Expert Debate: Novel Oral Anticoagulants

Speakers
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University of Nebraska Medical Center
College of Pharmacy

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Brigham and Women’s Hospital
Director of Pharmacy

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Clinical Pharmacy Specialist in Anticoagulation Management
The Johns Hopkins Hospital

Disclosures
• Paul Dobesh has served as a consultant for Daiichi Sankyo, Janssen, BMS/Pfizer, and Boehringer Ingelheim.
• John Fanikos has served as a consultant for Portola Pharmaceuticals.
• Maureen Smythe has served as a consultant for Portola Pharmaceuticals.

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Learning Objectives
• Discuss the risks and benefits associated with the use of novel oral anticoagulants (NOACs) and vitamin K antagonists in patients who require anticoagulation.
• Describe the results of clinical trials investigating the use of NOACs and warfarin for patients who require anticoagulation.
• Evaluate the appropriateness of NOAC use for complex patient case scenarios.
• Recommend appropriate NOAC dosing regimens based on a patient’s renal function.

• Target Audience: Pharmacists
• ACPE#: 0202-0000-16-025-L01-P
• Activity Type: Application-based
Growing Problem of Thromboembolic Events

AF and VTE are growing problems that result in significant negative outcomes.

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![Graph showing prevalence of AF and VTE](image)

Recent Approvals Have Changed the Anticoagulation Landscape

- 6/8/1954: Warfarin approved
- 10/19/2010: Dabigatran approved
- 1/8/2015: Apixaban approved
- 7/1/2011: Rivaroxaban approved
- 5/20/1956: JFK assassinated
- 7/20/1969: Neil Armstrong sets foot on the moon
- 8/9/1974: President Nixon resigns
- 11/9/1989: Berlin Wall falls
- 11/05/1964: Richard Nixon elected president
- 11/07/1960: John F. Kennedy elected president
- 11/07/1956: Dwight D. Eisenhower elected president
- 11/07/1948: Harry S. Truman elected president
- 11/07/1944: Franklin D. Roosevelt elected president
- 11/07/1940: Franklin D. Roosevelt elected president
- 11/07/1936: Franklin D. Roosevelt elected president
- 11/07/1932: Franklin D. Roosevelt elected president
- 11/07/1928: Herbert Hoover elected president
- 11/07/1924: Calvin Coolidge elected president
- 11/07/1920: Warren G. Harding elected president
- 11/07/1916: Warren G. Harding elected president
- 11/07/1912: Warren G. Harding elected president
- 11/07/1908: Warren G. Harding elected president
- 11/07/1904: Warren G. Harding elected president
- 11/07/1900: William McKinley elected president
- 11/07/1896: Grover Cleveland elected president
- 11/07/1892: Grover Cleveland elected president
- 11/07/1888: Grover Cleveland elected president
- 11/07/1884: Grover Cleveland elected president
- 11/07/1880: Grover Cleveland elected president
- 11/07/1876: Rutherford B. Hayes elected president
- 11/07/1872: Rutherford B. Hayes elected president
- 11/07/1868: Ulysses S. Grant elected president
- 11/07/1864: Abraham Lincoln elected president
- 11/07/1860: Abraham Lincoln elected president
- 11/07/1856: Franklin Pierce elected president
- 11/07/1852: Franklin Pierce elected president
- 11/07/1848: James Buchanan elected president
- 11/07/1844: James Buchanan elected president
- 11/07/1840: James Buchanan elected president
- 11/07/1836: James Buchanan elected president
- 11/07/1832: John Tyler elected president
- 11/07/1828: Andrew Jackson elected president
- 11/07/1824: Andrew Jackson elected president
- 11/07/1820: Andrew Jackson elected president
- 11/07/1816: Andrew Jackson elected president
- 11/07/1812: Andrew Jackson elected president
- 11/07/1808: John Adams elected president
- 11/07/1804: John Adams elected president
- 11/07/1800: John Adams elected president
- 11/07/1796: John Adams elected president
- 11/07/1792: John Adams elected president
- 11/07/1788: John Adams elected president
- 11/07/1784: John Adams elected president
- 11/07/1780: John Adams elected president
- 11/07/1776: John Adams elected president

The “Ideal” Anticoagulant

- Oral, fixed dosage (preferably once daily)
- Rapid onset
- Rapid offset of action
- No need for renal or hepatic adjustment
- Predictable pharmacokinetics/dynamics
- No need to ever “switch” therapies
- Wide therapeutic window
- No need for routine anticoagulation effect monitoring
- Low propensity for food/drug interactions
- Available antidote
- Reasonable cost

Clinical Case

- JG, a 70-year-old AA male (90 kg, 6’0”)
- Past medical history
  - Hypertension (BP 144/94): on HCTZ and lisinopril
  - Type 2 diabetes mellitus: on metformin
  - Depression: on citalopram
  - Blood glucose 150 mg/dL (not fasting); all other labs are within normal range
  - Serum creatinine (Scr) 1.1 mg/dL, estimated creatinine clearance (CrCl) 72 (IBW) to 80 (ABW) mL/min
  - Hepatic function: normal
  - EF 60%
- Currently admitted for AF and TIA symptoms

- HR on admission is 136 beats per minute
- Patient given an IV bolus of diltiazem and started on an IV infusion
- HR currently 80 beats per minute
- Decision is made that the patient needs chronic anticoagulation.
- What is the best antithrombotic option for JG

Clinical Case

- Currently admitted for AF and TIA symptoms
- HR on admission is 136 beats per minute
- Patient given an IV bolus of diltiazem and started on an IV infusion
- HR currently 80 beats per minute
- Decision is made that the patient needs chronic anticoagulation.
- What is the best antithrombotic option for JG

What would you recommend?

A. Aspirin
B. Aspirin plus clopidogrel
C. Warfarin target INR 2-3
D. Direct acting oral anticoagulant (DOAC)
Aspirin + Clopidogrel

Table 1: Comparison of ACTIVE A and ACTIVE W Trials

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Major Bleeding</th>
<th>Major Stroke</th>
<th>Vascular Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>2.0% /year</td>
<td>1.3% /year</td>
<td>7.6% /year</td>
</tr>
<tr>
<td>Warfarin</td>
<td>5.4% /year</td>
<td>3.9% /year</td>
<td>4.5% /year</td>
</tr>
</tbody>
</table>

A-Fib Risk Assessment Scoring Systems

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHF/LVEF &lt; 40%</td>
<td>1 points</td>
</tr>
<tr>
<td>HTN</td>
<td>1 point</td>
</tr>
<tr>
<td>Age &gt; 75</td>
<td>2 points</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1 point</td>
</tr>
<tr>
<td>Previous stroke, TIA, TE</td>
<td>2 points</td>
</tr>
<tr>
<td>Vascular disease, stroke, TIA, TE</td>
<td>5 points</td>
</tr>
<tr>
<td>Female</td>
<td>1 point</td>
</tr>
</tbody>
</table>

Total score: 9 points

Why Warfarin is the Best Option

- Efficacy
- Safety
- Reversibility
- Practical management considerations
  - Established ability to manage drug interactions
  - Ability to identify the degree of anticoagulation
  - Consequence of non-adherence due to half-life
- Need for downstream alteplase (t-PA) treatment

A-Fib Risk Assessment Scoring Systems

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</tr>
<tr>
<td>Female</td>
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</tr>
</tbody>
</table>

Total score: 9 points

What is the best agent for secondary prevention?

