Anticoagulants: Preventing Stroke and melting clots. Great Drugs!
Anticoagulants: They should be banned, buried and never thought of again!
I am a hospitalist! or: How I Learned to Stop Worrying and Love the Anticoagulants
Anticoagulants: New and Old (and what lies beneath)

Ted Arevalo, M.D
Assistant Professor
UT Health Science Center at San Antonio
October 21, 2015
• I have no financial disclosures
Goals and Objectives

• Review the mechanism of action and the method of monitoring medications used for systemic anticoagulation for stroke prophylaxis
• Review the agents available to reverse the effects of anticoagulation in the setting of hemorrhage
• Apply this knowledge in choosing the best preventive therapy
INJURY

Extrinsic Pathway

VIIa, TF
TXA

Intrinsic Pathway

IX
IXa, VIIIa

Thrombin

Fibrinogen

Prothrombin

Fibrin
Initiation

Propagation

Clot Formation

Fibrinogen → Fibrin
Indications and choices for Systemic Anticoagulation

- Stroke Prophylaxis for Non-valvular Atrial Fibrillation
A Case

- 66 y/o HF with DM, HTN, Hyperlipidemia, who presents with 6 months of palpitations. She indicates she has overall felt well, but she did not know if it was important, so she thought she would have it checked out. She takes metformin, enalapril, HCTZ, amlodipine
- Wt 65 kg
- AF, P 89, R 16, BP 155/92
- Pleasant, oriented
- Lungs clear
- Heart not tachycardic but is irregular
- No lower extremity edema
- Remainder of the examination is normal
Case

- Chemistries show Cr 1.1, otherwise normal
- ECHO
What is your recommendation?

- warfarin 5 mg daily and follow-up INR
- rivaroxaban 25 mg po daily
- dabigatran 150 mg po twice daily
- apixaban 5 mg po twice daily
- No therapy
Outline

• A tool to select appropriate patients
• Pharmacology/Advantages/Disadvantages/comparisons
• Reversal Agents
• Major bleeding
• Putting it all together
Antithrombotic therapy for prevention of stroke (ischemic and hemorrhagic) in patients with nonvalvular AF: adjusted-dose warfarin compared with placebo

Fuster, V. et al. Circulation 2001;104:2118-2150
<table>
<thead>
<tr>
<th>CHADS₂ Score</th>
<th>Description</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>Congestive Heart Failure</td>
<td>1 point</td>
</tr>
<tr>
<td>H</td>
<td>Hypertension</td>
<td>1 point</td>
</tr>
<tr>
<td>A</td>
<td>Age ≥ 75 y</td>
<td>1 point</td>
</tr>
<tr>
<td>D</td>
<td>Diabetes</td>
<td>1 point</td>
</tr>
<tr>
<td>S₂</td>
<td>Stroke</td>
<td>2 points</td>
</tr>
</tbody>
</table>

Maximum total score = 6 points.

American College of Cardiology/American Heart Association/Heart Rhythm Society 2006 Anticoagulation Recommendations:
Score = 0 aspirin. Score = 1 aspirin or oral anticoagulation. Score ≥ 2 oral anticoagulation.

What Happened?

• More recent studies showed poor correlation between CHADS2 scoring and thromboembolic events
• There were important risk factors for stroke that were not accounted for in CHADS2
• In some Cohorts there was a CHADS2 score of 1 in 30 to 50% with no clear recommendation for anticoagulation
Table 2  \( \text{CHA}_2\text{DS}_2\text{-VASc Score}^{15,16} \)

<table>
<thead>
<tr>
<th>Letter</th>
<th>Condition</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>Congestive Heart Failure</td>
<td>1 point</td>
</tr>
<tr>
<td>H</td>
<td>Hypertension</td>
<td>1 point</td>
</tr>
<tr>
<td>(A_2)</td>
<td>Age (\geq 75) y</td>
<td>2 points</td>
</tr>
<tr>
<td>D</td>
<td>Diabetes</td>
<td>1 point</td>
</tr>
<tr>
<td>(S_2)</td>
<td>Stroke</td>
<td>2 points</td>
</tr>
<tr>
<td>V</td>
<td>Vascular disease</td>
<td>1 point</td>
</tr>
<tr>
<td>A</td>
<td>Age (\geq 65) y</td>
<td>1 point</td>
</tr>
<tr>
<td>Sc</td>
<td>Sex category, female</td>
<td>1 point</td>
</tr>
</tbody>
</table>

Maximum total score = 9 points.

