NEW ANTITHROMBOTIC AGENTS FOR STROKE PREVENTION

INTRODUCTION

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SYRACUSE, NY

AAN Annual Meeting
Philadelphia, 2014
DISCLOSURES

• Serves on the editorial boards of Medlink, UpToDate.com, and the International Journal of Stroke
• Received royalties from Informa Healthcare, Cambridge University Press, and CliniGems
• Holds stock in Clinical Stroke Research, Inc.
BACKGROUND

• WHO has estimated that the prevalence of AF worldwide is 0.5%.

• The prevalence of atrial fibrillation (AF) in the United States was estimated to be 3.03 million persons in 2005 and is strongly associated with increasing age.

• Because AF is a major risk factor for cardioembolic stroke, there is an urgent need to develop strategies for identification of AF and prevention of cardioembolic stroke at all ages.

Evidence-based Guideline Update: Prevention of Stroke in Nonvalvular Atrial Fibrillation


Culebras A et al. Neurology 2014;82:716-724
For patients with NVAF, which therapies that include antithrombotic medication, as compared with no therapy or with another therapy, reduce stroke risk and severity with the least risk of hemorrhage?
PRACTICE RECOMMENDATIONS

To reduce the risk of stroke or subsequent stroke in patients with NVAF judged to require oral anticoagulants, clinicians should choose 1 of the following options (Level B):

– Warfarin, target INR 2.0–3.0
– Dabigatran 150 mg twice daily (if creatinine clearance [CrCl] > 30 mL/min)
– Rivaroxaban 15 mg/day (if CrCl 30–49 mL/min) or 20 mg/day
– Apixaban 5 mg twice daily (if serum creatinine <1.5 mg/dL) or 2.5 mg twice daily (if any two apply: serum creatinine >1.5 - <2.5 mg/dL, body weight <60 kg, age at least 80 years ).
POST-PUBLICATION RELEASE

• Edoxaban 30mg or 60 mg daily (not yet in the market)

Giugliano RP et al. NEJM 2013:369
LEVEL OF OBLIGATION

Clinician level of obligation assigned to recommendations

- Level A = Must, very strong
- Level B = Should, strong
- Level C = Might, weak
RECOMMENDATIONS

• Selection of patients
• Selection of antithrombotic medication
• Special populations
• Special circumstances
• Stratification schemes
UNCERTAINTIES

• Reach to more patients
• Novel oral anticoagulants
• Complexities have expanded
• Therapeutic uncertainties have increased
PROGRAM TIMELINE

• The ‘new’ oral anticoagulants for stroke prevention.
  Cathy Sila
• Periprocedural management of antithrombotic therapy.
  José Biller
• Management of bleeding complications.
  Julius Latorre
• Potential future uses of novel oral anticoagulants.
  Mitchell SV Elkind
• Discussion.
  Seemant Chaturvedi
PROGRAM TIMELINE

• POSTER ROUNDS
  – Discussion Leader. Timothy Ingall

• DATA BLITZ
New Antithrombotic Agents for Stroke Prevention
Overview of Pharmacology and Considerations for Special Populations

Cathy Sila MD
George M Humphrey II Professor and Vice Chair, Neurology
Director, Comprehensive Stroke Center
Program Director, Vascular Neurology Fellowship
# Drug Attributes and Implications for Therapy

<table>
<thead>
<tr>
<th></th>
<th>VKAs</th>
</tr>
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<tr>
<td><strong>Onset/ offset of action</strong></td>
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<tr>
<td><strong>Renal Clearance</strong></td>
<td>Minor</td>
</tr>
</tbody>
</table>
Traditional Anticoagulants

Intrinsic

XII → XI → IX → VIII

Extrinsic

TF

Heparin

FMWH

Warfarin

Fibrinogen

Fibrin Clot

Chest 2001; 95S-107S.
New Oral Anticoagulants

<table>
<thead>
<tr>
<th>Intrinsic</th>
<th>Extrinsic</th>
</tr>
</thead>
<tbody>
<tr>
<td>XII</td>
<td>TF</td>
</tr>
<tr>
<td>XI</td>
<td></td>
</tr>
<tr>
<td>IX</td>
<td></td>
</tr>
<tr>
<td>VIII</td>
<td></td>
</tr>
<tr>
<td>VII</td>
<td></td>
</tr>
<tr>
<td>X</td>
<td></td>
</tr>
<tr>
<td>V</td>
<td></td>
</tr>
<tr>
<td>IIa</td>
<td></td>
</tr>
</tbody>
</table>

