COAGULATION AND BLEEDING DISORDERS

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Disclosures

• NONE

Case #1

• 29 year old man presents with painful swelling in right leg x 1 day
  – He had pain in his right calf for 2 weeks
  – He denies any trauma
• Ultrasound:
  – Occlusive thrombus in the right popliteal and femoral vein

Treatment options include:

A. LMWH immediately and start warfarin after first dose of LMWH is received
B. Bolus with UFH followed by infusion and start warfarin after aPTT is therapeutic
C. Rivaroxaban orally
D. A and C

Direct Oral Anticoagulants (DOACs)

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran etexilate</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target</td>
<td>FIIa</td>
<td>FIIa</td>
<td>FIIa</td>
<td>FIIa</td>
</tr>
<tr>
<td>Peak activity</td>
<td>1-3 hr</td>
<td>1-3 hr</td>
<td>1-3 hr</td>
<td>0.5-2hr</td>
</tr>
<tr>
<td>Half-life</td>
<td>14-17 hr</td>
<td>7-11 hr</td>
<td>12 hr</td>
<td>8-10 hr</td>
</tr>
<tr>
<td>Standard dose</td>
<td>150 mg BID</td>
<td>20 mg daily*</td>
<td>5 mg BID</td>
<td>60 mg daily</td>
</tr>
<tr>
<td>FDA approved indications</td>
<td>NVAF, VTE</td>
<td>NVAF, VTE, TXA/THA</td>
<td>NVAF, VTE, TXA/THA</td>
<td>NVAF, VTE</td>
</tr>
</tbody>
</table>

DOACs vs Warfarin: Pharmacology

• Advantages:
  – Narrow Wide therapeutic index
  – Delayed Rapid onset and offset of effect
  – No Genetic variability
  – Minimal Drug interactions
  – No Dietary interactions
  – No Monitoring requirements
  – No Dose adjustment requirements

Eikelboom JW et al. Circulation 2010; 121: 1523;
Samama MM et al., Clin lab med 2014; 34: 503

* 15 mg BID after acute VTE
DOACs vs Warfarin: Pharmacology

- Disadvantages:
  - Renal elimination
    - Exception: Apixaban
  - Monitoring
    - Compliance issues
  - No antidote
    - Exception: dabigatran
  - Limited experience

DOACs vs Warfarin: Clinical evidence


Case #1, cont

- After three months of anticoagulation...
- Your patient returns for follow-up
- He wants to know how long he needs to be on the anticoagulation

Balance the Risks and Benefits

Bleeding

Venous thromboembolism (VTE)
What is the risk of bleeding?

- Rate of major bleeding:
  - Average ~2%/ year
  - Range: 0.8-10.6%/year
  - Rates sharply increase when INR > 5
  - ~10% of major bleeds are fatal

- Risk factors for bleeding:
  - Age >75 years
  - Prior GIB
  - Prior bleeding
  - Prior stroke
  - Renal or liver impairment
  - Thrombocytopenia
  - Concomitant anti-platelet therapy
  - Poor anticoagulant control
  - Cancer
  - Alcohol abuse

Estimating Risk of Bleeding

- Low risk:
  - No risk factors
  - 0.8% per year

- Moderate risk:
  - 1 risk factor
  - 1.6% per year

- High risk:
  - ≥ 2 risk factors
  - ≥ 6.5% per year

Balance the Risks and Benefits

Determinants of the Risk of Recurrent VTE

Is it a proximal or distal thrombosis?
- Proximal VTE more likely to recur
- Distal DVTs have 50% less risk of recurrence
  - A first, distal lower extremity DVT can be adequately treated with 3 months of anticoagulation even if unprovoked

Determinants of Risk of Recurrence

What was happening around the time of the thrombosis?
- Three risk groups:
  - Lowest risk: surgery within the past three months
  - Intermediate risk: non-surgical transient risk factors
    - Estrogens
    - Hospitalization
    - Trauma
    - Air travel > 8 hours
    - Pregnancy
  - Highest risk: Unprovoked (none of the above)
Thrombophilia testing: Why?

- **Identification of high risk thrombophilias**:
  - APLA, homozygous FVL, and combination defects
- **Potential to inform family members**
  - Important to remember that family history of thrombosis even in the absence of a specific thrombophilia carries an increased risk of VTE in first degree relatives
  - None of these inherited thrombophilias would lead to the use primary prevention with anticoagulation outside of risk situations

Thrombophilia testing: When?

