The Role of Thrombophilia Testing. Recent Discoveries and a Rational Approach to the Evaluation for Thrombophilia.

Richard H. White, MD
Director, Anticoagulation Service
UC Davis
Residents Think Finding a Thrombophilic Disorder is “Cool Stuff”

- Doctors love ordering tests to look for underlying disorders that may explain why a patient gets a disease.
An inherited or acquired condition that increases the risk of developing first-time (incident) deep-venous thrombosis or pulmonary embolism.
**What Are The Known 'Thrombophilic' Disorders**

- Factor V Leiden (FVL)
- Resistance to activated Protein C *(without F-V Leiden)*
- F-II mutation or “Prothrombin 20210A gene mutation”
- Protein C deficiency *(low or dysfunctional)*
- Protein S deficiency *(low or dysfunctional)*
- Anti-thrombin (AT) deficiency *(low or dysfunctional)*
- High levels of VIIIc
- High homocysteine levels *(? MTHFR C677T mutation)*
- Lupus Anticoagulant- Anti-phospholipid Ab syndrome
Hematological Risk Factors for Venous Thrombosis Among Patients With VTE

- APL Synd: ~8%
- Homocystenemia: ~10%
- AT Defic.: 2%
- Prot. S. Defic.: ~3%
- FVL 1

- F-II Mutation: 8%
- No Defect Found (majority)
- High VIII levels: ~8%
- Protein C Def.: ~3-4%
- AT Defic.: 2%
- APC-Resistance: ~5%
- FV Leiden: 10-20%
There are **MANY** Other Risk Factors for VTE

- Active cancer, esp. rapidly growing adenocarcinomas
- OCPs, Prem-Pro use in women with FVL, Factor II mutation
- Provoking risk factors (trauma, surgery, pregnancy)
- Obesity (BMI>30)
- Specific diseases (Lupus, IBD, hyperosmolar state, sepsis)
- Immobility-paralysis
- Venous insufficiency, varicosities
- Perhaps advancing age
- Low aPTT value (lowest quartile)
- Combinations of factors are **strongly** associated with VTE
So What Are The Key Questions We Ask That Might Prompt a Thrombophilia Work-Up?

- Should this patient be on life-long warfarin therapy? (Dr. Tracy Minichiello to discuss the initial duration)

  or, What is the relative risk of a recurrent clot (especially fatal PE) versus major bleeding (e.g., intracerebral hemorrhage)

- How intensely should I treat this patient? INR 2.5-3.5?

- Should this patient receive more aggressive heparin prophylaxis at the time of a procedure?

- Should this patient ever be placed on OCPs?
Why Test for a Thrombophilic Disorder?

Golden Rule of Test Ordering
If the test does not change your management of the patient, do not order it!

Commonly encountered practice rationales
- The tests are available, so I like to order them.
- If the patient has thrombophilia they should be Rx’d for life.
- If the patient has thrombophilia they need heparin prophylaxis for high risk situations.
- The patient’s family should be screened if thrombophilia +.
- You have to find patients with the APS syndrome.
A Nitty-Gritty Case Illustration

- #1 - 32 year old male develops idiopathic VTE, + FH, tests POSITIVE for a thrombophilic disorder.
- #2 - 32 year old male develops idiopathic VTE, + FH, but tests NEGATIVE for known thrombophilic disorder.

Do you treat them the same?

There is **no** evidence that having a single inherited thrombophilic disorder affects the long-term risk of VTE.

In general: **Phenotype Trumps Genotype**
Thrombophilia Testing


- “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”.

- 474 consecutive patients aged 18 to 70 years without a known malignancy treated for a first objectively confirmed thrombotic event at anticoagulation clinics in the Netherlands; F/U = 7.3 (± 2.7) years and complete follow-up was achieved in 447 (94%). 90 VTE events (19%) occurred.
Cumulative Incidence of Recurrent Thrombotic Events

Recurrence Rate for Number of Prothrombotic Laboratory Abnormalities in 474 Patients

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>None</th>
<th>1</th>
<th>&gt;1</th>
<th>Any</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence</td>
<td>22 (14-32)</td>
<td>25 (17-37)</td>
<td>30 (21-42)</td>
<td>28 (22-36)</td>
</tr>
<tr>
<td>Rate (95% CI)*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hazard ratio (95% CI)†</td>
<td>Referrent</td>
<td>1.2 (0.7-2.0)</td>
<td>1.4 (0.8-2.3)</td>
<td>1.3 (0.8-2.0)</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)‡</td>
<td>Referrent</td>
<td>1.2 (0.7-2.1)</td>
<td>1.6 (1.0-2.7)</td>
<td>1.4 (0.9-2.2)</td>
</tr>
</tbody>
</table>

Abbreviation: CI, confidence interval.
*Per 1000 patient-years.
†Relative to those without an abnormality (crude ratio).
‡Relative to those without an abnormality and adjusted for age, sex, and anticoagulation as a time-dependent covariate.

### Table 4. Recurrence Rates for Prothrombotic Laboratory Abnormalities in 474 Patients

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>No. of Recurrences</th>
<th>Incidence Rate (95% CI)*</th>
<th>Hazard Ratio (95% CI)†</th>
<th>Hazard Ratio (95% CI)‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor V Leiden</td>
<td>20</td>
<td>30 (18-46)</td>
<td>1.2 (0.7-1.9)</td>
<td>1.3 (0.8-2.1)</td>
</tr>
<tr>
<td>Prothrombin G20210A</td>
<td>4</td>
<td>19 (5-48)</td>
<td>0.7 (0.3-2.0)</td>
<td>0.7 (0.3-2.0)</td>
</tr>
<tr>
<td>Anticoagulant deficiency§</td>
<td></td>
<td></td>
<td>8</td>
<td>45 (19-88)</td>
</tr>
<tr>
<td>High factor¶</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VIII (&gt;166 IU/dL)</td>
<td>23</td>
<td>29 (18-43)</td>
<td>1.1 (0.7-1.8)</td>
<td>1.3 (0.8-2.1)</td>
</tr>
<tr>
<td>IX (&gt;129 U/dL)</td>
<td>13</td>
<td>21 (11-36)</td>
<td>0.9 (0.5-1.7)</td>
<td>1.2 (0.6-2.1)</td>
</tr>
<tr>
<td>XI (&gt;121 U/dL)</td>
<td>11</td>
<td>16 (8-29)</td>
<td>0.6 (0.3-1.1)</td>
<td>0.6 (0.3-1.1)</td>
</tr>
<tr>
<td>Hyperfibrinogenemia∥</td>
<td>22</td>
<td>38 (24-58)</td>
<td>1.6 (1.0-2.6)</td>
<td>1.7 (1.1-2.8)</td>
</tr>
<tr>
<td>Hyperhomocysteinemia#</td>
<td>14</td>
<td>23 (13-39)</td>
<td>0.9 (0.5-1.6)</td>
<td>0.9 (0.5-1.6)</td>
</tr>
</tbody>
</table>