**Pentasaccharide Factor Xa Inhibitors**
- Rivaroxaban (Xarelto®) 2011
- Apixiban (Eliquis®) 2012
- Edoxaban (Lixiana®)

**Direct Thrombin Inhibitors**
- Dabigatran (Pradaxa®) 2010

*Chest* 2001; 95S-107S.
Overview of New Oral Anticoagulations for AF

• All offer a simple, fixed-dose, unmonitored treatment option

• No direct comparisons of the different agents are available
  – Indirect comparisons are problematic due to differences in patient populations, interventions, outcomes events
  – Meta-analyses suggest consistent effects across agents; pooled data from the pivotal phase 3 trials demonstrate:
    • **significant reduction in the risk of hemorrhagic stroke** which drives the reduction in the primary efficacy endpoint of all stroke/systemic embolism and impacts the reduced all-cause mortality
    • No significant difference in Ischemic stroke with the high-dose regimens but may be less well prevented with low-dose regimens

Comparison of Efficacy and Safety of New Oral Anticoagulants vs Warfarin in AF

Meta-analysis of phase 3 trials of dabigatran, rivoroxaban, apixiban, edoxaban 42,411 receiving a new oral anticoagulant and 29,272 receiving warfarin

<table>
<thead>
<tr>
<th>Primary Outcomes</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke or Systemic Embolism</td>
<td>19% reduction</td>
</tr>
<tr>
<td></td>
<td>RR 0.81, 95% CI 0.73-0.91; p&lt;.0001</td>
</tr>
<tr>
<td>Major Bleeding</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>RR 0.86, 95% CI 0.73-1.00; p=.06</td>
</tr>
</tbody>
</table>

Secondary Outcomes

<table>
<thead>
<tr>
<th>Secondary Outcomes</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemorrhagic Stroke</td>
<td>51% reduction</td>
</tr>
<tr>
<td></td>
<td>RR 0.49, 95% CI 0.38-0.64; p&lt;.0001</td>
</tr>
<tr>
<td>Ischemic Stroke</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>RR 0.92, 95% CI 0.83-1.02; p&lt;.0003</td>
</tr>
<tr>
<td>All-cause Mortality</td>
<td>10% reduction</td>
</tr>
<tr>
<td></td>
<td>RR 0.90, 95% CI 0.85-0.95; p&lt;.0003</td>
</tr>
<tr>
<td>Intracranial Bleeding</td>
<td>52% reduction</td>
</tr>
<tr>
<td></td>
<td>RR 0.48, 95% CI 0.39-0.59; p&lt;.0001</td>
</tr>
<tr>
<td>Gastrointestinal Bleeding</td>
<td>25% increase</td>
</tr>
<tr>
<td></td>
<td>RR 1.25, 95% CI 1.01-1.55; p&lt;.04</td>
</tr>
<tr>
<td>Major Bleeding when TTR &lt; 66%</td>
<td>24% reduction</td>
</tr>
<tr>
<td></td>
<td>RR 0.69 vs RR 0.93; p=.022</td>
</tr>
</tbody>
</table>

## CHA$_2$ DS$_2$ VASc and HAS-BLED Scores

<table>
<thead>
<tr>
<th></th>
<th>CHA$_2$ DS$_2$ VASc</th>
<th>HAS-BLED Scores</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CHF or LVEF ≤ 40%</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>Age ≥ 75</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Age 65-74</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Stroke, TIA, TE</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stroke</td>
<td>1</td>
</tr>
<tr>
<td>1</td>
<td>Vascular- MI, PAD, aortic plaque</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Diabetes</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Female</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Abnormal liver function</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Abnormal renal function</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Bleeding predisposition</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Labile INR with warfarin</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Drugs or alcohol</td>
<td>1-2</td>
</tr>
</tbody>
</table>

Don’t consider the impact of dementia, functional decline with frailty, nonadherence to therapy.