- NOT during the acute hospitalization
- Will lead to false results
  - Protein C, protein S, and AT may be falsely low secondary to acute illness
  - Lupus anticoagulant testing may be transiently positive in the hospital setting
  - Difficult to have an informed discussion about testing at the onset of the illness
- Discuss pros and cons of testing at the end of the planned minimum period of anticoagulation
- Test for protein C and S at least 2 wks after warfarin discontinued

What to test: first line

- **AT activity**
- **Protein S activity**
- **Protein C activity**
- **FVL mutation**
- **Prothrombin gene mutation**
- **APLA**: Lupus anticoagulant, anticardiolipin (IgG/IgM) and anti-β2glycoprotein (2 positives, 12 weeks apart)

<table>
<thead>
<tr>
<th>RISK FACTOR</th>
<th>RELATIVE RISK OF RECURRENT VTE</th>
</tr>
</thead>
<tbody>
<tr>
<td>APLA</td>
<td>2 - 9</td>
</tr>
<tr>
<td>Homozygous FVL</td>
<td>4</td>
</tr>
<tr>
<td>Compound heterozygous: FVL &amp; Prothrombin gene mutation</td>
<td>2 - 5</td>
</tr>
<tr>
<td>Protein C, S and AT deficiency</td>
<td>1 - 3</td>
</tr>
<tr>
<td>Hyperhomocysteinemia</td>
<td>1 - 2</td>
</tr>
<tr>
<td>Heterozygous FVL</td>
<td>1.5</td>
</tr>
<tr>
<td>Heterozygous Prothrombin gene mutation</td>
<td>1</td>
</tr>
</tbody>
</table>
Other Considerations

• Higher risk of recurrence if...
  – Male [HR 1.8 (95% CI 1.4-2.5), excluding women with hormone-associated VTE]
  – An elevated d-dimer one month after cessation of anticoagulation [HR 3.2 (95% CI 1.3-8.0)]
  – Age
  – Signs/symptoms of post-thrombotic syndrome
  – Obesity

Case #1, cont

29 year-old unprovoked right femoral and popliteal vein thrombosis
• No significant PMH
• No FHx of thrombosis
• Major risk factor for recurrence: male gender

In this patient....

• D-dimer off anticoagulation: normal
  – APLA negative
  – Protein C + S, AT activities normal
  – Prothrombin gene mutation G20210A not present
  – Heterozygous for FVL mutation
• Despite increased annual risk of recurrence of 6-8%, he wishes to stop anticoagulation

6 months later....

• He presents with swelling and pain in the same leg
  – DDX:
    • Post-thrombotic syndrome vs. new VTE
  – Repeat ultrasound demonstrates new clot
    • Compared to ultrasound performed at the time coumadin was discontinued
  – Restarted on LMWH and bridged to coumadin
    • He again asks, “How long?”

Recurrent thrombosis

➢ Two unprovoked thromboses
➢ Risk of recurrence >10% per year
➢ Indefinite anticoagulation warranted
➢ Balance between risks and benefits
  ➢ These may change over time
➢ Recurrent provoked thromboses
  ➢ Aggressive prophylaxis during high risk situations

You recommend

- Indefinite anticoagulation:
  - INR 2-3 (same bleeding risk as INR 1.5-2.0)
  - Higher target INR is not necessary in those with APLA


Which of the following is most appropriate regarding genetic testing for factor V Leiden in family members?

A. Tell the patient that family members should be tested as soon as possible
B. Tell the patient that family members are possible carriers and should consider genetic counseling
C. Contact the sisters’ physicians and inform them of the patient’s condition
D. Avoid making recommendations for family members

His sister was tested and found to be heterozygous FV Leiden
- She is now pregnant
- She asks you whether any special precautions should be taken during her pregnancy.

Which of the following should you recommend?