ESC 2010 Anticoagulation Recommendations: Score = 0 no therapy or aspirin (no therapy preferred). Score = 1 aspirin or oral anticoagulation (oral anticoagulation preferred). Score \(\geq 2\) oral anticoagulation.

Now What?

Guidelines

• In patients with nonvalvular AF, the CHA2DS2-VASc score is recommended for assessment of stroke risk. (Class I, Level of Evidence B)
Guidelines

• For patients with nonvalvular AF with prior stroke, transient ischemic attack (TIA), or a CHA2DS2-VASc score of 2 or greater, oral anticoagulants are recommended. Options include: warfarin with INR goal 2.0 to 3.0, (Class I, Level of Evidence A), dabigatran (Class I, Level B), rivaroxaban (Class I, Level B), or apixababan (Class I, Level B)
What is your recommendation?

• warfarin 5 mg daily and follow-up INR
• rivaroxaban 25 mg po daily
• dabigatran 150 mg po twice daily
• apixaban 5 mg po twice daily
• No therapy
Outline

• A tool to select appropriate patients
• Pharmacology/Advantages/Disadvantages/Comparisons
• Reversal Agents
• Major bleeding
• Putting it all together
Warfarin

- Vitamin K antagonist
- Interferes with γ-carboxylation of proteins that ultimately become factors II, VII, IX, X resulting in reduced procoagulant activity
Warfarin

- Once Daily
- First approved for human use in 1954
- Drug/herb/food interactions
- INR monitoring associated costs, inconvenience of patient clinic visits
Dabigatran

- direct thrombin inhibitor
- Given as a prodrug dabigatran etexilate
- Drug levels peak within 2 hours
- ½ life is 14 to 17 hours
- Approved for use in the U.S. for non-valvular AFIB at a dose of 150 mg po BID CrCl > 30 mL/min
- 75 mg BID for CrCl 15 to 30 mL/min
Coagulation Cascade

FIGURE 1. The coagulation cascade and how the new oral anticoagulants block it.

Dabigatran

• Standardized dosing
• No anticoagulation monitoring needed
• Superior to Warfarin in reducing stroke (including hemorrhagic stroke) and systemic embolization, less major bleeding (RE-LY)

• Twice daily
• Renal function must be considered
• There are interactions with inhibitors of P-glycoprotein transporter
Rivaroxaban

- A direct inhibitor of factor Xa
- Plasma levels peak 2 to 3 hours after administration
- Half-life 7 to 11 hrs
- AFIB stroke prophylaxis
  - CrCl > 50 mL/min dose 20 mg po daily
  - CrCl 15 to 50 mL/min 15 mg po daily
FIGURE 1. The coagulation cascade and how the new oral anticoagulants block it.

Rivaroxaban

- Once daily dosing
- No anticoagulation monitoring
- At least as effective as warfarin for reduction in stroke and systemic embolization, less ICH and major bleeding (ROCKET-AF)

- Renal function must be considered
- Interactions with CYP 3A4 and P-glycoprotein transporter
Apixaban

- Selective direct inhibitor of factor Xa
- Levels peak 3 hours after administration
- Half-life 8 to 14 hours
- It is the least renal dependent elimination
- Nonvalvular AFIB Stroke Prophylaxis
- 5 mg po twice daily
FIGURE 1. The coagulation cascade and how the new oral anticoagulants block it.

Apixaban

- Reduced stroke and systemic embolization better than warfarin with less bleeding (ARISTOTLE)
Apixaban

- Use 2.5 mg po twice daily if any 2 of the following:
  - Age ≥ 80
  - Body weight ≤ 60 kg
  - serum Cr ≥ 1.5

Or

- patients taking drugs that dually inhibit CYP3A4 and P-glycoprotein (examples: ketoconazole, itraconazole, ritonavir, clarithromycin)
The more things change...

- Does a patient’s weight change?
- Does a patient age?
- Do the medications patients take change?
- Does a patient’s renal function change?
Stroke risk reductions from randomized trials of antithrombotic agents in atrial fibrillation.