*Chest 2010; 137:263 and 138:1093*
## Pharmacokinetics

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixiban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prodrug</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Bioavailability</td>
<td>6-8%</td>
<td>80%, with food</td>
<td>50%</td>
<td>60%</td>
</tr>
<tr>
<td></td>
<td>Cannot crush</td>
<td>Can crush, NG</td>
<td>Can crush, NG, J-tube</td>
<td></td>
</tr>
<tr>
<td>Protein bound</td>
<td>35%</td>
<td>95%</td>
<td>87%</td>
<td>50%</td>
</tr>
<tr>
<td>Time to Peak</td>
<td>0.5- 2 hrs</td>
<td>0.5- 2 hrs</td>
<td>1- 3 hrs</td>
<td>1- 2 hrs</td>
</tr>
<tr>
<td>Half-life</td>
<td>12- 17 hrs</td>
<td>7- 11 hrs</td>
<td>8- 15 hrs</td>
<td>9- 11 hrs</td>
</tr>
</tbody>
</table>

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![Graph of Rivaroxaban plasma concentrations](image)

Thrombosis J 2013; 11:10
Drug Interactions

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixiban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>P-glycoprotein transport</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>CYP3A4 metabolism</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

- Strong inducers of P-gp transport and CYP3A4 metabolism decrease anticoagulant effect and may lead to thrombosis
  - Carbamazepine, Phenytoin, Phenobarbital, Rifampin, St. John’s wort

- Strong inhibitors of P-gp transport and CYP3A4 metabolism increase anticoagulant effect and may cause bleeding
  - Azoles (Ketoconazole), Macrolides (Clarithromycin, Erythromycin), HIV protease inhibitors (Ritonavir), Ca blockers (Diltiazem, Verapamil), Calcineurin inhibitors (Cyclosporin, tacrolimus), Naproxen, Quinidine, Dronedarone, Amiodarone, Atorvastatin, Digoxin, Tamoxifen
## Renal Excretion

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixiban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Renal Excretion</strong></td>
<td>80%</td>
<td>35%</td>
<td>30%</td>
<td>60%</td>
</tr>
<tr>
<td><strong>Mild</strong> CrCl 60-80</td>
<td>10% increase</td>
<td>40% increase</td>
<td>16% increase</td>
<td></td>
</tr>
<tr>
<td><strong>Moderate</strong> CrCl 30-59</td>
<td>70% increase</td>
<td>50% increase</td>
<td>29% increase</td>
<td></td>
</tr>
<tr>
<td><strong>Severe</strong> CrCl 15-29</td>
<td>2.1-fold increase</td>
<td>60% increase</td>
<td>44% increase</td>
<td></td>
</tr>
<tr>
<td><strong>Adult Dosing for AF</strong></td>
<td>150 mg bid</td>
<td>20 mg daily</td>
<td>5 mg bid</td>
<td>60 mg daily</td>
</tr>
<tr>
<td><strong>Renal Dosing</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CrCl 15-50</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CrCl 15-30</td>
<td>75 mg bid</td>
<td>15 mg daily</td>
<td></td>
<td>30 mg daily</td>
</tr>
<tr>
<td>Cr &gt; 1.5</td>
<td>Not defined</td>
<td>Not advised</td>
<td>2.5 mg bid</td>
<td>Not studied</td>
</tr>
<tr>
<td>Failure, CrCl &lt; 15</td>
<td>Not defined</td>
<td>Not advised</td>
<td>Not studied</td>
<td></td>
</tr>
<tr>
<td><strong>Other Adjustments</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;80 yrs, Wt &lt;60 kg, &gt;75 yrs</td>
<td></td>
<td>15 mg daily</td>
<td>2.5 mg bid</td>
<td>30 mg daily</td>
</tr>
</tbody>
</table>
## Laboratory testing of Factor Xa Inhibitors

<table>
<thead>
<tr>
<th>Test</th>
<th>Description</th>
</tr>
</thead>
</table>
| Anti-Xa Assay | Chromogenic, calibrated for the specific drug  
Anti-Xa for rivaroxaban  
Anti-Xa for apixaban |
| PT          | Linear dose-response, varies with reagent.  
*A normal PT (with a sensitive reagent) at ~2 hr from dose should exclude a significant drug effect but does not exclude low concentrations of drug.* |
| aPTT        | Insensitive, minor elevations at peak.                                                         |
| Drug levels | Not widely available, very dependent on dosing time.                                          |

No “therapeutic ranges” have been established by clinical trials.
Laboratory testing of Direct Thrombin Inhibitors

