<table>
<thead>
<tr>
<th>CATEGORY</th>
<th>CONFLICT</th>
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<tbody>
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<td>Employment</td>
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<td>Research support</td>
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<td>Scientific advisory board</td>
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<td>Consultancy</td>
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<td>Major stockholder</td>
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<tr>
<td>Patents</td>
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<td>Honoraria</td>
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<tr>
<td>Travel support</td>
<td>No conflict of interest to disclose</td>
</tr>
<tr>
<td>Other</td>
<td>No conflict of interest to disclose</td>
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</tbody>
</table>
A Look at Antithrombotic Therapy and Novel Anticoagulants

Anne Greist, MD
Indiana Hemophilia & Thrombosis Center
Indianapolis, IN
1-877-CLOTTER
OBJECTIVES

- Review the pharmacology of the novel (target specific) oral anticoagulants
- Explore their indications and use
- Discuss monitoring, management of bleeding, reversal
Incidence of VTE

Adults

- 300,000 – 600,000 cases / year DVT
- 2.5 - 5% of general population
- 100,000 - 200,000 deaths / year PE
- Venous thromboembolism third most common CV disease

# Risk Factors for Venous Thrombosis

<table>
<thead>
<tr>
<th>Acquired Risk Factors</th>
<th>Inherited Risk Factors</th>
<th>Mixed/Unknown Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advancing age</td>
<td>Factor V Leiden (FVL)</td>
<td>↑ Homocysteine</td>
</tr>
<tr>
<td>Obesity</td>
<td>Prothrombin G20210A</td>
<td>↑ Factor VIII</td>
</tr>
<tr>
<td>Prior thrombosis</td>
<td>Protein C deficiency</td>
<td>APC resistance</td>
</tr>
<tr>
<td>Immobilization</td>
<td>Protein S deficiency</td>
<td>↑ Factor IX</td>
</tr>
<tr>
<td>Major surgery</td>
<td>Antithrombin deficiency</td>
<td>↑ Factor XI</td>
</tr>
<tr>
<td>Malignancy</td>
<td>Dysfibrinogenemias (rare)</td>
<td>↓ Free TFPI</td>
</tr>
<tr>
<td>Estrogens</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antiphospholipid antibody syndrome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myeloproliferative disorders, Malignancy, IBD, Nephrotic syndrome, Heparin induced thrombocytopenia</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Atrial Fibrillation

Most common sustained cardiac arrhythmia
Fivefold increased risk of stroke
Oral anticoagulation is treatment of choice for patients with CHAD$_2$ score $\geq 2$
May be indicated for CHAD$_2$ score = 1
VKA prevent stroke with a RR reduction of 65% compared with placebo

1. CHEST 2012; 141(2)(Suppl):e531S–e575S
**DISADVANTAGES OF VKAs**

Slow onset and offset of action
Need for INR monitoring
Interactions with diet and many other drugs
Small therapeutic window
Bleeding complications: 1.5-5.2% per year

TARGET-SPECIFIC ORAL ANTICAOGULANTS

Directly inhibit factor Xa:
- rivaroxaban
- apixaban
- edoxaban
- (betrixaban, darexaban)

Directly inhibits thrombin:
- dabigatran

Coagulation Cascade

Endothelial Cell
HK•PK → Kallikrein

XII

XIIa

HK • XI → Xla

Ca++

IX

VIII

VIIIa • IXa

PL Ca++

Start Common Pathway

Thrombin

Fibrinogen

Fibrin

Cross-linked Fibrin

Vascular Injury

TF

VIIa

Ca++

Extrinsic Pathway

V

Xa • Va • II

PL Ca++
Fibrinogen

VIIa

Tissue Factor

XIIa

XII

XIa

XI

IXa

IX

VIIa

VII

VIIIa

Va

Xa

X

Va

II

IIa

Dabigatran

Rivaroxaban
Apixaban
Edoxaban

Fibrin Clot
**Novel Oral Anticoagulants**

- Directly inhibit either Xa or IIa without requiring antithrombin
  - All heparinoids and pentasaccharides require antithrombin to function
- Do not require routine monitoring of levels
- No reliable method to reverse critical bleeding
- Short half-life so missed doses result in lack of protection
## Comparison of RR