Pro Warfarin: Dr. Fanikos
Pro DOAC: Dr. Smythe

Case Assumptions
- DOAC copay is manageable for patient
- Patient is adherent with medications
- Patient is managed by a health care system with an established Coumadin clinic
- Shared physician-patient decision making would occur

Pro Warfarin: Dr. Fanikos
Pro DOAC: Dr. Smythe

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Warfarin Reduces Stroke in AF Patients Compared With Placebo

- AFASAK
- SPAF
- BAATAF
- CAFA
- SPINAF
- EAF

Relative Risk Reduction (95% CI)
DOAC vs Warfarin Trials
All Randomized, Multi-center Non-inferiority Trials

<table>
<thead>
<tr>
<th>Variable</th>
<th>RELY (edoxaban)</th>
<th>ROCKET-AF (rivaroxaban)</th>
<th>ARISTOTLE (apixaban)</th>
<th>ENGAGE (edoxaban)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>18,113</td>
<td>14,266</td>
<td>18,206</td>
<td>21,105</td>
</tr>
<tr>
<td>Dose Frequency</td>
<td>BID</td>
<td>QD</td>
<td>BID</td>
<td>QD</td>
</tr>
<tr>
<td>Blinding</td>
<td>NO</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>% VKA Naive</td>
<td>50%</td>
<td>38%</td>
<td>43%</td>
<td>41%</td>
</tr>
<tr>
<td>TTR mean</td>
<td>64%</td>
<td>55%</td>
<td>62%</td>
<td>66%</td>
</tr>
<tr>
<td>Mean CHADS2</td>
<td>2.2</td>
<td>2.5</td>
<td>2.1</td>
<td>2.8</td>
</tr>
<tr>
<td>Previous stroke/TIA</td>
<td>55%</td>
<td>55%</td>
<td>19%</td>
<td>28%</td>
</tr>
<tr>
<td>Timeframe for enrollment of acute TIA patient</td>
<td>NR</td>
<td>3 days</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

TTR = Time in Therapeutic Range

BWH Anticoagulation Management Service (Warfarin Clinic)
- 30 year history
- 4,000 patients (AF, VTE, Heart valves, VADs)
- 350 patients per pharmacist

Meta-Analysis of Stroke Prevention in AF

Secondary outcomes
- Safety
- Efficacy
- Stroke or systemic embolism
- Combined
- Hospitalization
- In-hospital mortality
- In-hospital stroke
- In-hospital death
- In-hospital TIA

Understanding Non-Inferiority Trials
- Audience Question:
  Does non-inferiority mean equivalence?
  A. Yes
  B. No
  C. I don't know

Efficacy of Novel Anticoagulants Compared with Warfarin – AF Trials

Reduction of stroke or systemic embolism
- Dabigatran 110mg
  - Superior
  - Non-inferior

Reduction of ischemic stroke
- Superior
- Non-inferior

Understanding Non-Inferiority Trials
- Equivalence: not unacceptably different
- Non inferior: new intervention is not un acceptably worse
- Non-inferior designs used if new treatment offers advantage such as less side effects, improved quality of life, convenience
- Need to define what is statistically worse; define the margin or window of indistinguishability

It's time to pull the plug on the new oral anticoagulants for nonvalvular atrial fibrillation

Studies comparing dabigatran and similar agents with warfarin do not demonstrate noninferiority when warfarin is properly managed.


TTR time in therapeutic range, HS hemorrhagic stroke


Rate of Warfarin ICH Overstated in Multi-National Trials

Tightness of INR control important in addition to TTR, Sportif V 83% INR values between 1.8 and 3.2%

TTR time in therapeutic range, HS hemorrhagic stroke


GI Bleeding DOAC versus Warfarin – AF Trials

What is the most common site of anticoagulant hemorrhage?


BWH Anticoagulation Management Service (Warfarin Clinic)

Event Rate Per Patient Years


Anticoagulation monitoring and reversibility

• Bleeding risks are additive!

• Patients and providers want the ability to assess intensity of anticoagulation in timely manner

• Lack of reversal agent commonly cited as reason against DOAC agents

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Drug Interactions

- Warfarin drug interactions managed with INR monitoring and dose adjustment
- DOACs are substrates of P-gp or metabolised by CYP 450 system
- Common interacting drugs in AF include
  - Amiodarone AUC Dab 1 up to 60%
  - diltiazem AUC apix 40%
  - verapamil AUC Dabi ↑ 12–180%

Non-Adherence

- Warfarin non-adherence easily recognized
- Warfarin is long 1/2 protective during isolated episodes of non-adherence
- DOAC non-adherence not detectable
- DOAC short half life concerning with non-adherence

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AHA Acute Ischemic Stroke Guidelines

Intravenous rtPA (0.9mg/kg) maximum dose 90mg) is recommended for selected patients who may be treated within 3 hours of onset of ischemic stroke [Class I; level of evidence A]

EXCLUSION CRITERIA FOR TREATMENT WITHIN 3 Hours:
- Current use of direct thrombin inhibitors or direct factor Xa inhibitors with elevated sensitive laboratory tests (aPTT, INR, platelet count and ECT; TT or appropriate factor Xa activity assay)

Kernan WN, Stroke; 2014;45(7): 2160.

Why a DOAC is the Best Option!

- Efficacy
- Safety
- Reversibility doesn’t matter
- Practical management considerations
- Need for downstream rtPA treatment

Opinion, Not Fact

<table>
<thead>
<tr>
<th>Clinical situation</th>
<th>Preferred Agent</th>
<th>Evidence</th>
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</thead>
<tbody>
<tr>
<td>Prior ischemic stroke or transient ischemic attack</td>
<td>apixaban, edoxaban, rivaroxaban, dabigatran</td>
<td>All studies enrolled patients with prior history of stroke</td>
</tr>
<tr>
<td>Renal dysfunction (Estimated creatinine clearance 30 to 50 mL/min)</td>
<td>apixaban, edoxaban, rivaroxaban, dabigatran</td>
<td>All agents have dose reduction option</td>
</tr>
<tr>
<td>Co-administration of p-glycoprotein P inhibitors</td>
<td>edoxaban</td>
<td>Only agent to have dose reduction strategy with concomitant use</td>
</tr>
<tr>
<td>Vitamin K antagonist-naive patients</td>
<td>apixaban, edoxaban, or dabigatran</td>
<td>Lower bleeding rates with apixaban and edoxaban, improved efficacy with dabigatran</td>
</tr>
<tr>
<td>Ablation or cardioversion candidates</td>
<td>dabigatran, rivaroxaban, apixaban</td>
<td>Experience with small sub populations of the larger trials</td>
</tr>
<tr>
<td>Prior history of gastrointestinal bleeding</td>
<td>edoxaban</td>
<td>Reduction in gastrointestinal bleeding with 30 mg dose</td>
</tr>
</tbody>
</table>

AHA/ACC/HRS 2014 Guidelines

CHA2DS2-VASc ≥2: Warfarin (INR 2.0 – 3.0)
CHA2DS2-VASc ≥2: dabigatran or rivaroxaban or apixaban

AHA/ASA 2014 Guidelines

Warfarin or apixaban
Dabigatran
Rivaroxaban

Stroke Prevention in NVAF

AHA/ACC/HRS 2014 Guidelines

<table>
<thead>
<tr>
<th>Class</th>
<th>Level</th>
</tr>
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<tbody>
<tr>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>I</td>
<td>B</td>
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<td>B</td>
</tr>
<tr>
<td>IIa</td>
<td>B</td>
</tr>
</tbody>
</table>
Problems with Warfarin

1. Under-utilized
   - 55% of eligible patients with atrial fibrillation are not treated
   - Use is lower in elderly patients

2. Difficult to Use

Meta-Analysis of Stroke Prevention in AF

Net Clinical Benefit: DOAC vs Warfarin

Net Clinical Benefit defined as composite of:
- ischemic stroke + systemic embolism
- MI
- hemorrhagic stroke
- adjusted major bleeding

Meta-Analysis Stroke Prevention in AF: Focus on Mortality
Patient Concerns About AF

Warfarin: Walking a Tightrope

- Excessive dose or dose in therapeutic range precipitates hemorrhage
- Inadequate dose predisposes to thrombotic disease

Reversibility, Is it that important?
- DOAC agents: major bleeding is not higher than warfarin
- DOAC agents lower all cause mortality by ~ 10%
- DAOC major bleed mortality lower than with warfarin without a reversal agent
- Clinical trial results of patients with major bleed suggest favorable resource utilization outcomes with DOACs
- Initial registry data and claims data support favorable outcomes with DOACs in the real world setting
- Idarucizumab is here, andexanet-alfa is coming!