<table>
<thead>
<tr>
<th>Test</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombin Time</td>
<td>Very sensitive, would need to be standardized.</td>
</tr>
</tbody>
</table>
| aPTT                |Insensitive, especially at higher doses.  
*A normal aPTTT (with a sensitive reagent) at ~2 hr from dose should exclude a significant drug effect but does not exclude low concentrations of drug.* |
| Low-range ACT       |Insensitive, similar issues as aPTT                                                                                                          |
| PT                  |Insensitive, little effect at therapeutic levels.                                                                                              |
| Ecarin CT           |Sensitive but unavailable.                                                                                                                    |
| Dabigatran drug level |Not widely available, very dependent on dosing time.  
Wide range in trough levels (RE-LY,10-90th percentile) |

No “therapeutic ranges” have been established by clinical trials.

ASH 2012;1:460-465
Situations that may warrant Lab testing

- Unexpected thrombotic event warranting alternative treatment
- Unexpected bleeding events during treatment
- Evaluation for urgent surgery
- Renal failure with impaired drug clearance
- Suspected drug overdose
- Suspected noncompliance
- Uncertain GI absorption
- Risk factor profile (weight, advanced age) that could affect dosing
- Evaluation for tPA therapy for acute stroke
Plasma Concentrations and Outcomes

- Large variability in plasma concentrations (10th-90th percentile) with dabigatran 150 mg bid and 110 mg bid in RE-LY
- Plasma concentrations were related to bleeding events
  - 36-55% higher levels
  - Age >75 yrs
  - Moderate renal disease
  - Gender
  - Low body weight

JACC 2014; 63:321-328
### UHHS Clinical Practice Guideline for Acute Stroke; 2013

**Anticoagulant Use:** Warfarin use is suspected or the INR is > 1.7. Heparin use within 48 hours and an elevated aPTT.

- Low molecular weight heparin (enoxaparin) use within 3 days (or abnormal anti-Xa LMWH).
- Recent oral direct thrombin inhibitor or oral XIIa inhibitor use (or abnormal sensitive lab tests for these agents, when available).

As time is critical, IVtPA should not be delayed awaiting the results of coagulation tests unless anticoagulant use is unknown or suspected or a bleeding abnormality is suspected.
AAN Policy on Consent for IV-tPA

**IV tPA therapy within the standard of care for eligible patients with acute ischemic stroke**

- Patient or proxy decision maker with the capacity to decide: document discussion of risks, benefits, alternatives
  
  - signed informed consent only if required by local practice
- Patient lacks capacity and no proxy decision maker: may treat based on the principle of implied consent for emergency treatment
  
  - document patient’s lack of capacity, unsuccessful attempts to contact proxy decision maker and urgent need to proceed with treatment

**IV tPA therapy outside of the standard of care**

- Principle of implied consent for emergency treatment is not applicable
  
  - physicians should obtain informed consent

American Academy of Neurology Policy 2011.21
## Drug Attributes and Implications for Therapy

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<td>Standard dosing, no AC monitoring</td>
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<td>Wide- enhances safety/efficacy</td>
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<td>No- enhanced lifestyle</td>
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<td>Rapid from GI tract</td>
<td>Varies by agent</td>
</tr>
<tr>
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<td>Minor</td>
<td>Significant, varies by agent, warrants renal monitoring</td>
</tr>
</tbody>
</table>
Novel Oral Anti-Coagulants (NOACs)
Management of Bleeding Complications

2014 AAN Annual Meeting
New Antithrombotic Agents for Stroke Prevention (I2)

Julius Gene Latorre, MD, MPH
Associate Professor of Neurology and Neurosurgery
Director, Neurocritical Care Service, Department of Neurology
Upstate Medical University
Syracuse, NY
Disclosure

- No financial relationship with drug companies or equipment manufacturer

- May discuss non-FDA approved therapy for ICU care

- Research funds from NONIN Medical, Inc; B Braun, Inc
Learning Objectives

- Discuss bleeding problems with NOAC’s and the basis *(or lack thereof)* of currently available reversal agents.