<table>
<thead>
<tr>
<th>Event</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Embolism/stroke</td>
<td>0.77 (0.61-0.99)</td>
<td>0.93 (0.74-1.16)</td>
<td>0.96 (0.77-1.20)</td>
</tr>
<tr>
<td>VTE</td>
<td>1.1 (0.66-1.84)</td>
<td>0.70 (0.46-1.07)</td>
<td>1.13 (0.76-1.69)</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>0.26 (0.14-0.5)</td>
<td>0.58 (0.37-0.92)</td>
<td>0.51 (0.35-0.75)</td>
</tr>
<tr>
<td>GI bleeding</td>
<td>1.5 (0.99-2.28)</td>
<td>1.46 (1.19-1.78)</td>
<td>0.88 (0.68-1.14)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>0.90 (0.60-1.37)</td>
<td>1.03 (0.89-1.18)</td>
<td>0.70 (0.61-0.81)</td>
</tr>
</tbody>
</table>

* RR all relative to warfarin = 1.0

DABIGATRAN

- Avoid if CrCl <30
- Use 75 mg bid if CrCl 15-30
- Food delays but does not reduce absorption
- Affects TT>PTT>PT
- 85% renal clearance
- T_{1/2}: 12-17h; mild-moderate CKD 15-18h; severe CKD 28h
- Protein binding 35%

## Factor Xa Inhibitors

<table>
<thead>
<tr>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ Approved for VTE, AF and VTE prophylaxis</td>
<td>▪ Approved for VTE, AF and VTE prophylaxis</td>
</tr>
<tr>
<td>▪ Take with food</td>
<td>▪ Not affected by food</td>
</tr>
<tr>
<td>▪ Affects anti-Xa&gt;PT&gt;PTT</td>
<td>▪ Affects anti-Xa levels</td>
</tr>
<tr>
<td>▪ 66% renal clearance</td>
<td>▪ 27% renal clearance</td>
</tr>
<tr>
<td>▪ VTE: Avoid if CrCl &lt;30 mL/min</td>
<td>▪ Reduce dose if 2 of: age &gt;80, creatinine &gt;1.5, weight &lt;60 kg</td>
</tr>
<tr>
<td>▪ AF: 15 mg daily if CrCl 15-50</td>
<td>▪ T&lt;sub&gt;1/2&lt;/sub&gt;: ~12h</td>
</tr>
<tr>
<td>▪ T&lt;sub&gt;1/2&lt;/sub&gt;: 5-9h or 11-13h if elderly</td>
<td></td>
</tr>
<tr>
<td>▪ Not influenced by extremes of body weight</td>
<td></td>
</tr>
</tbody>
</table>

## PHARMACOKINETICS

<table>
<thead>
<tr>
<th></th>
<th>Warfarin</th>
<th>Dabigatran</th>
<th>Apixaban</th>
<th>Rivaroxaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bioavailability</strong></td>
<td>100%</td>
<td>6.5%</td>
<td>50%</td>
<td>80-100%</td>
<td>60%</td>
</tr>
<tr>
<td><strong>Max concentration</strong></td>
<td>4h</td>
<td>0.5-2h</td>
<td>3-4h</td>
<td>2-4h</td>
<td>1.5h</td>
</tr>
<tr>
<td><strong>Half-life</strong></td>
<td>20-60h</td>
<td>12-14h</td>
<td>12h</td>
<td>11-13h</td>
<td>10-14h</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5-9h (young)</td>
<td></td>
</tr>
<tr>
<td><strong>Renal clearance</strong></td>
<td>0%</td>
<td>85%</td>
<td>27%</td>
<td>66%</td>
<td>33%</td>
</tr>
<tr>
<td><strong>Protein binding</strong></td>
<td>99%</td>
<td>35%</td>
<td>87%</td>
<td>92-95%</td>
<td>40-59%</td>
</tr>
</tbody>
</table>