Christopher B. Granger, and Luciana V. Armaganijan
Circulation. 2012;125:159-164
Outline

• A tool to select appropriate patients
• Pharmacology/Advantages/Disadvantages/comparison
• Reversal Agents
• Major bleeding
• Putting it all together
Unfractionated Heparin

• Major anticoagulation action is mediated by the heparin/antithrombin (AT) interaction
• AT is converted from a slow to a rapid inhibitor of coagulation enzymes
• It has a short half-life, is completely reversible, and non-renal elimination
• Heparin-induced thrombocytopenia is the most-important non-hemorrhagic side effect
Unfractionated Heparin

- Catalyzes the inactivation of factor II, IIa, Xa, IXa, XIa, XIIa
- And more factors are inhibited at higher doses
Heparin

ANTITHROMBOTIC THERAPY AND PREVENTION OF THROMBOSIS, 9TH ED: ACCP GUIDELINES
Damaged surface

XII → XIIa

→ XI → Xla

→ IX → IXa

→ VIIa → VII

→ VIII

Prothrombin (II) → Xa → Thrombin (IIa) → Fibrinogen (I) → Fibrin (Ia)

→ Active Protein C

→ TFPI

→ Antithrombin

→ Common pathway

→ Trauma

→ Tissue factor

→ Trauma
Unfractionated Heparin

• Monitoring
  – aPTT
  – Antifactor Xa (Heparin Assay)
  – Protamine titration
Table 1. Preanalytic, Analytic, and Biologic Factors Known to Influence Activated Partial Thromboplastin Time and Anti-factor Xa Levels

<table>
<thead>
<tr>
<th>Factor</th>
<th>aPTT</th>
<th>Antifactor Xa</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preanalytic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood sampling in the evening (due to diurnal variation)</td>
<td>↑</td>
<td>↔</td>
</tr>
<tr>
<td>Blood sampling in the morning (due to diurnal variation)</td>
<td>↓</td>
<td>↔</td>
</tr>
<tr>
<td>High concentration of citrate in collection tube (3.2% is standard)</td>
<td>↑</td>
<td>↔</td>
</tr>
<tr>
<td>Improper blood sampling (obtaining sample too close to heparin administration site without proper flushing)</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Underfilled sample tubes</td>
<td>↑</td>
<td>↔</td>
</tr>
<tr>
<td>Delay in sample analysis (&gt; 2 hrs)</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Inadequate centrifugation (inadequate removal of platelets from sample)</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Gross hemolysis of sample</td>
<td>↔</td>
<td>↓</td>
</tr>
<tr>
<td><strong>Analytic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reagent used (change in lot numbers can also affect results)</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Coagulometer used</td>
<td>↔</td>
<td>↑</td>
</tr>
<tr>
<td><strong>Biologic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antithrombin deficiency</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Increased levels of acute phase reactants (factor VIII or fibrinogen)</td>
<td>↓</td>
<td>↔</td>
</tr>
<tr>
<td>Increased heparin-binding proteins (inflammation, infection, malignancy)</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Obesity (increased volume of distribution)</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Impaired renal function (decreased UFH elimination)</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Liver disease (decreased clotting factor production)</td>
<td>↑</td>
<td>↔</td>
</tr>
<tr>
<td>Consumptive coagulopathy</td>
<td>↑</td>
<td>↔</td>
</tr>
<tr>
<td>Lupus anticoagulant</td>
<td>↑</td>
<td>↔</td>
</tr>
<tr>
<td>Deficiencies of specific clotting factors (preallikrein and factors IX, XI, and XII)</td>
<td>↑</td>
<td>↔</td>
</tr>
<tr>
<td>Elderly</td>
<td>↑</td>
<td>↔</td>
</tr>
<tr>
<td>Recent use of low-molecular-weight heparins or fondaparinux (particularly in setting of impaired renal function)</td>
<td>↑</td>
<td>↔</td>
</tr>
<tr>
<td>Hypertriglyceridemia (triglyceride level &gt; 360 mg/dl)</td>
<td>↔</td>
<td>↑</td>
</tr>
<tr>
<td>Hyperbilirubinemia (total bilirubin level &gt; 6.6 mg/dl)</td>
<td>↔</td>
<td>↓</td>
</tr>
</tbody>
</table>

aPTT = activated partial thromboplastin time; ↑ = increase in laboratory result; ↓ = decrease in laboratory result; ↔ = little to no effect; † = variable response; UFH = unfractionated heparin.
**Heparin**

- A survey in 2004
  - 97% of institutions were using the aPTT
- Measuring antifactor Xa
  - Fewer laboratory tests
  - Fewer dosage adjustments
  - Counteracts the higher acquisition costs of the antifactor Xa reagents
  - Most coagulometers have the capability to perform colorimetric antifactor Xa (heparin assay) testing

*Pharmacotherapy 2012;32(6):546–558*
Heparin

• 2009
  – Heparin Assay (antifactor Xa)
  – Well established
  – Target therapeutic level of 0.3 to 0.7 U/mL
  – Dose recommendations did not change
  – Levels checked every 6 hours, until 2 consecutive levels in range, and then daily thereafter
  – If total bilirubin is > 6.6 mg/dL, aPTT should be used
Venous Thromboembolism Treatment (Target 0.3 - 0.7 U/mL)