- Review evidence *(or lack thereof)* on the use of current available methods of anticoagulant reversal vs NOAC-associated bleeding

- Review future directions in NOAC reversal management
# The Good News

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Dabigatran 150mgBID</th>
<th>Rivaroxaban 20mgQday</th>
<th>Apixaban 5mgBID</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Superiority vs. Warfarin</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Stroke and Systemic Embolism</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>- Ischemic Stroke only</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>- Intracranial Hemorrhage</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>- Death, all cause</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Non-inferiority vs. Warfarin</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Stroke and Systemic Embolism</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

## The Bad News

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Warfarin at INR 2-3</th>
<th>NOAC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Case Fatality Rate, Major Bleeding:</strong> ARISTOTLE</td>
<td>11.9% (55/462)</td>
<td>Apixaban 5mgBID 10.4% (34/327)</td>
</tr>
<tr>
<td><strong>Case Fatality Rate, ICH : RELY</strong></td>
<td>36% (32/90)</td>
<td>Dabigatran 150mgBID 35% (13/37)</td>
</tr>
<tr>
<td><strong>Case Fatality Rate, Major Bleeding:</strong> ROCKET-AF</td>
<td>14.25% (55/386)</td>
<td><strong>Rivaroxaban 20mgQday 6.84% (27/395)</strong></td>
</tr>
<tr>
<td><strong>Major Bleeding (Annual Rate):</strong></td>
<td>3.57% 3.4% 3.09%</td>
<td>Dabig-150BID: 3.32% Rivar-20QD: 3.6% <strong>Apix-5BID: 2.13%</strong></td>
</tr>
<tr>
<td><strong>GI Bleeding (Annual Rate):</strong></td>
<td>1.07% 2.2% 0.76%</td>
<td><strong>Dabig-150BID: 1.56% Rivar-20QD: 3.2%</strong> Apix-5BID: 0.86%</td>
</tr>
</tbody>
</table>

What to do when s**t happens?

**Dabigatran Product Insert**

**WARNINGS & PRECAUTIONS**

**Risk of Bleeding**

- A specific reversal agent for dabigatran is not available. Dialysis can remove dabigatran, however clinical experience for hemodialysis as a treatment for bleeding is limited. Activated prothrombin complex concentrates, recombinant factor VIIa, or concentrates of factors II, IX or X may be considered but their use has not been evaluated. Protamine sulfate and vitamin K are not expected to affect dabigatran anticoagulant activity. Consider administration of platelet concentrates where thrombocytopenia is present or long-acting antiplatelet drugs have been used.

**Rivoxaban Product Insert**

Q **How do I manage a bleed with RIVAROXABAN?**

A specific antidote for rivaroxaban is not available. Because of high plasma protein binding, rivaroxaban is not expected to be dialyzable. Protamine sulfate and vitamin K are not expected to affect the anticoagulant activity of rivaroxaban. Partial reversal of prothrombin time prolongation has been seen after administration of prothrombin complex concentrates (PCCs) in healthy volunteers. The use of other procoagulant reversal agents like activated prothrombin complex concentrate (APCC) or recombinant factor VIIa (rFVIIa) has not been evaluated.

**Apixaban Product Insert**

**WARNINGS AND PRECAUTIONS**

**Bleeding Risk:**

- There is no established way to reverse the anticoagulant effect of apixaban, which can be expected to persist for at least 24 hours after the last dose (i.e., about two half-lives). A specific antidote for apixaban is not available. Hemodialysis does not appear to have a substantial impact on apixaban exposure. Protamine sulfate and vitamin K would not be expected to affect the anticoagulant activity of apixaban. There is no experience with antifibrinolytic agents (tranexamic acid, aminocaproic acid) in individuals receiving apixaban. There is neither scientific rationale for reversal nor experience with systemic hemostatics (desmopressin and aprotinin) in individuals receiving apixaban.