A. Heparin in the third trimester and warfarin postpartum
B. Heparin for 6 weeks postpartum
C. Warfarin postpartum
D. No pre- or postpartum therapy

Risk of pregnancy related thrombosis

- No thrombophilia 0.1%
- FVL mutation heterozygous: 1.2%
- FVL mutation homozygous: 4.8%
- Prothrombin gene mutation heterozygous: 1%
- Protein C deficiency 0.7%
- Protein S deficiency: 0.5%
- AT deficiency: 0.7%

Bates et al. Chest 2012;e691S

Congenital thrombophilia and pregnancy without a prior history of thrombosis

- Homozygous FV Leiden or prothrombin gene mutation
  - + family VTE history: Antipartum and 6 weeks post-partum anticoagulation
  - - family VTE history: 6 weeks post-partum anticoagulation
- All other thrombophilias
  - + family history of VTE: 6 weeks post-partum anticoagulation
  - - family VTE history: no anticoagulation

Bates et al. Chest 2012;e691S
Which of the following should you recommend?

A. Heparin in the third trimester and warfarin postpartum.
B. Heparin for 6 weeks postpartum
C. Warfarin postpartum
D. No pre- or postpartum therapy

Take home points for thrombosis

- Defined periods of anticoagulation appropriate for distal and/or provoked VTE
- Unprovoked thrombosis: Duration of AC depends on risk and benefit
  - Gender
  - Decision rules that take into account risk factors may be helpful.
  - Identification of high risk thrombophilias [APLA, homozygous FVL and combined defects] may be relevant in some, but not all, patients
- Peripartum management depends on the thrombophilia, personal and family history of VTE

Case #2

- 76 year-old women is receiving heparin prophylaxis following right total hip replacement
- On POD #8 her platelet count is 105K
  - Immediate post-operative PLT was 250K
  - POD #5 PLT was 224K
- Cr = 3.2 mg/dl, unchanged from pre-op
- Review of blood smear confirms thrombocytopenia without platelet clumping

Which of the following should you do next?

A. Discontinue heparin and observe
B. Discontinue heparin and begin warfarin
C. Discontinue heparin and begin argatroban
D. Discontinue heparin and begin rivaroxaban

HIT clinical pretest probability

<table>
<thead>
<tr>
<th>Thrombocytopenia</th>
<th>2 points</th>
<th>1 point</th>
<th>0 points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ptt fall &gt;50% + nadir &gt; 20K</td>
<td>Ptt fall 30-50% or nadir 10-19K</td>
<td>Ptt fall &lt;30% or nadir &lt;10K</td>
<td></td>
</tr>
</tbody>
</table>

Timing

- Clear onset between 5-10d or ptt fall ≤ 1 d (prior heparin exposure with 30 d)
- Consistent w/ onset between 5-10 days, but not clear (e.g. missing ptt); onset >10 d or fall ≤ 1 d (prior heparin exposure 30-100 d ago)
- Ptt fall <4 d w/o recent exposure

Thrombosis or other sequelae

- New thrombosis; skin necrosis; acute systemic reaction post IV UFH
- Progressive or recurrent thrombosis; non-necrotizing (erythematous) skin lesions; suspected thrombosis (not proven)
- None

Other causes of thrombocytopenia

- None
- Possible
- Definite

Pre-test probability

- Low pretest probability (<3 points):
  - 0.8% ultimately diagnosed with HIT
  - Negative predictive value of 98-99%
  - No additional testing is necessary
- Intermediate pretest probability (4-5 points):
  - 11-25% ultimately diagnosed with HIT
- High pretest probability (6-8 points)
  - 30-100% ultimately diagnosed with HIT

Lo et al 2006 J Thromb Haemost 4(4)759-65
Which of the following should you do next?

A. Discontinue heparin and observe
B. Discontinue heparin and begin warfarin
C. Discontinue heparin and begin argatroban
D. Discontinue heparin and begin rivaroxaban

Take home points on HIT diagnosis

- Clinical pre-test probability is important
  - Low probability, very unlikely to be HIT.
    - No further testing is necessary
    - OK to continue heparin
  - Not all anti-heparin/PF4 antibodies detected on ELISA are pathogenic
  - Orders for testing, discontinuing heparin, and starting an alternative anticoagulant should occur nearly simultaneously

Case #3

- 78 year-old man on warfarin for atrial fibrillation presents with a severe headache and some mild confusion
- INR is 3.3
- CT scan demonstrates large subdural hematoma
- You are asked for recommendations on warfarin reversal

You recommend...