Abbreviation: CI, confidence interval.

*Per 1000 patient-years.

†Relative to those without the abnormality (crude ratio).

‡Relative to those without the abnormality and adjusted for age, sex, and anticoagulation as a time-dependent covariate.

§Deficiency of protein C, protein S, or antithrombin.

∥Cut-off points: protein C: <0.67 (0.33) IU/mL; protein S: <0.67 (0.33) IU/mL; antithrombin: <0.80 U/mL; fibrinogen: >4.1 g/L.

¶Cut-off points are in parentheses.

#Cut-off points: homocysteine: >16.7 µmol/L (Leiden); 19.8 µmol/L (Amsterdam); 20.3 µmol/L (Rotterdam).


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Baglin et al
Why We Should NOT Test for Thrombophilic Disorders!

a) A positive result rarely changes our management.
b) Values may be spurious (esp. functional assays)
c) Tests often misinterpreted (esp. ACL levels, Protein C & S)
d) May create angst in the patient ("I’m defective")
e) Medical Hx & family Hx tell us more than lab testing.
f) Absence of a defect does not ensure absence of disease!

NOTE: ~10% of Caucasians have FVL or FII
Stand up if you want to be tested right now!
Why **We Should** Test for Thrombophilic Disorders.

We need to find some very specific conditions that are associated with a high rate of recurrent VTE

1) Anti-Thrombin deficiency (0.1% of population)
2) Anti-phospholipid Antibody Syndrome (APS)
3) Patients with two or more inherited defects
   e.g. homozygous Factor V Leiden

[However, there is no hard evidence to support life-long Treatment of patients with 2 defects who develop VTE]
What We REALLY Need: A Prediction Rule for Recurrent VTE and PE!

- CANDIDATES (after unprovoked or idiopathic VTE)
  - Gender (recurrence higher in men)
  - D-dimer one month after 3-6 Mo. Rx with warfarin
  - Family history
  - Amount of residual clot on US
  - Post-phlebitic symptoms or skin changes
  - Presence of a specific thrombophilic disorder(s)
  - Obesity, immobility
  - Co-morbidity (number and/or severity)
  - Incident PE versus incident DVT
Returning Other Questions We Asked:

- How intensely should I treat this patient?
  SAME AS PATIENTS WITHOUT THROMBOPHILIA, EVEN THOSE WITH APS, THE TARGET is INR = 2.0-3.0.

- Should a patient with a thrombophilic disorder receive more aggressive heparin prophylaxis?
  NO EVIDENCE AMONG CASES WITH NO PRECEDING VTE.

- Should this patient be placed on OCPs?
  REASONABLE QUESTION, PARTICULARLY IF A PARENT HAD A VTE, ...BUT THERE IS LITTLE DATA.
My Recommendations:

- Careful history: Was it provoked?, and Is there any family history?

- Test for AT deficiency and APS (Lupus anticoagulant test and beta-2-glycoprotein I after 6 months Rx) repeat in 6-8 weeks if +. They appear to have a higher incidence of recurrent VTE.
Duration of Anticoagulation for Venous Thromboembolism

Tracy Minichiello, M.D.
Assistant Professor of Medicine
Director, UCSF Anticoagulation Service
Department of Medicine
University of California, San Francisco
Determine Duration of Anticoagulation for VTE

- Clinical scenario/patient risk factors
- Thrombophilia work up
- Residual vein thrombosis on ultrasound
- D-dimer testing
Determine Duration of Anticoagulation for VTE

Risk of bleeding if anticoagulation continued
Case fatality rate 0.3%/yr

Risk of clotting if anticoagulation discontinued
Case fatality 5% (DVT) - 25% (PE)

Keeling, D. Blood Reviews 2006.20:173
Recurrence of VTE According to Duration of AC

Streiff, Am J Hematol. 81:684
Provoked VTE

- Provoked
  - Major risk factors: major surgery, major trauma, cancer
  - Minor risk factors: OCP, HRT, pregnancy, airline travel, non-major surgery, minor trauma
  - Associated medical diseases- IBD, nephrotic syndrome, cancer, sickle cell, multiple myeloma, Waldentrom’s, MGUS, PNH, Bechets, MDS, P.Vera, ET
## Risk of VTE After Cessation of Therapy

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>RR recurrence</th>
<th>Risk Factor</th>
<th>RR recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temporary risk factor</td>
<td>0.3-0.6</td>
<td>Cancer</td>
<td>3.0</td>
</tr>
<tr>
<td>Calf vein</td>
<td>0.5-0.75</td>
<td>History of VTE</td>
<td>1.5-&gt;2.0</td>
</tr>
<tr>
<td>DC estrogen</td>
<td>&lt; 1</td>
<td>Thrombophilia</td>
<td>1.0-5.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Unprovoked</td>
<td>&gt;2.0</td>
</tr>
</tbody>
</table>
## Risk of VTE Recurrence After Cessation of VTE

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>1st yr</th>
<th>Next 5 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distal DVT</td>
<td>3% (6%)</td>
<td>&lt;10%</td>
</tr>
<tr>
<td>Major-transient</td>
<td>3%</td>
<td>10%</td>
</tr>
<tr>
<td>Minor-transient</td>
<td>5-6%</td>
<td>15%</td>
</tr>
<tr>
<td>Unprovoked</td>
<td>At least 10%</td>
<td>30%</td>
</tr>
<tr>
<td>Recurrent</td>
<td>&gt; 10%</td>
<td>&gt; 30%</td>
</tr>
</tbody>
</table>