- Use of procoagulant reversal agents such as prothrombin complex concentrate, activated prothrombin complex concentrate, or recombinant factor VIIa may be considered but has not been evaluated in clinical studies. Activated charcoal reduces absorption of apixaban thereby lowering apixaban plasma concentrations.
Can we truly reverse NOAC effect?
# NOAC Characteristics relevant to Anticoagulation Reversal

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target</strong></td>
<td>IIa, Free/bound</td>
<td>Xa, Free/bound</td>
<td>Xa, Free/bound</td>
</tr>
<tr>
<td><strong>Action</strong></td>
<td>Direct Inhibitor, Reversible</td>
<td>Direct Inhibitor, Reversible</td>
<td>Direct Inhibitor, Reversible</td>
</tr>
<tr>
<td><strong>Peak Plasma Conc/T ½</strong></td>
<td>2-3H/12-17H</td>
<td>2-4H/7-12H</td>
<td>1-3H/8-14H</td>
</tr>
<tr>
<td><strong>Plasma Protein Binding</strong></td>
<td>35%</td>
<td>93%</td>
<td>87%</td>
</tr>
<tr>
<td><strong>Renal Elimination</strong></td>
<td>80%</td>
<td>30-60%</td>
<td>25%</td>
</tr>
<tr>
<td><strong>Effect of Food on absorption</strong></td>
<td>Poss Delay</td>
<td>Poss Delay</td>
<td>No data</td>
</tr>
<tr>
<td><strong>Qualitative Tests</strong></td>
<td>aPTT Thrombin Time</td>
<td>PT</td>
<td>PT</td>
</tr>
<tr>
<td><strong>Quantitative Tests</strong></td>
<td>Ecarin Clotting Time Hemoclot Assay</td>
<td>Chromogenic Anti-Factor Xa Assay</td>
<td>Chromogenic Anti-Factor Xa Assay</td>
</tr>
</tbody>
</table>
Simplified Coagulation Cascade

Intrinsic System
- XII
- XI
- IX
- VIII

Extrinsic System
- Tissue Factor
- VII

Clot
Direct Thrombin Inhibitor

Intrinsic System:
- XII
- XI
- IX
- VIII

Extrinsic System:
- Tissue Factor
- VII

Clot
- Dabigatran

Factor XIa
- Factor Xa
- Factor Va
- Factor IIa
- Factor II
- Factor I
- Factor Ia
Hemostatic Agents

- **Blood Products:**
  - Platelets – no role unless thrombocytopenic
  - FFP – no role unless with associated factor deficiency
  - Cryoprecipitate – contains Fibrinogen, Factor VIII, von Willebrand Factor, Factor XIII, no role

- **Antifibrinolytics:**
  - aminocaproic acid, tranexamic acid, acts by preventing fibrinolysis, no role

- **DDAVP** – no role unless with platelet function abnormality.
NOAC Reversal Agents

- Activated charcoal
- Hemodialysis
- 4-F Prothrombin Complex Concentrate (PCC)
- Anti-Inhibitor Coagulant Complex (FEIBA)
- Recombinant activated Factor VII (rFVIIa)
# Prothrombin Complex Concentrates

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Type</th>
<th>US Avail</th>
<th>FII</th>
<th>FVII</th>
<th>FIX</th>
<th>FX</th>
<th>Prot C</th>
<th>Prot S</th>
</tr>
</thead>
<tbody>
<tr>
<td>Profilnine</td>
<td>3-F</td>
<td>Yes</td>
<td>87U</td>
<td>NT</td>
<td>69U</td>
<td>54U</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Bebulin</td>
<td>3-F</td>
<td>No</td>
<td>24-38U</td>
<td>&lt;5U</td>
<td>24-38U</td>
<td>24-38U</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>FEIBA</td>
<td>Activated</td>
<td>Yes</td>
<td>1.3U/FEIBA U</td>
<td>*0.9U/FEIBA U</td>
<td>1.4U/FEIBA U</td>
<td>1.1U/FEIBA U</td>
<td>1.1U/FEIBA U</td>
<td>0</td>
</tr>
<tr>
<td>Kanokad</td>
<td>4-F</td>
<td>No</td>
<td>14-35U</td>
<td>7-20U</td>
<td>25U</td>
<td>14-35U</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cofact</td>
<td>4-F</td>
<td>No</td>
<td>30U</td>
<td>13U</td>
<td>25U</td>
<td>26U</td>
<td>4U</td>
<td>21U</td>
</tr>
<tr>
<td>Beriplex</td>
<td>4-F</td>
<td>No</td>
<td>20-48U</td>
<td>10-25U</td>
<td>20-31U</td>
<td>22-60U</td>
<td>21-41U</td>
<td>12-34U</td>
</tr>
<tr>
<td>Kcentra</td>
<td>4-F</td>
<td>Yes</td>
<td>19-40U</td>
<td>10-25</td>
<td>20-31U</td>
<td>25-51U</td>
<td>21-41U</td>
<td>12-34U</td>
</tr>
</tbody>
</table>