Initial Bolus: 80 units/kg (Max Bolus 10,000 units)
Initial Infusion Rate: 18 unit/kg/hr (Max initial rate 2,000 units/hr)
Monitor: Heparin Assay 6 hours after initiation and 6 hours after each dosage change

<table>
<thead>
<tr>
<th>Heparin Assay AntiXa (U/mL)</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 0.15</td>
<td>80 unit/kg bolus, then increase by 4 units/kg/hr</td>
</tr>
<tr>
<td>0.15 - 0.29</td>
<td>-</td>
</tr>
<tr>
<td>0.3 - 0.7</td>
<td>No Change</td>
</tr>
<tr>
<td>0.71 - 1</td>
<td>Decrease by 2 units/kg/hr</td>
</tr>
<tr>
<td>&gt; 1</td>
<td>Stop infusion 1 hr then decrease by 3 units/kg/hr</td>
</tr>
</tbody>
</table>

Indications: DVT, PE, Atrial fibrillation

Acute Coronary Syndrome Cardiology (Target 0.3 – 0.7 U/mL)

Initial Bolus: 60 units/kg (Max Bolus 5,000 units)
Initial Infusion Rate: 12 unit/kg/hr (Max initial rate 1,000 units/hr)
Monitor: Heparin Assay 6 hours after initiation and 6 hours after each dosage change

<table>
<thead>
<tr>
<th>Heparin Assay AntiXa (U/mL)</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 0.15</td>
<td>80 unit/kg bolus, then increase by 4 units/kg/hr</td>
</tr>
<tr>
<td>0.15 - 0.29</td>
<td>-</td>
</tr>
<tr>
<td>0.3 - 0.7</td>
<td>No Change</td>
</tr>
<tr>
<td>0.71 - 1</td>
<td>Decrease by 2 units/kg/hr</td>
</tr>
<tr>
<td>&gt; 1</td>
<td>Stop infusion 1 hr then decrease by 3 units/kg/hr</td>
</tr>
</tbody>
</table>

Indications: Non-STEMI, STEMI, Unstable Angina

References
Protamine

• A basic protein derived from fish sperm
• Protamine sulfate rapidly reverses the anticoagulation effect of heparin
• Binds to heparin to form a stable salt
• aPTT (or the heparin assay) can be used to assess effectiveness
V. Treatment of IV Heparin Overdose
   a. Protamine sulfate injection – 1 mg of protamine sulfate neutralizes 100 heparin units
   b. Only the heparin dose given over the last 3-4 hours needs to be included in the protamine dose calculation. (Based on heparin half-life 45-60 min)
   c. Give dose by slow IV push, never to exceed 50 mg over a 10-minute period

References
2. Hirsh J, Bauer KA, Donati MB et al. Chest 2008;133(suppl)141S-155S.

Anticoagulation Safety Committee
Updated June 2009
Low Molecular Weight Heparin

- Derived from UFH
- The major anticoagulant effect is by AT-mediated inhibition of coagulation factors
- There is much greater inactivation of Xa than thrombin
- After subcutaneous injection, the bioavailability is as high as 90%
- There is a more predictable anticoagulant response
- Antifactor Xa levels peak 3 to 5 hours after dosing
- Antifactor Xa activity can be checked if needed
Reversal of LMWH

• No proven method
• Protamine sulfate can neutralize the effect, but it is variable
• Within 8 hours, give protamine sulfate at 1 mg per 100 antifactor Xa units (1mg enoxaparin equals approx 100 anti-Xa units) up to 50 mg. A second dose of 0.5 mg per 100 anti-Xa units should be given if bleeding continues.
• LMWH will inhibit any coagulation factors in FFP infused (so don’t use it).
Reversal of LMWH

• Heparin and LMWH will inhibit any coagulation factors in FFP infused (so don’t use it)
• Remember that FFP is a great source of AT
Immediate Reversal of Coumadin

- Fresh Frozen Plasma (FFP) has been the most widely used coagulation factor replacement for urgent reversal of coumadin anticoagulation.