Kearon, ASH Dec 2004
# Recurrence Risk and Thrombophilia

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>RR recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVL/PTG (hetero)</td>
<td>1-2.0</td>
</tr>
<tr>
<td>Protein C, S, AT</td>
<td>1-3</td>
</tr>
<tr>
<td>Homozygous FVL or FVL &amp; PTG</td>
<td>2-5</td>
</tr>
<tr>
<td>Elevated factor VIII (&gt; 200)</td>
<td>6</td>
</tr>
<tr>
<td>Homocysteine</td>
<td>2.7</td>
</tr>
<tr>
<td>APLA</td>
<td>2-4</td>
</tr>
</tbody>
</table>

Kearon, ASH Dec 2004
### Duration of Anticoagulation

<table>
<thead>
<tr>
<th>VTE event</th>
<th>Duration of Anticoagulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distal provoked</td>
<td>3 months</td>
</tr>
<tr>
<td>Distal unprovoked</td>
<td>6 months</td>
</tr>
<tr>
<td>Mildly provoked</td>
<td>6 months</td>
</tr>
<tr>
<td>Unprovoked</td>
<td>Minimum 6-12 months <strong>consider indefinite tx</strong></td>
</tr>
</tbody>
</table>

*Buller et al. CHEST 2004;126:401S*
## Duration of Anticoagulation

<table>
<thead>
<tr>
<th>Cancer related</th>
<th>Indefinitely or until cancer resolved</th>
</tr>
</thead>
<tbody>
<tr>
<td>AT, protein C, S, FVL or PTG mutations, factor VIII &gt; 90(^{th}) %ile</td>
<td>6-12 months; <em>suggest indefinite if unprovoked</em></td>
</tr>
<tr>
<td>Antiphospholipid antibodies or combined defect</td>
<td>12 months, indefinite AC suggested</td>
</tr>
<tr>
<td>Recurrent VTE</td>
<td>indefinite</td>
</tr>
</tbody>
</table>

*Buller et al. CHEST 2004;126:401S*
Predictive Value of Residual Thrombosis

- Prospective cohort study 600 patients with VTE followed for 6 years; minimum course of treatment 3 months
- Analyzed in three groups
  - Thrombophilia (25%)
  - Unprovoked (40%)
  - Secondary DVT (35%)

Miller et al. Radiology Rounds MGH. May 2005
## Recurrent VTE Risk in 1st 2 years

<table>
<thead>
<tr>
<th>Subgroup (percent recurrent events)</th>
<th>Normal ultrasound annual risk</th>
<th>Residual thrombus annual risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unprovoked (16%)</td>
<td>4%</td>
<td>23%</td>
</tr>
<tr>
<td>Thrombophilia (36%)</td>
<td>10%</td>
<td>23%</td>
</tr>
<tr>
<td>Provoked (8%)</td>
<td>0%</td>
<td>7%</td>
</tr>
</tbody>
</table>

**D-dimer and Residual venous obstruction and Recurrence Risk**

<table>
<thead>
<tr>
<th></th>
<th>D-dimer &lt; 500</th>
<th>D-dimer &gt; 500</th>
</tr>
</thead>
<tbody>
<tr>
<td>Residual thrombosis</td>
<td>10.4%</td>
<td>25%</td>
</tr>
<tr>
<td>No residual thrombosis</td>
<td>5.7%</td>
<td>22%</td>
</tr>
</tbody>
</table>

*Cosmi et al Thromb Haemost 2005;94:969*
## D-Dimer and VTE Recurrence

<table>
<thead>
<tr>
<th>Study</th>
<th>D-dimer cutoff</th>
<th>High d-dimer risk</th>
<th>Low d-dimer risk</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palareti 2002</td>
<td>500ng/ml</td>
<td>HR 2.45</td>
<td></td>
<td>96%</td>
</tr>
<tr>
<td>N=396</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eichinger N=610</td>
<td>250 ng/ml</td>
<td>11.5%</td>
<td>3.7%</td>
<td></td>
</tr>
<tr>
<td>Paraleti 2003</td>
<td>500ng/ml</td>
<td>16.5% (unprovoked)</td>
<td>7.0% (unprovoked)</td>
<td>93%</td>
</tr>
<tr>
<td>N=599</td>
<td></td>
<td>27% (thrombophilia)</td>
<td>4.2% (thrombophilia)</td>
<td>95%</td>
</tr>
</tbody>
</table>

Management Trial Using D-dimer Results to Determine Duration of Anticoagulation

Table 2. Main Outcomes (Intention-to-Treat Analysis).

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Normal D-Dimer Level (N=385)</th>
<th>Abnormal D-Dimer Level without Anticoagulation (N=120)</th>
<th>Abnormal D-Dimer Level with Anticoagulation (N=103)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients (%)</td>
<td>24 (6.2)</td>
<td>18 (15.0)</td>
<td>13 (2.9)</td>
</tr>
<tr>
<td>No. of events/100 person-yr</td>
<td>4.4</td>
<td>10.9</td>
<td>2.0</td>
</tr>
<tr>
<td>Type of recurrent venous thromboembolism — no. *</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deep-vein thrombosis</td>
<td>19</td>
<td>11</td>
<td>1†</td>
</tr>
<tr>
<td>Deep-vein thrombosis with pulmonary embolism</td>
<td>3</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Isolated pulmonary embolism</td>
<td>2</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Major bleeding episode</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

Risk of Recurrent Venous Thromboembolism According to Peak Thrombin Generation

Hron, G. et al. JAMA 2006;296:397-402.

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Duration of Anticoagulation
Unprovoked VTE

Unprovoked VTE
Consider indefinite Tx if PE

D-dimer > 500
Indefinite anticoagulation

D-dimer < 500
no RVO
At least 12 months anticoagulation

Evidence of RVO
Continue anticoagulation and repeat U/S
Questions?
When VTE patients on warfarin need surgery: A minimalist or aggressive strategy?

