total protein S < 68 U/dL (Odds ratio 0.90, 95 th CI 0.62-1.31)
- Free protein S < 53 U/dL (Odds ratio 0.82, 95 th CI 0.56-1.21)

Using a lower cut-off for free protein S (<0.10 th percentile):

- Free protein S < 33 U/dL (OR 5.4, 95 th CI 0.61-48.8)

Conclusion: Low protein S levels were not associated with VTE in this study. In the absence of a family history, hereditary protein S deficiency as a risk factor for VTE is rare.
Acquired Deficiencies in Antithrombin, Protein C, or Protein S

<table>
<thead>
<tr>
<th>ANTITHROMBIN</th>
<th>PROTEIN C</th>
<th>PROTEIN S</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy</td>
<td></td>
<td>Pregnancy</td>
</tr>
<tr>
<td>Liver Disease</td>
<td>Liver Disease</td>
<td>Liver Disease</td>
</tr>
<tr>
<td>DIC</td>
<td>DIC</td>
<td>DIC</td>
</tr>
<tr>
<td>Nephrotic syndrome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major surgery</td>
<td></td>
<td>Inflammation</td>
</tr>
<tr>
<td>Acute thrombosis</td>
<td>Acute thrombosis</td>
<td>Acute thrombosis</td>
</tr>
</tbody>
</table>

Treatment with:
- Heparin
- Warfarin
- Estrogens

Caveats:
1. Don’t draw these tests when patients present with VTE or are receiving anticoagulants.
2. Abnormal results drawn at presentation with VTE must be confirmed. Draw protein C and S after discontinuing warfarin for a minimum of 1 week.
Risk of Recurrent Venous Thrombosis in Patients with Inherited Thrombophilia

- Heterozygosity for Factor V Leiden (FVL) or Prothrombin G20210A do not substantially increase recurrence risk.

- A retrospective study found that the recurrence risk is not significantly higher in homozygotes with FVL and heterozygotes with both FVL and PT G20210A (Lijfering WM, Circulation 2010).

- Presence of high-risk thrombophilia increases recurrence risk
  - Antiphospholipid Antibody Syndrome
  - Antithrombin deficiency
  - Protein C or Protein S deficiency
What do the ACCP guidelines say about the presence of hereditary thrombophilia with respect to the duration of anticoagulation?

_Chest 2008; 133: 454S-545S_

The presence of hereditary thrombophilia has **not** been used as a major factor to guide duration of anticoagulation for VTE in these guidelines because evidence from prospective studies suggests that these factors are not major determinants of the risk of recurrence.
Agenda

- Risk Factors and Pathophysiology
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- Duration of anticoagulation/ Risk Stratification
Who Should Be Tested?

General population
Any patient with VTE
Any patient with spontaneous VTE
Younger patient with VTE
Younger patient with VTE + family history
Nobody

Liberal
Conservative
Testing for Hereditary Defects in Patients with Thrombosis and No Family History

**PRO**
- Improve understanding of pathogenesis of VTE
- Identify and counsel affected family members

**CON**
- Infrequently identify patients in whom the identification of an abnormality should alter their management
- No evidence of “direct particular benefit to family members” (because of low absolute risk of an initial VTE)
- Potential for overaggressive management of propositus and asymptomatic affected relatives (if screening undertaken)
- Cost of testing/consultations
- Create undue anxiety
  - (Negative insurance implications)
Who should be tested for hereditary thrombophilia?

Yes
VTE at age <50 with positive family history (1st degree relatives)
Cerebral venous thrombosis
Portal/ mesenteric vein thrombosis (r/ o MPD, PNH)

Reasonable
VTE in association with OCPs/ HRT or pregnancy
Pregnancy loss (2nd and 3rd trimester)

No
Patients > 50 with first spontaneous VTE
VTE in patients with active cancer
Elderly patients with postoperative VTE
Retinal vein thrombosis
Arterial thrombosis (save for true paradoxical emboli)
Asymptomatic patients with no personal or familial hx of VTE
Women going on OCPs with no familial hx of VTE
Agenda

- Risk Factors and Pathophysiology
- Initial Rx and Prognosis of VTE
- Acquired and inherited thrombophilias
- Duration of anticoagulation/ Risk Stratification
<table>
<thead>
<tr>
<th>Indication</th>
<th>Duration of Anticoagulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proximal DVT/ PE secondary to a transient risk factor</td>
<td>3 months</td>
</tr>
<tr>
<td>1st isolated, unprovoked distal DVT</td>
<td></td>
</tr>
<tr>
<td>Idiopathic proximal DVT or PE</td>
<td>3-6 months</td>
</tr>
<tr>
<td>2nd Unprovoked DVT or PE</td>
<td></td>
</tr>
<tr>
<td>VTE in setting of active cancer: LMWH for at least 3 months</td>
<td>Long-term</td>
</tr>
</tbody>
</table>
Duration of anticoagulant treatment
What do the ACCP guidelines say?