- Given the long half-life of coumadin and the short half-life of coagulants in plasma, Vitamin K must still be given to allow endogenous coagulants to be produced.
Fresh Frozen Plasma

- Severe allergic reactions
- May require large volumes – 15 to 20 mL/kg
- Potential carrier of infective agents
- Takes time to thaw
- Must be cross-matched if group specific plasma is to be used
- Transfusion associated circulatory overload (TACO)
TRALI

- Risk is greater than transmission of Hepatitis C and HIV
- Significant morbidity and mortality
- Most frequent cause of transfusion-related death
TRALI

• During or after transfusion; 6 hours
• Acute hypoxemia
• Leakage of fluid into the alveolar space
• Looks like ARDS
• Reported in all types of blood components
  – FFP is the most frequently implicated
  – Antibodies to leukocytes implicated in 65-90%
  – More common in female donors with history of pregnancy
Prothrombin Complex Concentrates (PCCs)

• More effective in correcting the INR
• Do not require cross-match
• Virally inactivated
• Can be infused in 15 to 30 minutes
• Do not pose risk for TRALI or TACO
Prothrombin Complex Concentrates

• Three factor products
  – II, IX, X (low in factor VII)
  – Profilnine

• Four factor products
  – II, VII, IX, X (also factor C & S)
  – Kcentra, recently approved in US for emergent reversal of Vitamin K antagonists
Prothrombin Complex Concentrates

• Potential complications
  – Thrombotic events
  – DIC
<table>
<thead>
<tr>
<th>Author</th>
<th>Study type</th>
<th>Patient population</th>
<th>Intervention</th>
<th>Result</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Makris et al. 1997</td>
<td>Prospective</td>
<td>16 patients with WAICH, along with 12 “similar subjects”</td>
<td>Vitamin K 1-5 mg IV given to all patients. 16 patients got PCC and 12 FFP</td>
<td>PCC repleted factors II, VII, IX, and X better than FFP. In patients given FFP, INR remained elevated. 28/29 patients given PCC had INR correction</td>
<td>Moderate</td>
</tr>
<tr>
<td>Fredriksson et al. 1992</td>
<td>Retrospective</td>
<td>17 patients with WAICH</td>
<td>All patients received vitamin K 10-20 mg IV. Of the 17 total patients, 10 received PCC and 7 received FFP</td>
<td>PCC significantly decreased the INR from 2.83 to 1.22 within 4.8 h, compared with a decrease in INR from 2.97 to 1.74 within 7.3 h in the FFP group. Signs and symptoms of ICH progressed more in those treated with FFP than with PCC</td>
<td>Low</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Patients</td>
<td>Interventions</td>
<td>Outcomes</td>
<td></td>
</tr>
<tr>
<td>---------------</td>
<td>-------------------------</td>
<td>---------------------------------</td>
<td>-------------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Boulis et al. 1999</td>
<td>Prospective, randomized controlled trial</td>
<td>13 patients with WAICH</td>
<td>All patients received vitamin K 10 mg subcutaneously. 8 patients received FFP. 5 patients received weight-based dosing of factor IX complex concentrate (FIXCC) in addition to FFP</td>
<td>Significant differences were found in time to correction, rate of correction, and volume of FFP required for correction between the FFP group (8.9, 2,700 ml) and the FIXCC + FFP group (2.95, 399 ml)</td>
<td></td>
</tr>
<tr>
<td>Cartmill et al. 2000</td>
<td>Prospective</td>
<td>12 patients with spontaneous WAICH</td>
<td>6 patients treated with 50 µg/kg IV PCC along with vitamin K 10 mg IV. 6 matched patients treated with 4 units of FFP and vitamin K 10 mg IV. INR re-checked 15 min after treatment</td>
<td>PCC group had significantly faster and complete reversal compared to the FFP group. Mean post-treatment INRs were 1.32 in PCC group and 2.3 in FFP group</td>
<td></td>
</tr>
<tr>
<td>Siddiq et al. 2008</td>
<td>Retrospective</td>
<td>19 patients with diagnosis of WAICH</td>
<td>10 patients treated with PCC, vitamin K, and FFP, and 9 patients treated with FFP and vitamin K</td>
<td>PCC along with FFP and vitamin K trends toward faster normalization of INR than with FFP and vitamin K alone</td>
<td></td>
</tr>
</tbody>
</table>
Recombinant activated factor VII

- Can generate a thrombin burst with both tissue factor dependent and tissue factor independent mechanisms
- Even with platelet dysfunction
- Potential for thrombotic events
- Recommended only for life-threatening bleeds and when other agents (i.e. PCC) are not available
- $$$$$$
Guideline for Use of 4-Factor Prothrombin Complex Concentrate (PCC) for Patients on Warfarin

Patient arrives with trauma and/or life-threatening hemorrhage (ICH, intra-abdominal, intra-thoracic) or needs emergent operative intervention