Society of General Internal Medicine
VTE Workshop
April 26, 2007

Andrew Dunn, MD, FACP
Director, Anticoagulation Service
Director, Hospitalist Services
Division of General Medicine
Mount Sinai Medical Center
New York, NY

Amir Jaffer, MD
Associate Section Head, Hospital Medicine
Medical Director, IMPACT (Internal Medicine Preoperative Assessment Consultation and Treatment) Center and The Anticoagulation Clinic
Section of Hospital Medicine
Cleveland, OH
You are seeing in the office a 45 year-old female with a history of ulcerative colitis.

The patient had a total colectomy 2 years ago, which was complicated by a PE in the post-operative period. The patient was treated with warfarin uneventfully for 6 months. The patient subsequently developed a spontaneous DVT 8 months ago and has been on warfarin since that time.

The patient is now scheduled for an ileoanal anastamosis.
THE PATIENT

Would you recommend bridging anticoagulation?
Choose one option:

1. Full-dose pre-op and post-op bridging (UFH or LMWH)
2. Prophylaxis-dose pre-op and post-op bridging
3. Full-dose pre-op and prophylaxis-dose post-op bridging
4. Full-dose pre-op bridging and no post-op bridging
5. No bridging pre-op and prophylaxis-dose post-op
6. No bridging
Scope of the Problem

- DVT/PE
- Atrial fibrillation: 2.3 million Americans
- Mechanical heart valves
- Miscellaneous indications
Scope of the Problem

The average elderly patient undergoes (each year):

- 2 dental extractions
- Colonoscopy (1-2 polyps)
- 1 joint replacement
- Cataract surgery
Defining the Problem

FACTORS IN YOUR DECISION:

- Risk of thromboembolism off anticoagulants
- Risk of postoperative bleeding after being started on full-dose anticoagulation soon after surgery
- Consequences of thromboembolism and bleeding
- Efficacy of anticoagulation
- Cost and inconvenience
Single-arm Study of Bridging Therapy with LMWH (Dalteparin)

Prospective, cohort study
MHV or Afib
11 Centers, N=224

Perioperative Strategy:

- Day -3. Dalteparin 200 IU/kg SC QD
- Day -2. Dalteparin 200 IU/kg SC QD
- Day -1. Dalteparin 100 IU/kg SC QD (am only)
- Day 0. No LMWH. Restart warfarin at 2x usual dose
- Day 1+. Dalteparin 200 IU/kg SC QD or 5000 IU (if at “high risk” for bleeding)

LMWH d/c’d when INR ≥ 2.0

## RESULTS

Follow-up 90 days  
N=224

<table>
<thead>
<tr>
<th>Event Type</th>
<th>Count (Rate)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleed, total</td>
<td>15 (6.7)</td>
</tr>
<tr>
<td>Intraop – 6h post-op</td>
<td>8 (3.6)</td>
</tr>
<tr>
<td>6h - 14d post-op</td>
<td>5 (2.2)</td>
</tr>
<tr>
<td>&gt;14d post-op</td>
<td>2 (0.9)</td>
</tr>
<tr>
<td>DVT</td>
<td>1</td>
</tr>
<tr>
<td>MI</td>
<td>5</td>
</tr>
<tr>
<td>CVA/TIA</td>
<td>2 (0.9)</td>
</tr>
<tr>
<td>TE, total</td>
<td>8 (3.6)</td>
</tr>
</tbody>
</table>

**Major Bleed**  
6%

**DVT**  
0.5%

260 patients with atrial fibrillation or prior VTE who require bridging

Enoxaparin 1.5 mg/k sc daily for 3 days prior to procedure and starting 12-24 hours after procedure

VTE patients, n = 96

### PROSPECT

#### Results

<table>
<thead>
<tr>
<th>Category</th>
<th>Count/Total</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>VTE</td>
<td>1/96</td>
<td>1.0%</td>
</tr>
<tr>
<td>Major Bleeding</td>
<td>9/260</td>
<td>3.5%</td>
</tr>
<tr>
<td>Invasive procedures</td>
<td>1/145</td>
<td>1%</td>
</tr>
<tr>
<td>Minor surgery</td>
<td>0/68</td>
<td>0%</td>
</tr>
<tr>
<td>Major surgery</td>
<td>8/40</td>
<td>20%</td>
</tr>
</tbody>
</table>
WHETHER TO BRIDGE
Decision-analysis

60 year-old hypertensive individual with AVR undergoing major abdominal surgery.

Baseline assumptions:

Annual stroke rate off ac 4%
Anticoagulation efficacy 75%
Increase in major bleed by ac 3%
Postop major bleed mortality 3%

Stroke consequences and utilities

<table>
<thead>
<tr>
<th>Level</th>
<th>Probability</th>
<th>Utility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>21%,</td>
<td>0.76</td>
</tr>
<tr>
<td>Moderate</td>
<td>9%,</td>
<td>0.39</td>
</tr>
<tr>
<td>Severe</td>
<td>40%,</td>
<td>0.07</td>
</tr>
<tr>
<td>Fatal</td>
<td>30%</td>
<td>0.0</td>
</tr>
</tbody>
</table>

WHETHER TO BRIDGE
Decision-analysis

60 year-old hypertensive individual with AVR undergoing major abdominal surgery.

RESULT: NO BENEFIT FROM BRIDGING

Sensitivity analyses: The minimalist strategy is preferred when the increase in postoperative major bleeding induced by heparin is $\geq 2.1\%$. 
Back to our patient....

45 year-old female with a history of ulcerative colitis, PE 2 years ago and DVT 8 months ago. Scheduled for an ileoanal anastamosis.