- **2008** We recommend that patients with a first idiopathic VTE be evaluated for long-term treatment. If no contra-indication, we recommend long-term treatment (Grade 1A).
  - Values and preferences: This recommendation attaches a relatively high value to prevention of recurrent VTE and a lower value to the burden of long-term anticoagulant therapy.

- **2012** In patients with a first VTE that is an unprovoked proximal DVT of the leg and who have a low or moderate bleeding risk, we suggest extended anticoagulant therapy over 3 months of therapy (Grade 2B).
Extension of anticoagulant treatment beyond 3 to 6 months

- **Recurrent VTE**
  - Risk (%/year) ~ 8%
  - Case Fatality Rate (4-12%) 0.3-1%

- **Bleeding**
  - Risk (%/year) ~ 2-6%
  - Case Fatality Rate (10%) 0.2-0.6%

**NO MORTALITY BENEFIT FROM LONG-TERM ANTI COAGULATION**

⇒ A recurrent VTE rate of <5% per year is considered "acceptable" (risk of anticoagulation > benefit).

*Douketis JD et al. Ann Intern Med 2007;147:766-774*
Extending anticoagulant treatment beyond 3-6 months in patients with unprovoked VTE

**Consider**

- **Recurrence risk**
  Unprovoked, D-dimer

- **Alternatives**
  Low-intensity INR, Rivaroxaban, aspirin

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

- **Patient preferences and values**
  (includes lifestyle and occupation)
Duration of anticoagulant treatment
Additional determinants of the risk of recurrence

Other elements that increase the risk of recurrence after stopping anticoagulant treatment include:

• Persistently elevated D-dimer levels off anticoagulants
• Male gender
• Residual thrombus on ultrasound (conflicting data difficult to standardize)

Clinical Prediction Models

• Vienna Prediction Model (gender, type of VTE, D-dimer on VKA)
• HERDOO (Hyperpigmentation, edema/leg redness, D-dimer, BMI, patient age)
• DASH (D-dimer post-VKA, age, gender, hormonal therapy)
D-Dimer As A Predictor of Recurrence Following a First Unprovoked VTE

D-dimer for VTE: Risk Stratification

<table>
<thead>
<tr>
<th>Palareti 2006 (Simplify)</th>
<th>Negative (&lt;500 ng/mL)</th>
<th>Positive (&gt;500 ng/mL)</th>
<th>HR 2.49 (95% CI, 1.35-4.59)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.4% per year</td>
<td>10.9% per year</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

D-Dimer < 500 ng/mL

<table>
<thead>
<tr>
<th>Sex</th>
<th>Age &lt; 65</th>
<th>Age &gt; 65</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>0.4% per year</td>
<td>6.6% per year</td>
</tr>
<tr>
<td>Male</td>
<td>5.1% per year</td>
<td>8.1% per year</td>
</tr>
</tbody>
</table>

D-Dimer for VTE Risk Stratification

1) Must use a quantitative D-dimer assay which has been studied (there is no D-dimer standard)

2) Separation between high and low risk groups using D-dimer alone < 2.5 fold

3) Only useful in patients with a 1st unprovoked VTE (OCP-related events included)

4) Kearon C, ISTH 2013: D-dimer to select patients with a first unprovoked VTE who have anticoagulants stopped at 3-7 months: a multicentre management study (D-Dimer Optimal Duration Study). 410 patients enrolled, mean age 51. 319 patients had a negative D-dimer on warfarin and then off warfarin 4 weeks later.

<table>
<thead>
<tr>
<th></th>
<th>Recurrent VTE</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entire Cohort (n=319)</td>
<td>6.7% per year</td>
<td>4.8-9.0</td>
</tr>
<tr>
<td>Men (n=179)</td>
<td>9.7% per year</td>
<td>6.7-13.7</td>
</tr>
<tr>
<td>Women (no estrogens=81)</td>
<td>5.4% per year</td>
<td>2.5-10.2</td>
</tr>
<tr>
<td>Women (estrogens=58)</td>
<td>0% per year</td>
<td>0.0-3.0</td>
</tr>
</tbody>
</table>
Kaplan–Meier:
Non-fatal and fatal VTE

Cumulative event rate (%)

Months

Placebo
Apixaban 2.5 mg
Apixaban 5 mg

No. at risk
Apixaban 2.5 mg 840 836 825 818 533
Apixaban 5 mg 813 807 799 791 513
Placebo 826 796 768 743 471

*
Other Considerations in Deciding on Long-Term Oral Anticoagulation

- **Site of thrombosis**
  - PE more likely to recur as PE, DVT as DVT

- **Severity of Thrombosis**
  - Massive PE
  - Ilio-femoral DVT
  - Severe post-phlebitic syndrome

- **Age of patient**
  - Prefer not to commit young patients to lifelong anticoagulation after a 1st event unless clearly very high risk for recurrence

- **IVC filters (>75% of retrievable filters never retrieved)**
  - ↑ risk of recurrent DVT especially if VTE unprovoked