A. Vitamin K 10 mg SC and 4 units of FFP
B. 4 units of FFP alone
C. Prothrombin complex concentrate (35 U/kg) alone
D. Vitamin K 10 mg IV and Prothrombin complex concentrate 35 U/kg
## Warfarin Reversal

<table>
<thead>
<tr>
<th>INR</th>
<th>Clinical Scenario</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;4.5</td>
<td>No Bleeding</td>
<td>Hold warfarin until INR in therapeutic range</td>
</tr>
<tr>
<td></td>
<td>Rapid reversal required</td>
<td>Hold warfarin. Consider vitamin K 2.5mg po</td>
</tr>
<tr>
<td>4.5-10</td>
<td>No Bleeding</td>
<td>Hold warfarin until INR in therapeutic range. Consider vitamin K 2.5mg po</td>
</tr>
<tr>
<td></td>
<td>Rapid reversal required</td>
<td>Hold warfarin. Give vitamin K 2.5mg po or 1mg IV infusion</td>
</tr>
<tr>
<td>&gt;10</td>
<td>No bleeding</td>
<td>Hold warfarin until INR in therapeutic range. Give vitamin K 2.5 po or 1-2mg IV repeat q4h as necessary</td>
</tr>
<tr>
<td>Any INR</td>
<td>Serious or life threatening bleeding</td>
<td>Give vitamin K 10mg IV infusion over 30 minutes. Give 2-4 units FFP or PCC* 25 units/kg for INR 2-4. NTE 2500 U* 35 units/kg for INR 4-6 NTE 3500 U* 50 units/kg for INR 6-9 NTE 5000 U*</td>
</tr>
</tbody>
</table>

*based on recent FDA approval

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### Take Home Points for Warfarin Reversal

- No role for subcutaneous vitamin K
- For INRs > 4.5, no bleeding, and rapid reversal not needed, oral vitamin K adequate
- Rapid reversal needed vitamin K 1 mg IV
- Major bleeding at any INR vitamin K 10 mg IV
- Major bleeding at any INR, in addition to vitamin K,
  - Use 4 factor PCC (Kcentra) if available
  - Or FFP 10-15 ml/kg if PCC not available

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## DOACs: Bleeding

- Short half life:
  - Dabigatran: 12-17 hrs
  - Xa inhibitors: 6-14 hrs
- Special situations warranting immediate correction:
  - Emergency surgeries
  - Life-threatening bleeding
- Challenges:
  - Lab tests do not indicate the level of drug.
  - No antidote except for dabigatran
  - Non-specific prohemostatic agents and coagulation factors

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### Idarucizumab for reversal of dabigatran


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### Take home points for DOACs reversal

Adapted from Blood. 2014;123(8):1152-1158
**Case #4**

- 32 year-old woman on routine laboratory testing is found to be anemic.
  - You determine that she has iron deficiency as the cause of her anemia.
  - On further questioning she tells you that she has had heavy menstrual periods since menarche.
  - You question whether she could have a bleeding disorder.

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**Bleeding disorders & menorrhagia**

- ~ 20% of women with menorrhagia have an underlying bleeding disorder.
- Clinical features most predictive of menorrhagia:
  - Clots > 1” in size
  - Change protection more frequently than 1 hr
  - Iron deficiency
  - > 7 days duration
  - Having to double up on protection

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**Evaluation of the bleeding patient**

- More common DDX:
  - Congenital bleeding disorder:
    - Platelet function defect
    - Von Willebrand disease
    - Hemophilia A (factor VIII deficiency) or B (factor IX deficiency)
    - Factor XI deficiency
  - Acquired bleeding disorder:
    - Liver disease
    - Medications
    - Surgery / trauma
    - Acquired factor inhibitor (factor VIII)

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**Initial laboratory evaluation**

- Platelet count
- Prothrombin time (PT)
- Activated partial thromboplastin time (aPTT)
- Thrombin time
- Fibrinogen
- Von willebrand testing:
  - Von Willebrand factor activity (ristocetin cofactor activity) and antigen
  - Factor VIII

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**Proceed to laboratory evaluation of bleeding disorder if 1 is positive**

1. Family history of a bleeding disorder
2. Bleeding from trivial wounds lasting >15 min or recurring spontaneously during the 7 days after the wound
3. Post-surgical bleeding
4. Bruising with minimal or no apparent trauma
5. Spontaneous epistaxis lasting > 10 min
6. Heavy, prolonged or recurrent bleeding after dental extraction
7. GI bleeding unexplained by a specific anatomic lesion
8. Anemia requiring treatment
Evaluation of a prolonged PT/PTT