Risk of VTE, without ac:

- Annual: 10-15%
- Daily: 0.04%
- Over 1 week: 0.29%

Increased up to 100-fold due to hypercoagulable state

Increased risk of major postop bleeding, with full-dose bridging ac:

- HIGH, possibly as high as 20%
- BEST GUESS: 5-10%
EFFICACY OF ANTICOAGULATION

Prophylaxis-dose: ESTIMATE: 66-75% effective

Treatment-dose: ESTIMATE: 80-90% effective
GUIDELINES / REVIEWS

ACCP

**Low-risk:** consider post-operative low-dose UFH or LMWH  
(example: no VTE within 3 months)

**Intermediate-risk:** bridge with low-dose UFH or LMWH before/after surgery

**High-risk:** bridge with therapeutic-dose IV UFH or LMWH  
(example: MVR)

Kearon/Hirsh

- **VTE <1 month prior to surgery:** Pre- and post-op full-dose bridging
- **VTE 1-3 months prior:** Admin only post-op full-dose bridging
- **Recurrent VTE (> 3 months prior):** Post-op proph-dose heparin/LMWH

Ansell J. *Chest.* 2004;126(3 Suppl):204S-233S.
## APPROACH

<table>
<thead>
<tr>
<th>VTE RISK</th>
<th>EXAMPLES</th>
<th>STRATEGY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk</td>
<td>1 prior VTE &gt;6 months ago</td>
<td>No bridging</td>
</tr>
<tr>
<td>Moderate risk</td>
<td>≥2 VTE or 1 VTE 3-6 months ago</td>
<td>Bridging unlikely to be beneficial for most patients, particularly for major surgery. If bridging chosen for major surgery, consider post-operative proph-dose.</td>
</tr>
<tr>
<td>High risk</td>
<td>VTE within 3 months</td>
<td>Bridge with full-dose anticoagulation. For high bleed risk procedures, careful monitoring for post-operative bleeding.</td>
</tr>
</tbody>
</table>
When VTE patients on warfarin need surgery: A minimalist or aggressive strategy?

SGIM
Toronto, April 26, 2007

Amir Jaffer, MD
Associate Professor of Medicine
Cleveland Clinic Lerner College of Medicine of Case Western Reserve University
Medical Director, The IMPACT (Internal Medicine Preoperative Assessment Consultation & Treatment) Center and The Anticoagulation Clinic
Dept. of General Internal Medicine
Cleveland Clinic
Disclosures

• Consultant
  – Sanofi-Aventis, Astra-Zeneca

• Research and Grant Support
  – Astra-Zeneca

• Speakers Bureau
  – Sanofi-Aventis, Roche Diagnostics

• Board Member
  – SPAQI, Anticoagulation Forum
The Patient

You are seeing in the office a 45 year-old female with a history of ulcerative colitis.

The patient had a total colectomy 2 years ago, which was complicated by a PE in the post-operative period. The patient was treated with warfarin uneventfully for 6 months. The patient subsequently developed a spontaneous DVT 8 months ago and has been on warfarin since that time.

The patient is now scheduled for an ileoanal anastomosis.
The Patient

Would you recommend bridging anticoagulation?

Choose one option:

1. Full-dose pre-op and post-op bridging (UFH or LMWH)
2. Prophylaxis-dose pre-op and post-op bridging
3. **Full-dose pre-op and prophylaxis-dose post-op* initially followed by escalation to full dose**
4. Full-dose pre-op bridging and no post-op bridging
5. No bridging pre-op and prophylaxis-dose post-op
6. No bridging
The Facts

• 3 Million patients on Warfarin in North America
  – 400,000 patients are assessed annually for bridging anticoagulation \(^1\)
• “..this is a management dilemma that is too important to say there is no answer…” \(^2\)

1. 2002 Heart and Stroke Statistical Update. Dallas, Tx: American Heart Association; 2001
How long before elective surgery should Warfarin be discontinued?

- INR decreases exponentially
- Wide interpatient variation
- Increased age --> slower decrease
- INR 2-3, and goal INR<1.2, hold warfarin for 4 doses
- INR 3-4, and goal INR<1.2, hold warfarin for 5 doses
- Always check INR before surgery

How should you manage our patient on warfarin undergoing an elective surgery or procedure?

1. Identify the indication for Anticoagulation
2. Quantify risk of thrombosis
   - Patient’s risk factors for thromboembolism
   - Type of Surgery/Procedure
   - Time off anticoagulation
3. Quantify the risk of bleeding
   - Bleeding from surgery/procedure
4. Weigh the consequences of
   - Thromboembolism & bleeding
5. Determine the need for bridging therapy
# Risk of Recurrent VTE after Completing Course of Anticoagulant Therapy

<table>
<thead>
<tr>
<th>Variable</th>
<th>Relative Risk</th>
<th>~Recurrence Yr 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transient risk factor</td>
<td>0.5</td>
<td>3 %</td>
</tr>
<tr>
<td>Protein C or S or Antithrombin</td>
<td>1-3</td>
<td>&lt;10%</td>
</tr>
<tr>
<td>Unprovoked VTE</td>
<td>≥ 2</td>
<td>10%</td>
</tr>
<tr>
<td>Cancer</td>
<td>3</td>
<td>20%</td>
</tr>
<tr>
<td>Antiphospholipid Ab</td>
<td>2-4</td>
<td>20%</td>
</tr>
<tr>
<td>Estrogen DC’ed</td>
<td>&lt;1</td>
<td>5%</td>
</tr>
<tr>
<td>D-Dimer elev.</td>
<td>~2</td>
<td>20%</td>
</tr>
<tr>
<td>Heterozygous FVL or G20210A</td>
<td>1-2</td>
<td>5%</td>
</tr>
<tr>
<td>Homozygous FVL</td>
<td>4.1</td>
<td>&gt;10%</td>
</tr>
</tbody>
</table>

Adapted from Kearon et al. Circulation 2004;110(I):I10-I18
Risk of VTE in Colorectal surgery

2. Gallus et al. NEJM 1973; 288:545
The Perioperative Period and Warfarin Cessation are associated with Hypercoagulability

• The surgical milieu can induce a hypercoagulable state
• The risk of VTE is 100-fold greater during the perioperative period relative to the non-operative period
  – Increased levels of plasminogen activator inhibitor-1.
• Studies demonstrate increases in factors that suggest “Rebound Hypercoagulability” may occur after discontinuation of oral anticoagulation
  – Prothrombin fragments F1+2
  – Thrombin-antithrombin (TAT) complexes
  – Fibrinopeptide A
  – D-dimer
  – Factor VIII