# Dosing Considerations

<table>
<thead>
<tr>
<th>Condition</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver disease</td>
<td>Use caution</td>
<td>Contraindicated if Child’s B or C</td>
<td>Caution if Child’s B; Contraindicated if Child’s C</td>
</tr>
<tr>
<td>CrCl 15-30</td>
<td>Adjust dose if used for AF (contraindicated in Canada)</td>
<td>Not recommended</td>
<td>Caution*</td>
</tr>
<tr>
<td>CrCl &lt;15</td>
<td>Contraindicated</td>
<td>Contraindicated</td>
<td>Not recommended‡</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Category C; not recommended</td>
<td>Category C</td>
<td>Category B; still not recommended</td>
</tr>
<tr>
<td>Lactation</td>
<td>Unknown if excreted in breast milk; not recommended</td>
<td>Unknown if excreted</td>
<td>Unknown if excreted; not recommended</td>
</tr>
</tbody>
</table>

* Reduce dose if at least 2 are true: creatinine ≥1.5, age ≥80 years, or weight <60 kg.
‡ Label approves use in ESRD, but American Heart Association recommends against use.
# Selected Drug Interactions

<table>
<thead>
<tr>
<th>Medications</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antacids</td>
<td>Not recommended, May reduce absorption</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Azole antifungals (excludes fluconazole)</td>
<td>Not recommended</td>
<td>Avoid combination</td>
<td>Avoid combination</td>
</tr>
<tr>
<td>HIV/HCV antivirals</td>
<td>Monitor therapy</td>
<td>Avoid combination</td>
<td>Avoid combination</td>
</tr>
<tr>
<td>Rifamycins</td>
<td>Avoid combination</td>
<td>Avoid combination</td>
<td>Avoid combination</td>
</tr>
<tr>
<td>Quinidine</td>
<td>Not recommended</td>
<td>Monitor therapy</td>
<td>Monitor therapy</td>
</tr>
<tr>
<td>Dronedarone</td>
<td>Not recommended</td>
<td>Avoid combination</td>
<td>Monitor therapy</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>Consider alternative, monitor therapy</td>
<td>Monitor therapy</td>
<td>Monitor therapy</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>May increase levels, monitor therapy</td>
<td>May increase levels, monitor therapy</td>
<td>Avoid combination</td>
</tr>
</tbody>
</table>

HOW TO ADDRESS BLEEDING IN PATIENTS TAKING TARGET SPECIFIC ORAL ANTICOAGULANTS

PUTTING THE BRAKES ON
## Drug Monitoring

<table>
<thead>
<tr>
<th></th>
<th>PT</th>
<th>aPTT</th>
<th>TT</th>
<th>Dilute TT</th>
<th>Anti-Xa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>+/-</td>
<td>↑</td>
<td>↑↑↑</td>
<td>↑↑</td>
<td>NA</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>↑</td>
<td>+/-</td>
<td>NA</td>
<td>NA</td>
<td>↑↑</td>
</tr>
<tr>
<td>Apixaban</td>
<td>↑</td>
<td>+/-</td>
<td>NA</td>
<td>NA</td>
<td>↑↑</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>↑</td>
<td>↑↑</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
</tr>
</tbody>
</table>

+/- May increase or produce no change. Reagent and individual dependent.
↑ Variable Increase
↑ ↑ Predictable increase that may be calibrated
↑ ↑ ↑ High sensitivity increase, often exceeding upper limit of assay

Procoagulants Measured by Screening Tests

APTT sensitive to intrinsic and common pathway factors or inhibition of the coagulation process

PT sensitive to extrinsic and common pathway factors or inhibition of the coagulation process

TT sensitive to quantity and quality of fibrinogen or inhibition of the fibrin clot formation
# Risk Factors for Bleeding with Anticoagulant Therapy & Estimated Risk of Major Bleeding in Low-, Moderate-, & High-Risk Categories

**Risk Factors**

- Age > 65 years
- Age >75 years
- Previous bleeding
- Cancer
- Metastatic cancer
- Renal failure
- Liver failure
- Thrombocytopenia
- Previous stroke
- Diabetes
- Anemia
- Antiplatelet therapy
- Poor anticoagulant control
- Comorbidity & reduced functional capacity
- Recent surgery
- Frequent falls
- Alcohol use