DOAC Adherence and Persistence
- DOAC adherence: patient transition of care plan is needed despite no need for laboratory monitoring
- Persistence:
  - DOAC persistence comparable with warfarin in trials
  - Persistence decreases in elderly regardless of agent
  - Ongoing, prospective non-interventional registry: rivaroxaban discontinuation rate at 1 year ~ 15%
  - Post-marketing data indicate improved persistence with dabigatran versus warfarin

DOAC use in the elderly vs warfarin
- Dabigatran use in age > 75 years:
  - Trend toward ↑ extra-cranial bleeding
  - ↓ in ICH

- Rivaroxaban use in age > 75 years:
  - ↑ combination of major and CRNM bleeding
  - No difference in ICH

- Apixaban use in age 65-75 years and > 75 years:
  - Greater net clinical benefit
  - DECREASES major bleeding and ICH
  - Greater reduction in stroke and systemic embolism

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Apixaban Safety and Net Clinical Benefit: Data from ARISTOTLE

The impact of Age


DOAC for Secondary Stroke Prevention

<table>
<thead>
<tr>
<th>Trial Subgroup analysis</th>
<th>Meta-analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RELY</strong></td>
<td>• N = 7876 DOAC patients &amp; 6651 warfarin patients</td>
</tr>
<tr>
<td><strong>ROCKET –AF</strong></td>
<td>• All with history of stroke or TIA</td>
</tr>
<tr>
<td>• Dabi 150mg: superior for SSE prevention &amp; similar major bleeding</td>
<td></td>
</tr>
<tr>
<td>• DOACs</td>
<td>• DOACs</td>
</tr>
<tr>
<td>• Riva similar safety and efficacy to those without stroke or TIA</td>
<td></td>
</tr>
<tr>
<td>• 15% ↓ composite of SSE</td>
<td></td>
</tr>
<tr>
<td>• 10% ↓ major bleeding</td>
<td></td>
</tr>
<tr>
<td>• 56% ↓ hemorrhagic stroke</td>
<td></td>
</tr>
</tbody>
</table>

ARISTOTLE

• 5mg BID superior to warfarin for SSE prevention

SSE stroke and systemic embolism


DOAC Drug Interactions

- DOACs are substrates of P-gp and CYP 450 system
- Dependence of CYP 3A4 for metabolism: rivaroxaban > apixaban > edoxaban
- Despite similar mechanisms of drug interactions, considerable variability in product labeling
- May need to consider renal function along with concomitant drugs
- Labeling for managing drug interactions varies across regulatory agencies
- Aspirin significantly increases bleed risk with all DOACs, evaluate concomitant indication

DOAC Measurement

- aPTT*
- Ecarin Clotting Time (ECT)
- Thrombin Time (TT)
- Dilute TT (dTT)
- Anti-factor Xa activity calibrated to agent
- PT* For Dabigatran

*qualitative indicator of presence if sensitive reagent is used
Always assess time of last dose
Normal ECT, TT, dTT (dabigatran) or calibrated anti-Xa level (direct acting Xa) exclude clinically relevant drug concentrations


DOAC and Acute Ischemic Stroke: Thrombolysis

- Controversial area with limited evidence
- Document time of last dose
- Consider impact of renal impairment and drug interactions on drug exposure
- Consider thrombolysis if history and laboratory evidence indicate absence of anticoagulant effect


A DOAC is preferred!

- Patient is elderly, high stroke risk, not at high bleed risk, no significant drug interactions, adherent to medications
- Clinical benefit of DOACs aligns with patient important events
  - Reduction in hemorrhagic stroke
  - Reduction in mortality
  - Significant reduction in ICH which carries ~50% mortality rate

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A DOAC is preferred!

- Safety established in secondary stroke prevention
- Apixaban is level 1A recommendation by 2014 AHA/ASA guidelines for stroke prevention in NVAF

Recombinant Factor VIIa: FXa inhibitor
- Fast reversal
- Provides rapid reversal for major bleeding
- Can be given at 1 mg/kg IV

A patient of yours has a new prescription for dabigatran for her new onset atrial fibrillation. While the physician covered some things about the medication, she wants to know what happens if she needs a major surgery or has a major bleeding episode.

**Specific Reversal Agents for NOACs: Approved and in Development**

<table>
<thead>
<tr>
<th>Antidote</th>
<th>Target</th>
<th>Mechanism of Action</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idarucizumab</td>
<td>FXa inhibitors</td>
<td>Humanized Fab specifically binds dabigatran (binding affinity ≈350 x higher than binding of dabigatran to thrombin), NO reversal for FXa inhibitors or LMWH/fondaparinux</td>
<td>Approved by US FDA, October 10, 2015 for use in patients on dabigatran during emergency situations when there is a need to reverse dabigatran’s blood-thinning effects</td>
</tr>
<tr>
<td>Andexanet alfa</td>
<td>FXa inhibitors</td>
<td>Recombinant FXa analogue that binds to direct FXa inhibitors and antithrombin, so provides reversal for rivaroxaban, apixaban, edoxaban, LMWH, fondaparinux NO reversal for dabigatran</td>
<td>Phase 2 completed for rivaroxaban, apixaban, enoxaparin, ongoing for edoxaban</td>
</tr>
<tr>
<td>Cinaparibant</td>
<td>Universal</td>
<td>Synthetic small molecule that binds to NOACs, heparin and fondaparinux</td>
<td>Phase 1 completed for edoxaban</td>
</tr>
</tbody>
</table>

**Recommended Dosing of Concentrated Clotting Factor Products for OAC Repletion**

<table>
<thead>
<tr>
<th>Preparation Agent</th>
<th>Dosing Information</th>
<th>Dose(s) for Repletion of Specific OAC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban</td>
<td>Up to 25 units/kg</td>
<td>Up to 25 units/kg with severe bleeding response; possibly extrapolate doses from warfarin reversal</td>
</tr>
<tr>
<td>Idarucizumab</td>
<td>90 µcg/kg (no data available)</td>
<td>No data available; possibly extrapolate doses from warfarin reversal</td>
</tr>
<tr>
<td>Any OAC</td>
<td></td>
<td>17.7-50.4 µg/kg up to 250 µg/kg</td>
</tr>
</tbody>
</table>

**Case Study**

A patient of yours has a new prescription for dabigatran for her new onset atrial fibrillation. While the physician covered some things about the medication, she wants to know what happens if she needs a major surgery or has a major bleeding episode.

**Question**

What would you tell her is the appropriate management of major bleeding or needing a major surgery?