Grip et al. European Heart Journal 1991;1225-1233
Palareti et al. Thrombosis and Haemostasis 1994; 72:222-226
Kearon et al. NEJM 1997;336:1506-11
Consequences of Venous Thromboembolism and Bleeding

- Case-fatality rate of recurrent DVT or PE among patients presenting with PE is 26.4% \(^1\)
- 9-13\% of Major bleeding events are fatal \(^3\) but rarely result in permanent disability

Patients at Low Risk of Perioperative Thromboembolic Event
(<5%/year ATE or <2% per month risk of VTE)

- Atrial Fibrillation without risk factors
- Venous thromboembolism
  - Over 6 months ago
  - Heterozygous Factor V Leiden

Modified from Jaffer et al. CCJM 2003;70:973
Patients at Intermediate Risk of Perioperative Thromboembolic Event
(5-10%/year of ATE or 2-10%/ month risk of VTE)

- Atrial fibrillation with CHADS2 $\geq$ 3
- Cerebrovascular disease with 2 or more strokes or TIAs
- Mechanical Aortic valve
- Venous thromboembolism
  - Within the past 3-6 months
  - Idiopathic

Modified from Jaffer et al. CCJM 2003; 70:973
Patients at High Risk of Perioperative Thromboembolic Event
(>10%/year of ATE or >10%/ month risk of VTE)

- VTE or Arterial embolism in the past 3-months
- Valvular Atrial Fibrillation
- Atrial Fibrillation with history of cardioembolism
- Atrial Fibrillation plus Mechanical valve
- Mechanical heart valve with a previous embolism
- Hypercoagulable state with h/o life threatening VTE
- Mechanical valve in the Mitral Position
- Acute intracardiac thrombus visualized by Echo

Modified from Jaffer et al. CCJM 2003; 70:973
Seventh ACCP Recommendations

Management of Oral Anticoagulation during Invasive procedures (Grade 2C)

- Low Risk of Thromboembolism
  - Stop warfarin 4-days pre-op consider UFH or LMWH post-op and perhaps pre-op as well. Re-start warfarin post-op.

- Intermediate Risk of Thromboembolism
  - Stop warfarin 4-days pre-op, start prophylactic dose of UFH or LMWH pre-op and post-op. Re-start warfarin post-op.

- High risk of Thromboembolism
  - Stop warfarin 4-days pre-op, start full dose UFH or LMWH pre-op and then full-dose UFH or LMWH post-op. Re-start warfarin post-op.

Ansell et al. *Chest* 2004; 204S-233S
## Rates of thromboembolism and risk reduction with anticoagulation

<table>
<thead>
<tr>
<th>Indication</th>
<th>Rate without therapy (%)</th>
<th>Risk Reduction with therapy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute venous thromboembolism*</td>
<td>40</td>
<td>80</td>
</tr>
<tr>
<td>Month 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Months 2 and 3</td>
<td>10</td>
<td>80</td>
</tr>
<tr>
<td>Recurrent venous thromboembolism*†</td>
<td>15‡</td>
<td>80</td>
</tr>
<tr>
<td>Nonvalvular atrial fibrillation</td>
<td>4.5‡</td>
<td>66</td>
</tr>
<tr>
<td>Nonvalvular atrial fibrillation and previous embolism</td>
<td>12‡</td>
<td>66</td>
</tr>
<tr>
<td>Mechanical heart valve</td>
<td>8‡</td>
<td>75</td>
</tr>
<tr>
<td>Acute arterial embolism</td>
<td>15</td>
<td>66</td>
</tr>
<tr>
<td>Month 1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

‡ = Annual Rate  
* = 100-fold increase in risk of VTE is not included in these rates  

### Prospective Bridging Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>VTE/Total</th>
<th>Follow-up (mo)</th>
<th>Recurrent VTE (%)</th>
<th>Major Bleeding (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spandorfer (1999)</td>
<td>4/20</td>
<td>1</td>
<td>NA</td>
<td>1.0%</td>
</tr>
<tr>
<td>Tinmouth (2001)</td>
<td>6/24</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Wilson (2001)</td>
<td>26/48</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Constans (2007)</td>
<td>12/98</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Spyropoulos (2006)</td>
<td>230/825</td>
<td>1</td>
<td>0.5%</td>
<td>3.1%</td>
</tr>
<tr>
<td>Dunn (2006)</td>
<td>81/260</td>
<td>1</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>Hallbritter (2007)</td>
<td>59/311</td>
<td>1</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Jaffer (2006)</td>
<td>18/65</td>
<td>1</td>
<td>0</td>
<td>2%</td>
</tr>
</tbody>
</table>

Pooled risk of VTE with bridging =0.6% (95% CI:0.13-1.7)
Clinical Outcomes with LMWH or UFH: The Regimen Registry

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>UFH (n = 164)</th>
<th>LMWH (n = 668)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event, n (%)</td>
<td>28 (17.1%)</td>
<td>108 (16.2%)</td>
</tr>
<tr>
<td>Arterial/venous thromboembolism, major bleed, or death</td>
<td>13 (7.9%)</td>
<td>28 (4.2%)</td>
</tr>
<tr>
<td>Adverse events, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arterial thromboembolism</td>
<td>4* (2.4%)</td>
<td>4† (0.6%)</td>
</tr>
<tr>
<td>Venous thromboembolism</td>
<td>0 (0)</td>
<td>2‡ (0.3%)</td>
</tr>
<tr>
<td>Major bleed</td>
<td>9 (5.5%)</td>
<td>22 (3.3%)</td>
</tr>
<tr>
<td>Minor bleed</td>
<td>15 (9.1%)</td>
<td>80 (12.0%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>2 (1.2%)</td>
<td>3 (0.4%)</td>
</tr>
<tr>
<td>Death</td>
<td>2 (1.2%)</td>
<td>4 (0.6%)</td>
</tr>
</tbody>
</table>