- Send PT/INR 5-10
- 25 units/kg IV x 1
- Max dose: 2500 units

- INR 1.4-3.9
- 35 units/kg IV x 1
- Max dose: 3500 units

- INR 4-6
- 50 units/kg IV x 1
- Max dose: 5000 units

Recheck INR 30 minutes after PCC dose
Dose based on actual body weight up to 100 kg
Cannot redose 4-Factor PCC
Antidotes

• Reversal
  – Initial studies using PCCs as potential antidotes for NOACs were in mice and baboons
Antidotes

• Reversal
  – Healthy volunteer studies suggest PCCs have potential for the reversal of rivaroxaban and dabigatran
Guideline for Use of 4-Factor PCC for Patients on Novel Oral Anticoagulants (NOAC) (i.e. Direct thrombin inhibitors or Factor Xa inhibitors)

Patient arrives with trauma and/or life-threatening hemorrhage (ICH, intra-abdominal, intra-thoracic) or needs emergent operative intervention

\[
\text{INR} < 1.4 \text{ AND NOAC within 24 hrs, } \\
25 \text{ units/kg IV } x 1 \\
\text{Max dose: 2500 units}
\]

For patients on oral direct thrombin inhibitors, consider emergent dialysis

If patient has signs/symptoms of allergic reaction to infusion – stop infusion.
Avoid use in patients with history of HIT or known allergy to albumin.

Prepared by: Rachel Garvin, M.D.
Edited by: Colleen Barthol, PharmD, BCPS, Crystal Franco-Martinez, PharmD, BCPS, Patricia Favila, PharmD, BCPS
Approved by P&T: May 9, 2014; Revised May 2015
Antidotes

• Reversal
  – Portola (Bristol-Myer-Squibb, Pfizer)
  – Universal Factor Xa Inhibitor antidote “Andexanet”
  – Modified version of human factor Xa
  – Sequesters inhibitors
  – Could be useful for LMWH and fondaparinux
Antidote

• Dabigatran, There is no antidote? -> Idarucizumab (Praxbind)

• Management of life-threatening bleeding
  – Early volume replacement
  – Appropriate RBC transfusion
  – At therapeutic drug levels, aPTT will be prolonged but is not as specific as ECT (not readily available in most labs) for activity.
Outline

- A tool to select appropriate patients
- Pharmacology/Advantages/Disadvantages/comparison
- Reversal Agents
- Major bleeding
- Putting it all together
Original Investigation

Anticoagulant Reversal, Blood Pressure Levels, and Anticoagulant Resumption in Patients With Anticoagulation-Related Intracerebral Hemorrhage

Joji B. Kuramatsu, MD; Stefan T. Germer, MD; Peter D. Schellinger, MD; Jörg Glahn, MD; Matthias Endres, MD; Jan Sobesky, MD; Julia Flechsenhar, MD; Hermann Neugebauer, MD; Eric Jüttler, MD; Armin Grau, MD; Frederick Palm, MD; Joachim Röther, MD; Peter Michels, MD; Gerhard F. Hamann, MD; Joachim Hüwel, MD; Georg Hagemann, MD; Beatrice Barber, MD; Christoph Terborg, MD; Frank Trostdorf, MD; Hansjörg Bäzner, MD; Aletta Roth, MD; Johannes Wöhrle, MD; Moritz Keller, MD; Michael Schwarz, MD; Gerold Reimann, MD; Jens Volkman, MD; Wolfgang Müllges, MD; Peter Kraft, MD; Joseph Classen, MD; Carsten Hobohm, MD; Markus Horn, MD; Angelika Milewski, MD; Heinz Reichmann, MD; Hauke Schneider, MD; Eik Schimmel, MD; Gereon R. Fink, MD; Christian Dohmen, MD; Henning Stetefeld, MD; Otto Witte, MD; Albrecht Günther, MD; Tobias Neumann-Haefelin, MD; Andras E. Racs, MD; Martin Nueckel, MD; Frank Erbguth, MD; Stephan P. Kloska, MD; Arnd Dörlfer, MD; Martin Köhrmann, MD; Stefan Schwab, MD; Hagen B. Huttner, MD
Anticoagulant Reversal

- A large cohort of patients with oral anticoagulant-related intracerebral hemorrhage (OAC-ICH)
- Reversal of INR below 1.3 (and a systolic BP < 160) at 4 hours was associated with lower rates of hematoma enlargement
Figure 3. Adjusted Graphical Regression Analysis of Combined Associations of INR Reversal, Systolic Blood Pressure, and Timing With Hematoma Enlargement