A. aPCC  
B. Dialysis  
C. FFP  
D. Recombinant factor VIII  
E. Vitamin K  
F. None of the above

**Answer**

A DOAC is preferred!
Idarucizumab: A Specific Reversal Agent for Dabigatran

- Humanized Fab fragment
- Binding affinity = 350 x higher than dabigatran to thrombin
- IV administration, immediate onset of action
- Short half-life
- No procoagulant or anticoagulant effects expected

Idarucizumab for Dabigatran Reversal

- Prospective cohort study to determine safety of 5 g IV idarucizumab, its capacity to reverse anticoagulant effects of dabigatran
  - Group A (n=51): Serious bleeding
  - Group B (n=39): Required urgent procedure
- Median maximum percentage reversal 100% (95% CI, 100–100)\(^a\)
- Normalized test results in 88% to 98%, effect evident within minutes
- Median maximum percentage reversal 100% (95% CI, 100–100)\(^a\)

Interim Results: Dabigatran Reversal With Idarucizumab Based on dTT, Group B

- Among 68 patients with an elevated dilute thrombin time and 81 with an elevated ECT at baseline
- One thrombotic event within 72 h after idarucizumab administration
- In group B (N=36) pts who underwent a procedure
  - 23 pts: normal intraoperative hemostasis reported
  - 2 pts: mildly abnormal hemostasis
  - 1 pt: moderately abnormal hemostasis
- In group A (N=35 evaluable pts) hemostasis restored at median of 11.4 h
- One thrombotic event within 72 h after idarucizumab administration in a patient in whom anticoagulants had not been reinitiated

RE-VERSE AD: Ongoing Multicenter, Single-arm, Open-label Phase 3 Study

- Prospective cohort study to determine safety of 5 g IV idarucizumab, its capacity to reverse anticoagulant effects of dabigatran
- Group A: Emergency surgery or procedure + dabigatran treated
- Group B: Uncontrolled bleeding + dabigatran-treated

Interim Results: Dabigatran Reversal With Idarucizumab Based on dTT, Group A

- Of 36 patients undergoing surgery: 33 patients had normal intraoperative hemostasis (as judged by the physician)
  - 1 pt: moderately abnormal

Andexanet alfa: Antidote for Factor Xa Inhibitors

- Engineered version of human FXa, lacking direct catalytic activity of native protein
- Binds with high-affinity, blocking inhibition of FXa

Clinical outcomes

- Of 36 patients undergoing surgery: 33 patients had normal intraoperative hemostasis (as judged by the physician)
  - 1 pt: moderately abnormal

Properties

- Preclinical data collected in numerous models
- Phase 2 dose response assessments in 144 healthy volunteers indicated initial significant, dose-dependent decreases in anti-Xa activity followed by slow increases in anti-Xa activity to high levels
- 3 studies in healthy subjects aged 50–75 y investigating reversal of rivaroxaban\(^2\) and apixaban
- Phase 3 study in 35 healthy volunteers: “immediately and significantly” reversed anticoagulation of rivaroxaban
ANNEXA - A (apixaban) and R (rivaroxaban)

Part 1: All Subjects received 4 days DOAC therapy
- Apixaban 5 mg twice daily (55-73 years old)
- Rivaroxaban 20 mg once daily (50-65 years old)

Andexanet bolus only
- Apixaban – 400 mg
- Rivaroxaban – 800 mg
- Placebo

Part 2: All Subjects received 4 days DOAC therapy
- Apixaban 5 mg twice daily (50-73 years old)
- Rivaroxaban once daily

Andexanet bolus + 2 hour infusion
- Apixaban – 400 mg + 480 mg (4 mg/min)
- Rivaroxaban – 800 mg + 960 mg (8 mg/min)
- Placebo

Primary Endpoint: Anti-fXa
- Met primary endpoint: mean percent change in anti-fXa from baseline to post-infusion nadir was 92% (apixaban) and 97% (rivaroxaban)
- P < 0.0001 vs. placebo in both cases

ANNEXA (Bolus + Infusion)


Ciraparantag (PER977)
- A synthetic small molecule (approximately 500 daltons), IV
- Reverses anticoagulant effect of NOACs, fondaparinux, and LMWH
- Phase 2 study with edoxaban showed complete and sustained reversal of steady-state edoxaban on day 3


To prevent stroke and systemic embolism you would recommend:

A. Warfarin adjusted to INR 2 - 3
B. Dabigatran 150mg BID
C. Apixaban 2.5mg BID
D. Rivaroxaban 15mg daily
E. Dabigatran 75mg BID
F. Edoxaban 60mg daily

Stages of Chronic Kidney Disease

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>GFR (ml/min/1.73m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Kidney damage with normal or increased GFR</td>
<td>&gt; 90</td>
</tr>
<tr>
<td>II</td>
<td>Mild</td>
<td>60 - 89</td>
</tr>
<tr>
<td>III</td>
<td>Moderate</td>
<td>30 - 59</td>
</tr>
<tr>
<td>IV</td>
<td>Severe</td>
<td>15 – 29</td>
</tr>
<tr>
<td>V</td>
<td>ESRD or renal failure</td>
<td>&lt; 15</td>
</tr>
</tbody>
</table>


Case Study

A 68 year old male patient (5’10”, 80kg) with history of HTN, DM and stage III chronic kidney disease (CKD) develops new onset atrial fibrillation.

Concurrent medications propranolol & amiodarone
- Scr (stable) 1.8 mg/dl
- eGFR 38 ml/min/1.73m²
- Clcr 41 ml/min
- CHADS₂ 2
- CHA₂DS₂-VASc 3

WBCT, whole blood clotting test

Stages based on K/DOQI criteria:
http://www2.kidney.org/professionals/KDOQI/guidelines_ckd/p4_class_g1.htm

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Chronic Kidney Disease and Atrial Fibrillation

Increased Thrombotic Risk
- Hazard ratio for stroke: 1.5
- Abnormalities in coagulation system
- CKD might be marker for end organ damage
- Stage III CKD is moderate stroke risk regardless of CHADS2

Increased Bleed Risk
- CKD increases bleed risk with all anticoagulants
- Defect in platelet adhesion & aggregation
- Defects likely secondary to uremic toxins

Warfarin Efficacy and Safety in CKD for Atrial Fibrillation

<table>
<thead>
<tr>
<th>Observational Studies</th>
<th>Clinical Trial Sub-Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Several, conflicting results</td>
<td>SPAF III 805 patients with stage 3 CKD</td>
</tr>
<tr>
<td>12 year Danish study 3587 non dialysis CKD patients</td>
<td>Warfarin (INR 2-3) vs low dose warfarin + aspirin</td>
</tr>
<tr>
<td>Warfarin use: 10% ↓ SSE 36% ↓ bleeding</td>
<td></td>
</tr>
</tbody>
</table>

Randomized Controlled Trials
- None!
- NCT01668901 warfarin vs aspirin for SSE prevention in AF with CKD

Capodanno D. Circ 2012; 125: 2649.
Warfarin Efficacy and Safety in CKD for Atrial Fibrillation

Warfarin Efficacy and Safety for Atrial Fibrillation Patients on Hemodialysis

Warfarin Use and the Risk for Stroke and Bleeding in Patients With Atrial Fibrillation Undergoing Dialysis
Circ 2014; 129: 1196-1203.
Warfarin not beneficial in stroke prevention and increases bleed risk

Net Clinical Benefit of Antithrombotic Therapy in Patients With Atrial Fibrillation and Chronic Kidney Disease
A Nationwide Observational Cohort Study
| Warfarin beneficial in stroke prevention in renal replacement therapy with CHADS2/VASc ≥ 2 |


Warfarin Efficacy and Safety for Atrial Fibrillation Patients on Hemodialysis

- No randomized controlled trials
- Data conflicting; some suggest harm
- Little evidence to support efficacy
- Significant variability in study design and endpoints

2012 Focused Update of the Canadian Cardiovascular Society Atrial Fibrillation Guidelines

Caution with Cross Trial Comparisons

Renal Properties of DOACs

<table>
<thead>
<tr>
<th>Apixaban</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Half-life in hours by CrCl (mL/min)</td>
<td>8-15</td>
<td>14-17</td>
<td>5-9h</td>
</tr>
<tr>
<td>CrCl &gt; 80</td>
<td>14.6</td>
<td>16.6</td>
<td>8.7</td>
</tr>
<tr>
<td>CrCl 50 – 79</td>
<td>17.3</td>
<td>27.5</td>
<td>9.5</td>
</tr>
<tr>
<td>CrCl 30 – 49</td>
<td>17.6</td>
<td>18.7</td>
<td>9.0</td>
</tr>
<tr>
<td>CrCl &lt; 30</td>
<td>17.3</td>
<td>27.5</td>
<td>9.5</td>
</tr>
</tbody>
</table>