- PTT only
  - Factors XII, XI, IX, VIII
- PT only
  - Factor VII
- Both PTT and PT
  - Factors X, V, II, and fibrinogen

von Willebrand disease: Testing

- vWF antigen assay (VWF:Ag)
- Protein quantification
- vWF activity: Ristocetin cofactor activity (vWF:RCo)
  - Functional assay using patient’s plasma and normal fixed platelets
- FVIII clotting activity (FVIII:C)
  - Activity often parallels vWF levels
- vWF multimer analysis
  - vWF protein displayed on agarose gel
  - vWF multimers are separated by size

<table>
<thead>
<tr>
<th>vWF antigen</th>
<th>Low</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCo activity</td>
<td>Low</td>
<td>Normal</td>
</tr>
<tr>
<td>PFA-100</td>
<td>Prolonged</td>
<td>Prolonged (insensitive)</td>
</tr>
<tr>
<td>FVIII</td>
<td>&lt;40%</td>
<td>Low / normal</td>
</tr>
</tbody>
</table>

Adapted from MKSAP14

von Willebrand disease: Classification

- **Type 1**
  - Accounts for 70% of VWD
  - Mild reduction in vWF antigen
  - Antigen and activity correlate
- **Type 2**
  - Loss of vWF activity is out of proportion to antigen level (ratio activity to antigen <0.6)
  - 2A, 2B, 2N, and 2M
- **Type 3**
  - Absence of protein leads to severely reduced activity levels

Case #3: Laboratory testing

- Normal PT, PTT, fibrinogen, thrombin time, and platelet count
- vWF antigen 22% (nl 50-150)
- RCo activity 28% (nl 50-150)
- FVIII activity 52% (nl 50-150)
- Multimers: normal distribution but reduced intensity

**Dx: von Willebrand disease type 1**
She is now preparing to have wisdom teeth extracted. What do you recommend for management?

A. No treatment  
B. Humate P (vWF-containing concentrate) prior to the procedure and amicar following the procedure  
C. Test for DDAVP responsiveness, and if responsive, use DDAVP prior to the procedure and amicar following.  
D. Humate P only if bleeding occurs

Case: diagnosis and management of type 1 vWD

• Referral to a comprehensive bleeding disorders clinic  
  – Education  
  – Active management at the time of procedures and child birth  
• Options of treatment  
  – Hormonal  
  – DDAVP - causes release of vWF from storage sites.  
    • Responsiveness should be confirmed prior to use  
  – Amicar – antifibrinolytic  
  – Humate P if DDAVP unresponsive or intolerant

Take home points: Bleeding disorders

• Up to 20% of women with menorrhagia have a bleeding disorder  
• A careful history can assist in identifying women with underlying bleeding disorder  
• Testing for vWD includes RCo activity, vWF antigen, FVIII and multimer analysis  
• Mixing studies help differentiate a factor deficiency from an inhibitor

THANK YOU

Answers

• Slide #4: D-Most appropriate treatment options for acute DVT (and PE) are both LWMH (or fondaparinux) followed by warfarin (a) and rivaroxaban alone (c). These two options are preferred over use of UFH (Kearon et al. Chest Guidelines 2012)

• Slide #32: B-Family members can be informed that they may carry an inherited thrombophilia, but the pros and cons of testing that family member should be considered prior to testing.

Answers

• Slide #37: B-Given that she is heterozygous factor V leiden and has a family history of VTE, she should receive 6 weeks of anticoagulation with a heparin (typically LMWH) in the post partum period. If she did not have a family history of VTE, she could be observed without any anticoagulation.
Answers

• Slide #45: C-She has a high clinical pre-test probability for HIT, she should have her heparin discontinued and an alternative anticoagulant started while laboratory (ELISA) confirmation is obtained. Argatroban is currently the only approved medication for treatment of HIT. Some institutions are using fondaparinux. Given this patient's renal dysfunction, this would not be wise. Warfarin should be avoided until she has a platelet count > 150K.

Answers

• Slide #48: D- For patients on warfarin with major bleeding at any INR treatment should include vitamin 10 mg IV in combination with PCC (Kcentra-preferred as this is the only 4 factor PCC available in US) or FFP (10-15 ml/kg)

Answers

• Slide # 67: C-The patient has type 1 VWD and likely will respond to DDAVP. No treatment or humate P only if bleeding puts her at risk of having bleeding complications. Amicar can help to reduce the action of the fibrinolytic enzymes in the mouth.