<table>
<thead>
<tr>
<th></th>
<th>No. of Patients</th>
<th>Patients With Hematoma Enlargement, No. (%)</th>
<th>OR (95% CI)</th>
<th>Favors Prevention of Hematoma Enlargement</th>
<th>Does Not Favor Prevention of Hematoma Enlargement</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>INR &lt; 1.3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Achieved</td>
<td>432</td>
<td>116 (26.9)</td>
<td>0.37</td>
<td>(0.26-0.59)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Did not achieve</td>
<td>421</td>
<td>191 (45.4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>INR &lt; 1.3 within 4 hours</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Achieved</td>
<td>217</td>
<td>43 (19.8)</td>
<td>0.27</td>
<td>(0.15-0.43)</td>
<td></td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Did not achieve</td>
<td>636</td>
<td>264 (41.5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>INR &lt; 1.3 within 4 hours and systolic BP &lt; 160 mm Hg within 4 hours</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Achieved</td>
<td>193</td>
<td>35 (18.1)</td>
<td>0.17</td>
<td>(0.11-0.33)</td>
<td></td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Did not achieve</td>
<td>498</td>
<td>220 (44.2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Multivariable model for the combined associations, ie, extent and timing of international normalized ratio (INR) reversal and systolic blood pressure (BP), with hematoma enlargement. Hematoma enlargement was defined as relative volume increase of >33% on follow-up imaging. Adjustments consisted of all non-modifiable parameters associated with hematoma enlargement, ie, time from symptom onset to imaging, deep intracerebral hemorrhage location, National Institutes of Health Stroke Scale score, and comorbidity (eTable 2 in the Supplement). OR indicates odds ratio.
Figure 6. Long-term Functional Outcome of the Entire Cohort

Distribution of functional outcome at discharge, 3 months, and 1 year using the modified Rankin Scale (mRS). An mRS of 0 indicates no symptoms; mRS 1, no significant disability, able to carry out all activities prior to stroke, some symptoms; mRS 2, slight disability, unable to carry out all activities prior to stroke, able to look after own affairs; mRS 3, moderate disability, requiring help, walking with cane or walker but without assistance; mRS 4, moderately severe disability, unable to attend bodily needs and to walk without assistance; mRS 5, severe disability, bedridden, requiring constant nursing care and attention; and mRS 6, death.
Risk of Thromboembolism, Recurrent Hemorrhage, and Death After Warfarin Therapy Interruption for Gastrointestinal Tract Bleeding

Daniel M. Witt, PharmD, FCCP, BCPS; Thomas Delate, PhD; David A. García, MD; Nathan P. Clark, PharmD; Elaine M. Hylek, MD; Walter Ageno, MD; Francesco Dentali, MD; Mark A. Crowther, MD
Resuming Warfarin after GI bleed

- 442 patients with warfarin associated GIB
- 260 patients resumed warfarin therapy
  - 1 (0.4%) had a thrombotic event (DVT)
- 182 patients did not resume warfarin therapy
  - 10 (5.5%) had thrombotic events
- 10% of patients who resumed warfarin had recurrent GIB, 5.5% who did not resume warfarin had a GIB (P=0.09)
- None of the recurrent GIB were fatal. 3 of 5 strokes in patients where warfarin was not resumed, were fatal
## Table 3. Description of Thrombotic Events

<table>
<thead>
<tr>
<th>Patient No./Sex/Age, y</th>
<th>Indication</th>
<th>Resumed Warfarin Therapy</th>
<th>Days From the Index GIB to Thrombosis</th>
<th>Thrombosis Type</th>
<th>Fatal</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/M/74</td>
<td>Deep vein thrombosis</td>
<td>No</td>
<td>90</td>
<td>Pulmonary embolism</td>
<td>No</td>
</tr>
<tr>
<td>2/F/85</td>
<td>Atrial fibrillation</td>
<td>No</td>
<td>8</td>
<td>Systemic embolism</td>
<td>No</td>
</tr>
<tr>
<td>3/M/75</td>
<td>Deep vein thrombosis</td>
<td>Yes</td>
<td>74</td>
<td>Deep vein thrombosis</td>
<td>No</td>
</tr>
<tr>
<td>4/M/85</td>
<td>Atrial fibrillation</td>
<td>No</td>
<td>27</td>
<td>Stroke</td>
<td>No</td>
</tr>
<tr>
<td>5/F/84</td>
<td>Atrial fibrillation</td>
<td>No</td>
<td>8</td>
<td>Stroke</td>
<td>Yes</td>
</tr>
<tr>
<td>6/M/76</td>
<td>Atrial fibrillation</td>
<td>No</td>
<td>23</td>
<td>Stroke</td>
<td>Yes</td>
</tr>
<tr>
<td>7/M/65</td>
<td>Pulmonary embolism</td>
<td>No</td>
<td>39</td>
<td>Pulmonary embolism and deep vein thrombosis</td>
<td>No</td>
</tr>
<tr>
<td>8/M/71</td>
<td>Stroke</td>
<td>No</td>
<td>8</td>
<td>Stroke</td>
<td>No</td>
</tr>
<tr>
<td>9/F/91</td>
<td>Atrial fibrillation</td>
<td>No</td>
<td>73</td>
<td>Stroke</td>
<td>Yes</td>
</tr>
<tr>
<td>10/M/62</td>
<td>Pulmonary embolism</td>
<td>No</td>
<td>13</td>
<td>Pulmonary embolism</td>
<td>No</td>
</tr>
<tr>
<td>11/F/95</td>
<td>Pulmonary embolism</td>
<td>No</td>
<td>17</td>
<td>Deep vein thrombosis</td>
<td>No</td>
</tr>
</tbody>
</table>
Outline