Dialyzable
- Unlikely
- Yes
- Unlikely
- Unlikely

Decreased renal function is associated with an increase in response to coagulation tests

Adapted from Am J Hematol 2012; 87: 5141.
Key Differences in DOAC AF Trials

- Study design
- Baseline population risk:
  - CHADS2 score, prior warfarin use,
- Distribution of participating countries
- Dose adjustment for renal impairment
- Primary safety endpoint
- Timeframe of major bleeding, GI bleed
- Statistical analysis
- Duration of follow up
- Time in therapeutic range

Event rate of warfarin arm of studies

DOAC: direct oral anticoagulant, AF: atrial fibrillation, *number/100 patient years

DOAC Clinical Trial CKD Sub-Analysis

<table>
<thead>
<tr>
<th>Event</th>
<th>DOAC</th>
<th>Renal Exclusion</th>
<th>CKD n (%, total)</th>
<th>CKD % of total</th>
<th>Reduced dose</th>
<th>*CKD: Stroke and Bleed Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safety</td>
<td>Dabigatran-RELY</td>
<td>Clcr &lt; 30 ml/min</td>
<td>3554 (19)</td>
<td>30 - 49</td>
<td>Yes (110mg)</td>
<td>Yes</td>
</tr>
<tr>
<td>Safety</td>
<td>Rivaroxaban-ROCKET-AF</td>
<td>Clcr &lt; 30 ml/min</td>
<td>2950 (21)</td>
<td>30 - 49</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Major Bleeding</td>
<td>Apixaban-ARISTOTLE</td>
<td>Sc &gt; 2.5 mg/dl Clcr &lt; 25 ml/min</td>
<td>3017 (17)</td>
<td>25 - 50</td>
<td>Not for renal function alone</td>
<td>Yes</td>
</tr>
<tr>
<td>Major Bleeding</td>
<td>Apixaban-AVERROES</td>
<td>Sc &gt; 2.5 mg/dl Clcr &lt; 25 ml/min</td>
<td>1198 (21)</td>
<td>25 - 50</td>
<td>Not for renal function alone</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*estimated using Cockcroft Gault equation, ml/minute

Effect RE-LY

Dabigatran 110mg

Dabigatran 150mg

ROCKET-AF

Rivaroxaban

ARISTOTLE

Apixaban

AVERROES

Meta-Analysis of Renal Function on the Safety and Efficacy of Novel Oral Anticoagulants for Atrial Fibrillation

Ann J Cardiol 2016;117:69–75

DOAC Clinical Trial CKD Sub-Analysis

DOAC vs Warfarin SSE Prevention

DOAC vs Warfarin Major Bleeding

Mild Impairment

Moderate Impairment

Mild Impairment

Moderate Impairment

SSE stroke and systemic embolism

RR 0.71 (0.62 – 0.81)

RR 0.88 (0.7 – 0.91)

RR 0.79 (0.66 – 0.94)

RR 0.8 (0.7 – 0.91)

DOAC Dosing AFIB (kinetic modeling in red box)

Drugs

Dosing

Dabigatran

150mg po BID with Clcr > 30 ml/min

75mg po BID with Clcr 15-30 ml/min

75mg po BID with trimedexamore/ketoconazole with Clcr 30-50ml/min or avoid use

Not recommended if Clcr < 30ml/min with pGP inhibitors

Not recommended if Clcr < 15ml/min or dialysis

Rivaroxaban

20mg po daily with Clcr > 50ml/min

15mg po daily with Clcr 15-50 ml/min

Clcr 15-30ml/min not studied

Not recommended for Clcr < 15ml/min

Apixaban

5mg po BID

3mg po BID if on maintenance hemodialysis

2.5mg po BID if > 2 of the following: age ≥ 80 yrs, weight ≤ 60kg or Scr > 1.5mg/dl

2.5mg BID with certain pGP inhibitors*

Edoxaban

60mg po daily with Clcr > 50ml/min

30mg po daily with Clcr 15 – 50ml/min

Clcr 15-30ml/min not studied

Not recommended with Clcr > 95ml/min

*reduce dose with ketoconazole, itraconazole, clarithromycin and ritonavir

Bleeding Risk with Apixaban in Renal Impairment

As compared to control group in Phase III clinical trials

- Using CKD-EPI apixaban decreases stroke and systemic embolism with eGFR < 50ml/min/1.73m² in ARISTOTLE


*reduce dose with ketoconazole, itraconazole, clarithromycin and ritonavir
DOAC Renal Dose Adjustments Vary by Indication!

Apixaban Dosing: Atrial Fibrillation and Hemodialysis Patients
- Open label, parallel-group, single dose study in 8 hemodialysis subjects compared to 8 subjects with normal renal function
- ESRD on hemodialysis associated with
  - $\text{AUC}_{\text{inf}}$ 36%
  - $\text{C}_{\text{max}}$ 10%
- 4 hour hemodialysis session resulted in
  - $\text{AUC}_{\text{inf}}$ 14%
  - $\text{C}_{\text{max}}$ 13%
- Apixaban relatively insensitive to coagulation parameter changes with no differences between groups

ESRD end stage renal disease

Recommendations for Prevention of Thromboembolism in NVAF—Renal Function

<table>
<thead>
<tr>
<th>Renal function should be evaluated prior to and re-evaluated at least annually with dabigatran, rivaroxaban, or apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class</td>
</tr>
<tr>
<td>-------</td>
</tr>
<tr>
<td>Renal function should be evaluated prior to and re-evaluated at least annually with dabigatran, rivaroxaban, or apixaban</td>
</tr>
<tr>
<td>For patients with a CHA$_2$DS$_2$-VASc score ≥ 2 and who have end stage CKD (eGFR &lt; 15 mL/min) or are hemodialysis</td>
</tr>
<tr>
<td>For patients with a CHA$_2$DS$_2$-VASc score ≥ 2 and who have moderate-to-severe CKD, it is reasonable to consider reduced doses of dabigatran, rivaroxaban, or apixaban, but safety and efficacy have not been established.</td>
</tr>
<tr>
<td>Dabigatran and rivaroxaban are not recommended in patients with AF and end-stage CKD or on hemodialysis due to lack of clinical trial evidence (no benefit)</td>
</tr>
</tbody>
</table>


Caution with DOAC Use in Acute Kidney Injury (AKI)
- Monitor renal function with DOAC use
  - Every 6 months with Clcr 30-60ml/min, fragile or on dabigatran
  - Every 3 months if Clcr 15 to 30ml/min
  - As needed with conditions known to result in altered renal function
- DOAC agents may need to be held
- Failure to recognize AKI will increase bleed risk
- Accumulation of dabigatran exceeds other DOACs


Stroke Prevention in AF AHA/ACC/HRS 2014 Guidelines

To prevent stroke and systemic embolism you would recommend:
A. Warfarin adjusted to INR 2 -3
B. Dabigatran 150mg BID
C. Apixaban 2.5mg BID
D. Rivaroxaban 15mg daily
E. Dabigatran 75mg BID
F. Edoxaban 60mg daily

Case Study
A 68 year old male patient (5’10”, 80kg) with history of HTN, DM and stage III chronic kidney disease (CKD) develops new onset atrial fibrillation.
Concurrent medications propranolol & amiodarone
- Scr (stable) 1.8 mg/dl
- eGFR 38 ml/min/1.73m$^2$
- Clcr 41 ml/min
- CHADS$_2$ 2
- CHA$_2$DS$_2$-VASc 3

To prevent stroke and systemic embolism you would recommend:
A. Warfarin adjusted to INR 2 -3
B. Dabigatran 150mg BID
C. Apixaban 2.5mg BID
D. Rivaroxaban 15mg daily
E. Dabigatran 75mg BID
F. Edoxaban 60mg daily
Research Questions: Anticoagulation and Chronic Kidney Disease

- Value of anticoagulation in stage IV and V CKD
- Safety and efficacy of warfarin and apixaban in hemodialysis
- Frequency of renal function monitoring in DOAC patients
- eGFR vs Clcr for renal function assessment


Anticoagulation Management

Dr. Fanikos—“No” to everything.
Dr. Smythe—“Yes to everything”

Case Assumptions

- You are employed by the Medical Home, practicing CDTM
- You will manage this patient’s medications including anticoagulation.
- There is no established Coumadin clinic
- Shared physician-patient decision making would occur

Clinical Case

Chief Complaint:
Shortness of breath

HPI:
- BL is a 25 YO female with no past medical history.
- Returned from Antigua 3 weeks ago where she celebrated her wedding ceremony, on “honeymoon” with her husband (8 hours in air).
- At the resort, participated in water sports on the ocean and may have experienced intermittent mosquito bites. She was not ill throughout her stay, neither was her husband.
- She is an avid rower and runner and returned to these activities when arriving home.
- However, since her return she began to feel nauseous, developed lightheadedness daily (without losing consciousness). She also developed leg cramps after exercise. She attributed this to “falling out of shape” and continued her workouts.