## Estimated Absolute Risk of Major Bleeding %

<table>
<thead>
<tr>
<th>Categorization of Risk of Bleeding</th>
<th>Low Risk (0 Risk Factors)</th>
<th>Moderate Risk (1 Risk Factor)</th>
<th>High Risk (&gt; 2 Risk Factors)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anticoagulation 0-3 Months</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline risk (%)</td>
<td>0.6</td>
<td>1.2</td>
<td>4.8</td>
</tr>
<tr>
<td>Increased risk (%)</td>
<td>1.0</td>
<td>2.0</td>
<td>8.0</td>
</tr>
<tr>
<td>Total risk (%)</td>
<td>1.6</td>
<td>3.2</td>
<td>12.8</td>
</tr>
<tr>
<td><strong>Anticoagulation after first 3 months</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline risk (% per year)</td>
<td>0.3</td>
<td>0.6</td>
<td>&gt; 2.5</td>
</tr>
<tr>
<td>Increased risk (% per year)</td>
<td>0.5</td>
<td>1.0</td>
<td>&gt; 4.0</td>
</tr>
<tr>
<td>Total risk (% per year)</td>
<td>0.8</td>
<td>1.6</td>
<td>&gt; 6.5</td>
</tr>
</tbody>
</table>

ANTICOAGULATION REVERSAL

- Blocking absorption
- Removing the circulating drug
- Increasing excretion
- Inactivating the drug
- Increasing the targeted clotting factor
- Promoting coagulation
**Anticoagulation Reversal**

- **Increasing the target**
  - PCC: Kcentra® 50 units/kg
  - aPCC: FEIBA® 50 units/kg

- **Promoting coagulation**
  - rFVIIa: NovoSeven® 90 mcg/kg
SPECIFIC ANTIDOTES

- Idarucizumab: RE-VERSE AD
- Andexanet alfa
- PER977

A Study of the RE-VERSal Effects of Idarucizumab on Active Dabigatran

Patients on dabigatran
  • Active major bleeding
  • Needing emergency surgery
  • Given idarucizumab 5 gm IV
  • Data obtained on bleeding, clotting assays and dabigatran levels

Suggested strategy for management of TSOAC-associated bleeding.

Risk stratification

- Minor bleeding
  - Local hemostatic measures
  - Consider anticoagulant withdrawal (balance thrombotic and bleeding risks)

- Moderate bleeding
  - General measures
    - Anticoagulant withdrawal
    - Mechanical compression
    - Monitor hemodynamic status
    - Volume replacement
    - Definitive interventions
  - Blood product transfusion
    - RBC transfusion for anemia
    - Plasma for coagulopathy (e.g., DIC, dilutional)
    - Consider platelets for patients on antiplatelet agents

- Severe/life-threatening bleeding
  - General measures and blood product transfusion as per moderate bleeding
    - Intensive care setting
    - Hemodynamic support
    - Consider:
      - 4-factor PCC (50 U/kg)*
      - Activated PCC (80 U/kg)**
  - Adjunctive therapies
    - Oral charcoal for dabigatran ingestion within 2 hours
    - Hemodialysis for dabigatran removal
    - Desmopressin
    - Antifibrinolytic agents

Siegal D M et al. Blood 2014;123:1152-1158

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CONCLUSIONS

1. These drugs seem to have comparable efficacy when compared with warfarin, with fewer intracranial hemorrhages
2. Risk of major bleeding is reduced with apixaban, but equivalent with rivaroxaban and dabigatran
3. Dabigatran and rivaroxaban seem to increase the rate of GI bleeding
4. We cannot measure levels to adjust for drug interactions
5. The recommendations for reversal of these drugs are based on studies in animals and healthy volunteers, or nonrandomized trials
6. Long term side effects may still be unknown
Summary

- Novel anticoagulants are appealing, but should be used with caution.
- As TSOACs become more widespread, automated testing will be needed in routine hospital laboratories.
- Bleeding from novel anticoagulants is primarily supportive unless life threatening, in which case PCC or aPCC could be used; there are specific antidotes in development.