Predictors of Major Bleeding using Multivariate Regression Analysis

<table>
<thead>
<tr>
<th>Strategy</th>
<th>OR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment (full-dose) UFH/LMWH</td>
<td>4.8 (1.7-15.4)</td>
<td>0.004</td>
</tr>
<tr>
<td>- Adj. for Indication, bleeding risk</td>
<td>5.8 (1.9-19.5)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Conclusions

- Patients who receive full-dose bridging post-operatively had a 6-fold increased risk of major bleeding.
- Wait a couple days prior to starting full dose heparin and perhaps use prophylactic doses of LMWH/UFH in the interim

Jaffer et al.  Presented at ISTH 2005
Pre-op Protocol

- If pre-op INR 2-3, stop warfarin 5 days before surgery (4 doses).
- If pre-op INR 3-4.5, stop warfarin 6 days before surgery (5 doses).
- Start Enoxaparin 1 mg/kg SQ or Dalteparin 100IU/kg q 12 hours, 36 hours after last warfarin dose.
- Last dose of LMWH approximately 24 hours prior to procedure.
- Written instructions for patient.
- Discuss plan with Surgeon, anesthesiologist and patient.
- Risks and benefits of low-molecular-weight heparin
- Instruction on self administration
- Signs and symptoms of bleeding and thromboembolism
- What to do in the event of an emergency

Surgery/Procedure

Jaffer et al. CCJM 2003; 70:973
Bridge Therapy Protocol

Post-op Protocol

- Restart LMWH approx. 24 hours post procedure at full doses for minor surgeries; Use prophylactic doses at least on post-op day 1-2 if patients are high risk for bleeding.
- Discuss post-op timing of anticoagulant therapy with surgeon
- Re-start Coumadin at pre-op dose on post-op day one
- Daily PT/INR until patient is discharged and periodically thereafter until INR is in therapeutic range
- CBC with platelets at day 3 and 7 (HIT screening)
- Discontinue LMWH when INR is 2-3 for two consecutive days

Jaffer et al. CCJM 2003; 70:973
Conclusions

• Patients with history of VTE especially with prior PE have high case-fatality rate
• Patients undergoing Colorectal surgery are at high risk for post-op VTE
• Sudden cessation of warfarin therapy may be associated with a hypercoagulable state
• Preoperative bridging therapy with UFH/LMWH is associated with minimal risk as long as it is stopped 24-hrs before surgery
• Post-operative prophylaxis is absolutely essential after major surgery
Diagnosis of PE

Venous Thromboembolism: State of the Art

SGIM

Toronto

27 April 2007

Scott Kaatz, DO, FACP

Henry Ford Health System

Detroit
Full Disclosure

- Grant support
  - Sanofi-Aventis
  - Amgen
  - Boehringer-Ingelheim
- Honorarium
  - Sanofi-Aventis
- Consultant
  - Sanofi-Aventis
  - Boehringer Ingelheim
  - Astra-Zeneca
Diagnosis of PE

- Clinical prediction rules
- D-dimer
- CT scan
- Diagnostic algorithm
Clinical Prediction Rules
Strength of Evidence

Step 1. Derivation
Identification of factors with predictive power

Step 2. Validation
Evidence of reproducible accuracy
Narrow Validation
Application of rule in a similar clinical setting and population as in Step 1
Broad Validation
Application of rule in multiple clinical settings with varying prevalence and outcomes of disease

Step 3. Impact Analysis
Evidence that rule changes physician behavior and improves patient outcomes and/or reduces costs

McGinn TG. JAMA. 2000 Jul 5;284(1):79-84. PMID: 10872017
Clinical Prediction Rules

- Geneva score
  - Level 1
  - Requires ABG
- Modified Geneva score
  - Level 3
- Wells original criteria
  - Level 1
  - Low, moderate and high probability
- Wells simplified criteria
  - Level 1
  - “Likely” and “unlikely”
Wells Simplified PE Rule

- Clinical signs and symptoms of DVT (minimum of leg swelling and pain with palpation of the deep veins) [3.0 points]
- An alternative diagnosis is less likely than PE [3.0 points]
- Heart rate greater than 100 [1.5 points]
- Immobilization or surgery in the previous four weeks [1.5 points]
- Previous DVT/PE [1.5 points]
- Hemothysis [1.0 points]
- Malignancy (on treatment, treated in the last six months or palliative) [1.0 points]

**Original**
- < 2 points = low
- 2-6 points = moderate
- > 6 points = high

**Simplified**
- < 4 points = unlikely
- ≥ 4 points = likely

Wells PS. Thromb Haemost. 2000 Mar;83(3):416-20 PMID: 10744147
Diagnosis of PE

- Clinical prediction rules
- *D*-dimer
- CT scan
- Diagnostic algorithm
# D-dimer Assays

<table>
<thead>
<tr>
<th>Assay</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ELISA</td>
<td>95-99</td>
<td>32-46</td>
</tr>
<tr>
<td>Latex agglutination</td>
<td>78-96</td>
<td>48-72</td>
</tr>
<tr>
<td>Red blood cell agglutination (SimpliRED)</td>
<td>77-100</td>
<td>54-75</td>
</tr>
<tr>
<td>Rapid ELISA (Vidas DD)</td>
<td>92-100</td>
<td>29-62</td>
</tr>
</tbody>
</table>

Diagnosis of PE

- Clinical prediction rules
- D-dimer
- **CT scan**
- Diagnostic algorithm
Table 5. Positive and Negative Predictive Values of CTA, as Compared with Previous Clinical Assessment.*

<table>
<thead>
<tr>
<th>Variable</th>
<th>High Clinical Probability</th>
<th>Intermediate Clinical Probability</th>
<th>Low Clinical Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No./Total No.</td>
<td>Value (95% CI)</td>
<td>No./Total No.</td>
</tr>
<tr>
<td>Positive predictive value of CTA</td>
<td>22/23</td>
<td>96 (78–99)</td>
<td>93/101</td>
</tr>
<tr>
<td>Positive predictive value of CTA or CTV</td>
<td>27/28</td>
<td>96 (81–99)</td>
<td>100/111</td>
</tr>
<tr>
<td>Negative predictive value of CTA</td>
<td>9/15</td>
<td>60 (32–83)</td>
<td>121/136</td>
</tr>
<tr>
<td>Negative predictive value of both CTA and CTV</td>
<td>9/11</td>
<td>82 (48–97)</td>
<td>114/124</td>
</tr>
</tbody>
</table>