Presentation:
- Today BL developed dull left sided, non-radiating chest pain, worsening with deep breaths. SOB has worsened.

Vital signs:
- BP 114/65, HR 65, RR 24-25, and SaO2 was 100% on RA.

Hospital Course:
- EKG normal
- CT-PE study was performed:
  - +saddle embolus ~5-mm in thickness spanning right and left main pulmonary artery.
  - Right ventricle (RV) is greater than left ventricle (LV) diameter and interventricular septum bows toward LV.

Family History
- Two Aunts with DVT.

Medications
- Ocella (Ethinyl Estradiol/Drospirenone) initiated 3 months PTA.

Spectrum of Disease

HIGH RISK-Massive PE (~5%)
- Hypotension, syncope, cardiogenic shock, cardiac arrest
- Respiratory failure
- Often fatal if aggressive care not instituted

INTERMEDIATE RISK-Submassive PE (~40%)
- Normotensive
- Right ventricular (RV) dysfunction is present
- Increased risk of adverse outcomes

LOW RISK-PE with normal BP and RV function (~55%)
- Normotensive
- Normal RV function
- Excellent prognosis with anticoagulation alone

Clinical Case (cont.)

Hospital Course:
- Follow-up CT shows slight filling defect in right pulmonary artery.
- Right ventricle (RV) returned to normal.
- Hospital Day 5-Unfractionated heparin converted to enoxaparin 1 mg per kg and warfarin initiated per protocol (5 mg) until INR reached 2-3.
- Discharge is planned for the AM.
- Follow-up visits scheduled for 1 week, 1 month, 3 months.

Patient Questions and Concerns:
- "How often does this happen to people?"
- "Do I have something genetically wrong with me?"
- "Can't I just take an aspirin?"
- "Are there any side effects with this stuff?"

Clinical Case (cont.)

VTE Incidence: Increasing

Contemporary VTE Acute Treatment

<table>
<thead>
<tr>
<th>Study Drug</th>
<th>No. patients</th>
<th>PE or PE and DVT, % (n)</th>
<th>DVT, % (n)</th>
<th>Unprovoked, % (n)</th>
<th>Previous VTE, % (n)</th>
<th>INR on VKA, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban</td>
<td>2539</td>
<td>1836 (34)</td>
<td>3532 (65)</td>
<td>4845 (90)</td>
<td>872 (16)</td>
<td>61</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>2539</td>
<td>786 (31)</td>
<td>1749 (69)</td>
<td>Not reported</td>
<td>649 (26)</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>2568</td>
<td>815–819 (32)</td>
<td>1748–1750 (68)</td>
<td>Not reported (17.5)</td>
<td>57</td>
<td></td>
</tr>
<tr>
<td>Edoxaban</td>
<td>8240</td>
<td>3319 (40)</td>
<td>4921 (60)</td>
<td>5410 (66)</td>
<td>1520 (18)</td>
<td>64</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>3449</td>
<td>23 (1)</td>
<td>3405 (99)</td>
<td>2138 (62)</td>
<td>666 (19)</td>
<td>58</td>
</tr>
<tr>
<td></td>
<td>4832</td>
<td>4832 (100)</td>
<td>0 (0)</td>
<td>3117 (65)</td>
<td>944 (20)</td>
<td>63</td>
</tr>
</tbody>
</table>


Acute VTE: Meta-analysis of Efficacy/Safety

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Pooled Absolute Risk Difference, % (95% CI)</th>
<th>NNT With NOAC to Prevent 1 Event (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent VTE</td>
<td>-0.24 (-0.60–0.11)</td>
<td>417 (167 to -909)</td>
</tr>
<tr>
<td>Fatal PE</td>
<td>0.01 (-0.06–0.08)</td>
<td>10 000 (1067 to -1250)</td>
</tr>
<tr>
<td>Overall mortality</td>
<td>-0.19 (-0.47–0.10)</td>
<td>1500 (213 to -137)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>-1.13 (1.33 to -2.91)</td>
<td>140 (88–476)</td>
</tr>
<tr>
<td>Non-fatal bleeding, critical site</td>
<td>-0.38 (-0.65 to -0.10)</td>
<td>263 (153–1000)</td>
</tr>
<tr>
<td>CHM bleeding</td>
<td>-1.77 (-2.40 to -1.15)</td>
<td>56 (29–86)</td>
</tr>
<tr>
<td>Non-fatal ICH</td>
<td>-0.14 (-0.31–0.03)</td>
<td>714 (323 to -333)</td>
</tr>
<tr>
<td>Major GI bleeding</td>
<td>-0.16 (-0.42–0.11)</td>
<td>625 (238–909)</td>
</tr>
<tr>
<td>Fatal bleeding</td>
<td>-0.09 (-0.17–0.00)</td>
<td>1111 (588–4)</td>
</tr>
</tbody>
</table>

Acute VTE: Meta-analysis of Efficacy/Safety

Summary:
Efficacy
- All 4 novel agents are noninferior to LMWH/VKA for efficacy, regardless of weight, PE versus DVT, chronic kidney disease, and cancer
- Edoxaban: prespecified submassive PE subgroup showed superiority
Safety of NOACs combined
- 39% less major bleeding
- 64% less fatal bleeding
- 63% less ICH than LMWH/VKA

Recurrent VTE -0.24 (-0.60–0.11) 417 (167 to -909)
Fatal PE 0.01 (-0.06–0.08) 10 000 (1667 to -1250)
Overall mortality -0.10 (-0.47–0.28) 1000 (213 to -357)
Major bleeding -0.67 (-1.13 to -0.21) 149 (88–476)
Non-fatal bleeding, critical site -0.38 (-0.65 to -0.10) 263 (153–1000)
CRNM bleeding -1.77 (-3.40 to -0.15) 56 (29–667)
Non-fatal ICH -0.14 (-0.31–0.03) 714 (323 to -3333)
Major GI bleeding -0.16 (-0.42–0.11) 625 (238–909)
Fatal bleeding -0.09 (-0.17–0.00) 1111 (588–0)


Clinical Case (cont.)
Patient Questions and Concerns:
- “How often does this happen to people?”
- “Do I have something genetically wrong with me?”
- “How long am I going to have to take a blood thinner?”
- “Can’t I just take an aspirin?”
- “Are there any side effects with this stuff?”