• A tool to select appropriate patients
• Pharmacology/Advantages/Disadvantages/comparison
• Reversal Agents
• Major bleeding
• Putting it all together
Anticoagulation Algorithm for Nonvalvular Atrial Fibrillation

CHA₂DS₂-VASc Score

- Score = 0
  - Reasonable to omit antithrombotic therapy

- Score = 1
  - Warfarin or no antithrombotic therapy or Aspirin may be considered

- Score = 2
  - Preferred therapy is Warfarin

Candidate for oral anticoagulation but unable to take warfarin:
- Unable to follow up for routine INR checks
- Unable to maintain therapeutic INR, not attributed to medication noncompliance
- Prohibited drug interaction, adverse reaction, or allergy to warfarin
- May consider as an alternative in cases of warfarin inefficacy

Rivaroxaban (Xarelto)
- CrCl >50 mL/min: 20mg once daily with evening meal
- CrCl 15-70 mL/min: 15mg once daily with evening meal
- Caution if CrCl <30 mL/min. These patients excluded from ROCKET AF trial. Use only if potential benefit outweighs the risk and consider assessing renal function more frequently (every 3 months).
- CrCl <15 mL/min or on hemodialysis: Do not use

Apixaban (Eliquis)
- 5mg twice daily unless patient has 2 of the following, then reduce dose to 2.5mg twice daily:
  - Age <80 years, body weight >60 kg, or Scr <1.5 mg/dL
- ESRD requiring hemodialysis: 5mg twice daily, or reduce to 2.5mg twice daily if age >80 year or body weight >60 kg
- Caution: These patients were excluded from clinical trials. Use only if potential benefit outweighs the risk.

Do not use these medications if:
- Active bleeding, significant liver disease, concomitant therapy with dual CYP3A4 and Pgp inhibitors or inducers,
- Epidural/spinal anesthesia, active endocarditis, hypersensitivity to rivaroxaban or apixaban, pregnancy

See Rivaroxaban and Apixaban Guidelines posted to the Clinical Intranet for appropriate use and more information

Prepared by Dr. Manoj Panday and edited by the UHS Anticoagulation Safety Committee
P&T Approved July 2013, Rev June 2014, Rev and P&T Approved Jan 2015
Plan for NVAFIB Stroke Prophylaxis

• Risk stratify each patient for stroke with CHA2DS2-VASc
• Discuss with patients why (or why not) anticoagulation is recommended, decide, TEACH BACK, document
• Check for drug interactions
• Check the CrCl
• Choose/initiate drug therapy
• Follow-up the INR or CrCl
• Patients change over time
Case

- This is a 52 year-old Caucasian woman brought to the ER after falling from standing and hitting the floor hard. She is found to have a subdural hematoma. During her laboratory screening she was found to have a PT of 50 and an aPTT 190. Further history indicated she had undergone knee surgery 6 months ago without any pre-surgery clotting tests, and had no (bleeding) complications
Case

- This patient made a rapid recovery and had complete resolution of the subdural hematoma without re-bleeding and without treatment
Case (continued)

• The inhibitor was discovered to be an antithrombin IgA paraprotein
• This antibody has been synthesized and is in extensive pre-clinical testing.
• It is thought to work by binding to and inactivating exosite 1, the part of the thrombin molecule that cleaves fibrinogen into fibrin
• And, most curiously, clot that occurs at vascular tears or cuts is unaffected, but intraluminal clot formation is inhibited
Ichorcumab

• This novel anticoagulant, could be the next generation anticoagulant that leaves good clot alone and prevents bad clot from forming.

• Named after “Ichor” the Greek Mythological “blood of the gods” that made them immortal