* The clinical probability of pulmonary embolism was based on the Wells score: less than 2.0, low probability; 2.0 to 6.0, moderate probability; and more than 6.0, high probability. CI denotes confidence interval.
† To avoid bias for the calculation of the negative predictive value in patients deemed to have a low probability of pulmonary embolism on previous clinical assessment, only patients with a reference test diagnosis by ventilation–perfusion scanning or conventional pulmonary DSA were included.
Diagnosis of PE

- Clinical prediction rules
- D-dimer
- CT scan
- *Diagnostic algorithm*
Wells criteria: Low

Kearon C.
Ann Intern Med.
2006 Jun 6;144(11):812-21
PMID: 16754923
Christopher Trial

Wells simplified

VIDAS D or Tinaquant
### Diagnostic Algorithm

#### Table 3. Venous Thromboembolic Events (VTEs) During 3-Month Follow-up (n = 3138) *

<table>
<thead>
<tr>
<th>Variable</th>
<th>No.</th>
<th>Total VTEs, No. (%) [95% CI]</th>
<th>Fatal Pulmonary Embolism, No. (%) [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary embolism unlikely and normal D-dimer test result</td>
<td>1028</td>
<td>5 (0.5) [0.2-1.1]</td>
<td>0 (0) [0.0-0.3]</td>
</tr>
<tr>
<td>Pulmonary embolism excluded by CT</td>
<td>1436</td>
<td>18 (1.3) [0.7-2.0]</td>
<td>7 (0.5) [0.2-1.0]</td>
</tr>
<tr>
<td>CT normal</td>
<td>764</td>
<td>9 (1.2) [0.5-2.2]</td>
<td>3 (0.4) [0.1-1.1]</td>
</tr>
<tr>
<td>CT alternative diagnosis</td>
<td>672</td>
<td>9 (1.3) [0.6-2.5]</td>
<td>4 (0.6) [0.1-1.5]</td>
</tr>
<tr>
<td>Pulmonary embolism diagnosed by CT</td>
<td>674</td>
<td>20 (3) [1.8-4.6]</td>
<td>11 (1.6) [0.8-2.9]</td>
</tr>
</tbody>
</table>
Pharmacogenetics of Warfarin Therapy

Brian F. Gage, MD, MSc
Associate Professor of Medicine,
Washington University Medical Center

Medical Director,
Barnes-Jewish Hospital Blood Thinner Clinic
SGIM
314-454-8369; bgage@im.wustl.edu
Case

• You have been referred an elderly man for warfarin initiation for Afib.
  – He takes ASA, amiodarone, and a statin
• What does of warfarin would you prescribe?
• Could pharmacogenetics-based dosing improve his safety profile?
• Would www.WarfarinDosing.org help you tailor his warfarin dose?
CYP2C9

CYP1A1

CYP1A2

CYP3A4

Warfarin

R-warfarin

S-warfarin

CYP2C9

Vitamin K Reductase

Oxidized Vitamin K

Reduced Vitamin K

CO₂

O₂

γ-glutamyl carboxylase

Calumenin

Osteocalcin, MGP

Gage B & Eby C.
Pharmacogenomics J. 2004
# Retrospective Study: Warfarin Dose Revision

## Table 1. Demographic and clinical factors in the 92 participants reaching therapeutic dose

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>58. (15.5)</td>
</tr>
<tr>
<td>BSA - m², mean (SD)</td>
<td>2 (0.3)</td>
</tr>
<tr>
<td>White, N (%)</td>
<td>79 (86)</td>
</tr>
<tr>
<td>African-american, N (%)</td>
<td>13 (14)</td>
</tr>
<tr>
<td>Female, N (%)</td>
<td>44 (48)</td>
</tr>
<tr>
<td>Therapeutic warfarin dose, geometric mean (SD)</td>
<td>4.9 (2.5)</td>
</tr>
<tr>
<td>EBL, geometric mean (SD)</td>
<td>376 (670)</td>
</tr>
<tr>
<td>Entry into model</td>
<td>Variable</td>
</tr>
<tr>
<td>------------------</td>
<td>----------</td>
</tr>
<tr>
<td>-</td>
<td>Intercept</td>
</tr>
<tr>
<td>1</td>
<td>INR3</td>
</tr>
<tr>
<td>2</td>
<td>1st warfarin dose, per mg</td>
</tr>
<tr>
<td>3</td>
<td>CYP2C9*3, per allele</td>
</tr>
<tr>
<td>4</td>
<td>2nd warfarin dose, per mg</td>
</tr>
<tr>
<td>5</td>
<td>CYP2C9*2, per allele</td>
</tr>
<tr>
<td>6</td>
<td>EBL x INR3</td>
</tr>
<tr>
<td>7</td>
<td>Smokes</td>
</tr>
<tr>
<td>8</td>
<td>VKORC1 haplotype A, per copy</td>
</tr>
</tbody>
</table>
R\(^2\) = 79%
N = 92

Millican E, et al.
*Blood*, 2007
Case

• He was found to be homozygous for CYP2C9*3
  – Very slow metabolizer
• He was found to be homozygous for VKORC1 -1639/3673 AA
  – Very warfarin sensitive
• His INR after 3 mg x 3 was 1.5
• A stat INR was 2.2 after his 4th 3 mg dose.
• We Rx’d 0, 0, 0.5 mg, with his next INR 2.1
Warfarin Pharmacogenetics: Summary

- The maintenance warfarin dose can be estimated from clinical and pharmacogenetic factors
  - Patients with certain *VKORC1* genotypes are warfarin sensitive and more likely to have an INR > 3.5 initially
  - Patients with CYP2C9*2 or 2C9*3 are poor metabolizers
- Pharmacogenetics dose refinement can esp. benefit these pts. and has excellent predictive accuracy (R^2 \sim 79\%)