Thrombophilia: Prevalance

<table>
<thead>
<tr>
<th>Thrombophilia</th>
<th>General Population (%)</th>
<th>Patients with 1st VTE (%)</th>
<th>Family History of Thrombosis (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor V Leiden</td>
<td>3-7</td>
<td>20</td>
<td>50</td>
</tr>
<tr>
<td>Prothrombin Gene Mutation</td>
<td>1-3</td>
<td>6</td>
<td>18</td>
</tr>
<tr>
<td>Hyperhomocysteinemia</td>
<td>5-10</td>
<td>10-25</td>
<td>7</td>
</tr>
<tr>
<td>Antiphospholipid Antibodies</td>
<td>0-7</td>
<td>5-15</td>
<td>7</td>
</tr>
<tr>
<td>Protein C Deficiency</td>
<td>0.2-0.4</td>
<td>3</td>
<td>6-8</td>
</tr>
<tr>
<td>Antithrombin Deficiency</td>
<td>0.02</td>
<td>1</td>
<td>4-8</td>
</tr>
<tr>
<td>Protein S Deficiency</td>
<td>NA</td>
<td>1-2</td>
<td>3-13</td>
</tr>
</tbody>
</table>

Rosendaal FR. Semin Hematol 1997;34:171.

Arguments against the Utility of Thrombophilia Testing

- Thrombophilia testing does not impact therapy
- Thrombophilias are uncommon
- Thrombophilias do not predict VTE risk
- Thrombophilia testing is not cost effective
- Anticoagulant therapy can interfere with testing


Arguments For the Utility of Thrombophilia Testing

- In RIETE, Thrombophilia was detected in 32% of the 21,367 patients.
- Estrogen-based BCPS in patients with thrombophilia are associated with a 20-to-40-fold increase in the risk of VTE.
- Thrombophilia testing in DVT patients with a hypercoagulable condition was more cost-effective ($54,820; 23.76 QALYs) than usual care (6 months of anticoagulation without testing) ($55,260; 23.72 QALYs).

Clinical Case (cont.)

Presentation:
- BL returns for her 6 month appointment.
- Genetic testing results were negative.
- She has no leg pain or SOB.

Vital signs:
- BP 130/70, HR 60, RR 22-24, Temp 98.6°.
- All other WNL.

ROS:
- Bruising on upper arm.
- “I’ve found a few bruises on my arms and legs.”
- “I’m still actively running and rowing and hoping to run the marathon in the Fall.”
- “The INR testing is a pain. When can I stop.”

Clinical Case (cont.)

Patient Questions and Concerns:
- “How often does this happen to people?”
- “Do I have something genetically wrong with me?”
- “How long am I going to have to take a blood thinner?”
- “Can’t I just take an aspirin?”
- “Are there any side effects with this stuff?”

Question
What would you recommend for anticoagulation?
A. Warfarin, target INR 1.5-2.0.
B. Apixaban 2.5 mg twice daily.
C. Edoxaban 30 mg once daily.
D. Rivaroxaban 20 mg once daily.
E. Dabigatran 150 mg twice daily.
F. None of the above.

Optimal Duration of Anticoagulation

<table>
<thead>
<tr>
<th>Acute PE</th>
<th>Provoked</th>
<th>Indeterminate</th>
<th>Unprovoked (diaphyseal)</th>
<th>Consider indefinite duration anticoagulation if low bleeding risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treat with 3-6 months of anticoagulation</td>
<td>Assess individual risk of VTE recurrence</td>
<td>Consider indefinite duration anticoagulation if low bleeding risk</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


cancer
Consider prolonged anticoagulation as long as cancer is active

Clinical risk factors:
- Past/family history of VTE
- Bleeding risk
- Male gender
- Thrombophilia
- Chronic medical conditions (COPD, heart failure, inflammatory disorders)
- Obesity
- Chronic immobilization

Goldhaber SZ. Circulation 2011;123:664.

Continue Anticoagulation? YES

Recurrence is high. Drugs are effective.

<table>
<thead>
<tr>
<th>Author</th>
<th>Bleeding Risk Low</th>
<th>Bleeding Risk High</th>
<th>Bleeding Risk Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bates et al, 1992</td>
<td>0-2</td>
<td>20</td>
<td>1 point for presence of each, 1 point for severe bleeding</td>
</tr>
<tr>
<td>Versteegh et al, 1998</td>
<td>0</td>
<td>1-2</td>
<td>3 points for each, 1 point for major bleeding</td>
</tr>
<tr>
<td>Raj et al, 2014</td>
<td>0-1</td>
<td>3-5</td>
<td>2 points for each, 1 point for severe bleeding</td>
</tr>
<tr>
<td>Enrrix et al, 2009</td>
<td>0-1</td>
<td>3-5</td>
<td>2 points for each, 1 point for major bleeding</td>
</tr>
<tr>
<td>Prandoni et al, 2003</td>
<td>0-2</td>
<td>3</td>
<td>3 points for each, 1 point for major bleeding</td>
</tr>
<tr>
<td>Lane DA. Circulation 2012;126:860-865.</td>
<td>0-3</td>
<td>3-10</td>
<td>3 points for each, 1 point for major bleeding</td>
</tr>
<tr>
<td>Giménez N. Thromb Haemost 2006;100:255.</td>
<td>0</td>
<td>3</td>
<td>3 points for each, 1 point for major bleeding</td>
</tr>
<tr>
<td>Byeth RJ. Am J Med 1996;100:95.</td>
<td>0</td>
<td>3</td>
<td>3 points for each, 1 point for major bleeding</td>
</tr>
</tbody>
</table>

Study Intervention Recurrent VTE
PREVENT Warfarin, INR 1.5-2 vs. placebo ↓64%
ELATE Warfarin, INR 2-3 vs. INR 1.5-2 ↓63%
THRIVE III Ximelagatran vs. placebo ↓84%
EINSTEIN DVT Rivaroxaban vs. placebo ↓82%
AMPLIFY EXT Apixaban vs. placebo ↓81%
RE-SONATE Dabigatran vs. placebo ↓93%
RE-MEDY Dabigatran vs. warfarin, INR 2-3 Non-inferior

Goldhaber SZ. Circulation 2011;123:664.
Martínez C. Thromb Haemost 2014; 112: 255.
**AM P L I F Y - E X T: A p i x a b a n v s. P l a c e b o f o r E x t e n d e d V T E P r e v e n t i o n**

Dose reduced apixaban 2.5 mg twice daily: same efficacy, lower bleeding risk


---

**HOKUSAI Efficacy (n=8,240)**

<table>
<thead>
<tr>
<th></th>
<th>Edoxaban (N=4118)</th>
<th>Warfarin (N=4122)</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent VTE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>130 (3.2)</td>
<td>146 (3.5)</td>
<td>0.89 (0.70-1.13)</td>
</tr>
<tr>
<td>DVT Patients</td>
<td>83 (3.4)</td>
<td>81 (3.3)</td>
<td>1.02 (0.75-1.38)</td>
</tr>
<tr>
<td>PE Patients</td>
<td>47 (2.8)</td>
<td>65 (3.9)</td>
<td>0.73 (0.50-1.06)</td>
</tr>
<tr>
<td>Severe PE (N=938)</td>
<td>15 (3.4%)</td>
<td>30 (6.2%)</td>
<td>0.52 (0.28-0.98)</td>
</tr>
</tbody>
</table>


---

**Continue Anticoagulation? No**

- Genetic testing was negative.
- Bruise are cosmetically unappealing and concerning.
- Birth control pills are the obvious culprit (no events since she stopped).
- She is of child-bearing age.
- Eliminate the burden of drug therapy and cost.
- Amplify-EXT dose reduction was after 6 months of treatment.
- Other options exist:
  - Compression stockings
  - Aspirin


---

**Select the Optimal Agent for Extended Therapy**

---

**Novel Anticoagulants in Cancer-Yes**

<table>
<thead>
<tr>
<th>No Cancer</th>
<th>Active Cancer at Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivaroxaban (n=3563)</td>
<td>Edoxaban + VKA (n=2504)</td>
</tr>
<tr>
<td>Recurrent VTE</td>
<td>85 (2%)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>31 (10%)</td>
</tr>
<tr>
<td>Clin Relevant Bleeding</td>
<td>315 (9%)</td>
</tr>
<tr>
<td>Mortality</td>
<td>33 (11%)</td>
</tr>
<tr>
<td>Net clinical benefit</td>
<td>100 (3%)</td>
</tr>
</tbody>
</table>

**Novel Anticoagulants in Cancer-No**

### VTE
- **Prophylaxis in the Surgical Patient**
  - LMWH, fondaparinux, or UFH with out of hospital prophylaxis for up to 4 weeks postoperatively.
  - “All patients with malignant disease undergoing major surgery should be considered for pharmacologic prophylaxis, for at least 7-10 days, and up to 4 weeks postoperatively.”
- **Prophylaxis in the Hospitalized Cancer Patient**
  - Anticoagulation for all inpatients with a diagnosis of active cancer who do not have a contraindication.
  - “Patients receiving routine VTE prophylaxis in the absence of bleeding or other contraindications to anticoagulation.”
  - “Routine prophylaxis is not recommended.”
  - Patients receiving thienological or low molecular weight heparin should receive thromboprophylaxis with aspirin or LMWH.
- **Treatment of Established VTE**
  - LMWH is preferred over UFH for the first 5-10 days.
  - LMWH, for at least 6 months, is preferred over VKAs for long term anticoagulant therapy.

### Study Results

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Cancer in Medical History</th>
<th>Active Cancer at Baseline</th>
<th>Cancer Diagnosed During Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivaroxaban</td>
<td>Enoxaparin+VKA</td>
<td>Enoxaparin+VKA</td>
<td>Enoxaparin+VKA</td>
</tr>
<tr>
<td>Lung: VTE</td>
<td>0/3</td>
<td>0/3</td>
<td>0/21</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>0/3</td>
<td>0/3</td>
<td>0/21</td>
</tr>
<tr>
<td>GI: VTE</td>
<td>1/24</td>
<td>0/25</td>
<td>0/41</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>0/24</td>
<td>1/45</td>
<td>1/41</td>
</tr>
<tr>
<td>Home: VTE</td>
<td>1/10</td>
<td>1/12</td>
<td>1/42</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>0/10</td>
<td>0/12</td>
<td>1/42</td>
</tr>
</tbody>
</table>

### Meta-Analysis: Risk of Recurrent VTE
- Patient populations from LMWH cancer trials have substantially different VTE & bleeding risks compared to the NOAC populations.
- Under powered
- Selection bias
- Cancer characteristics: tumor type, stage, treatment status
  - What cancer patients will benefit?
  - Compatibility with chemotherapy?
  - Periods of thrombocytopenia?
  - Need studies dedicated to cancer patients

### Clinical Case (cont.)
- **Patient Questions and Concerns:**
  - “How often does this happen to people?”
  - “Do I have something genetically wrong with me?”
  - “How long am I going to have to take a blood thinner?”
  - “Can’t I just take an aspirin?”
  - “Are there any side effects with this stuff?”

- **Presentation:**
  - BL requests an urgent visit.
  - Upper respiratory infection last 3 days, seen at a local urgent care center.
  - She reports worsening fatigue, and rash over upper back.
  - She has no leg pain or SOB.
  - **Vital signs:**
    - BP 120/65, HR 55, RR 21-23, Temp 98.6°F.
  - **Labs:**
    - All other WNL.
  - **RDS:**
    - CT of the head, neck, and chest were all normal.
    - Telemetry and ECG were also normal.
  - **Medications**
    - She started rivaroxaban 20 mg once daily in preferring a single daily dose at last office visit.
    - At urgent care center, prescribed erythromycin 500 mg three times daily.
Question
What would you recommend for BL’s medications?
A. Stop the apixaban and start an alternative anticoagulant
B. Stop the erythromycin.
C. Stop both apixaban and erythromycin and start an alternative anticoagulant.
D. None of the above.

Select Drug Interactions

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mechanism</th>
<th>Dabigatran</th>
<th>Apixaban</th>
<th>Edoxaban</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clarithromycin/erythromycin</td>
<td>Moderate P-gp, CYP3A4 inhibition</td>
<td>&lt;18%</td>
<td>No data</td>
<td>&lt;90% (reduce dose by half)</td>
<td>&lt;30-54%</td>
</tr>
<tr>
<td>Rifampin</td>
<td>P-gp/BCRP and CYP3A4/CYP2</td>
<td>48%</td>
<td>-54%</td>
<td>Avoid, -35% but increase of active metabolites</td>
<td>-50%</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>Moderate CYP3A4 inhibition</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>&lt;42% (systemic administration)</td>
</tr>
<tr>
<td>Itra, Kato, Proks, Voriconazole</td>
<td>Potent P-gp and BCRP competition, CYP3A4 inhibition</td>
<td>&lt;150%, reduce dose to 75 mg BID if CrCl = 30-50 mL/min</td>
<td>&lt;100%</td>
<td>&lt;87-95% (reduce NOAC dose by 50%)</td>
<td>Up to +160%</td>
</tr>
<tr>
<td>HIV protease inhibitors (e.g. ritonavir, saquinavir, lopinavir, etc)</td>
<td>P-gp and BCRP competition, CYP3A4 inhibition</td>
<td>No data</td>
<td>Strong increase</td>
<td>No data</td>
<td>Up to +150%</td>
</tr>
</tbody>
</table>

Stop Rivaroxaban-No

<table>
<thead>
<tr>
<th>Event</th>
<th>Rivaroxaban</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain</td>
<td>10 (1.7%)</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>8 (1.3%)</td>
<td>4 (0.7%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>6 (1.0%)</td>
<td>3 (0.5%)</td>
</tr>
<tr>
<td>Soreness</td>
<td>7 (1.2%)</td>
<td>2 (0.5%)</td>
</tr>
<tr>
<td>URI</td>
<td>7 (1.2%)</td>
<td>3 (0.5%)</td>
</tr>
<tr>
<td>Back pain</td>
<td>23 (3.7%)</td>
<td>7 (1.2%)</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>10 (1.7%)</td>
<td>5 (0.8%)</td>
</tr>
<tr>
<td>Pruritis</td>
<td>90 (2.1%)</td>
<td>78 (1.6%)</td>
</tr>
<tr>
<td>Blisters</td>
<td>63 (1.4%)</td>
<td>40 (0.9%)</td>
</tr>
</tbody>
</table>

Stop Rivaroxaban-Yes

<table>
<thead>
<tr>
<th>Event</th>
<th>Rivaroxaban</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight gain:</td>
<td>Unintentional weight gain from rivaroxaban is anecdotally reported on the internet.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Among 4,669 patients who have reported side effects while taking Xarelto® to the FDA and on social media, 4 have reported unintentional weight gain (see link <a href="http://www.ehealthme.com/ds/xarelto/weight+gain+-+unintentional">http://www.ehealthme.com/ds/xarelto/weight+gain+-+unintentional</a>)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Similarly, there are reports on fluid retention. “After retaining more and more water I stopped taking it after three months. I started with a weight of 120 lb at a height of 5’8 and now I weigh 157 lb. I eat less than I always did before even while I exercise. All doctors couldn’t find the one thing that changed through Xarelto.” (see link <a href="http://www.medschat.com/Discuss/Xarelto/">http://www.medschat.com/Discuss/Xarelto/</a>)</td>
<td></td>
</tr>
<tr>
<td>Acne:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Acne and similar skin eruptions from rivaroxaban are anecdotally reported on the internet.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>“I have been on this medication for over a year and I am getting sores all over my face, arms, legs, private areas and chest.”</td>
<td></td>
</tr>
<tr>
<td></td>
<td>“I have been taking Xarelto for about 4 months post PE I have gained about 20 pounds and am breaking out horrible non stop especially on and around my nose.” (see link <a href="http://www.medschat.com/Discuss/Xarelto/">http://www.medschat.com/Discuss/Xarelto/</a>)</td>
<td></td>
</tr>
</tbody>
</table>