Note: *FEIBA contains mostly activated FVII, mostly inactivated FII, FIX, FX

Miyares 2013; Kalus 2013
Intrinsic System

- XII to XIIa
- XI to Xla
- IX to IXa
- VIII to VIIIa
- X to Xa
- V to Va
- II to IIa

Extrinsic System

- VIIa to VII
- Tissue Factor
- XIIIa to XIII
- XIa to XI
- IX to IXa
- X to Xa
- Va to Va
- II to IIa

Dabigatran

Clot
4 factor-PCC

Intrinsic System
- XII
- XI
- IX
- VIII

Extrinsic System
- Tissue Factor
- VII

Dabigatran
- Va
- Xa
- IXa
- VIa
- IIa

Clot
- Ia
- I
- XIIIa
- XIII
RFVIIa

Intrinsic System
- XIIa
- XIa
- IXa
- VIIIa
- Xa

Extrinsic System
- VIIa
- Tissue Factor
- VII

Additional Points:
- Rivaroxaban
- Apixaban
- Clot
Summary 1

- **Manufacturer** = No known reversal agent
- **Hemostatic agents** = No role
- **Blood products** = only if with additional specific conditions
- **Promising reversal strategies based on MOA/drug characteristics/pharmacokinetics**
  - Activated charcoal
  - Hemodialysis
  - Factor concentrates (non-activated and activated)
Putting Theory into Practice:

NOAC reversal studies
<table>
<thead>
<tr>
<th>Reversal Agent</th>
<th>Lab Assay</th>
<th>Animal Bleeding</th>
<th>Human Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activated Charcoal</td>
<td>Van Ryn 2010, Wao 2012</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemo dialysis</td>
<td>Van Ryn 2010, Lange 2012, Stangier 2010, Wagner 2011</td>
<td>Prevent ICH expansion in mice (Zhou 2011), renal bleeding in rabbit (Pragst 2010)</td>
<td>Multiple case reports of bleeding reversed by HD, Most patients have renal dysfunction at baseline, HD done within 8 hours</td>
</tr>
<tr>
<td>4F-PCC</td>
<td>No correction to partial correction of coagulation parameters</td>
<td>Did not reduce blood loss murine model (Lambourne 2012)</td>
<td>Case report only, Reversal of post-op bleeding (Mastrobuoni 2012), No effect on bleeding (Lillo-Le Louet 2012)</td>
</tr>
<tr>
<td>rFVIIa</td>
<td>No correction to partial correction of coagulation parameters</td>
<td>Did not prevent ICH expansion (Zhou 2011) or blood loss (van Ryn 2008, Lambourne 2012)</td>
<td>Case reports only, No effect on bleeding (Garber 2012, Lillo-Le Louet 2012, Harinstein 2013)</td>
</tr>
<tr>
<td>aPCC</td>
<td>Complete reversal of lab parameters in most studies in animal and human in vitro studies</td>
<td>Reduced bleeding (Perzborn 2007, van Ryn 2011), No effect on blood loss (Lambourne 2012)</td>
<td>Case report only, Bleeding controlled with low dose FEIBA (26 IU/kg) Dager 2013</td>
</tr>
</tbody>
</table>

Legend:  
- **Not effective**  
- **Mixed Results**  
- **Effective**  
- **No studies**
## Rivaroxaban Reversal Studies

<table>
<thead>
<tr>
<th>Reversal Agent</th>
<th>Lab Assay</th>
<th>Animal Bleeding</th>
<th>Human Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activated Charcoal</td>
<td>Rat in vivo study (Kaatz 2013)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemo dialysis</td>
<td>Partial correction to complete correction of rivaroxaban-induced coagulopathy in animal and human in vitro studies</td>
<td>Prevent ICH expansion in mice (Zhou 2013), reduced bleeding in rats (Perzborn 2013)</td>
<td></td>
</tr>
<tr>
<td>4F-PCC</td>
<td>Mostly partial correction of coagulation parameters in animal and human in vitro studies</td>
<td>Prevent ICH expansion in mice (Zhou 2013), reduced bleeding in rats (Perzborn 2013)</td>
<td>Did not reduce blood loss rabbit model (Godier 2012)</td>
</tr>
<tr>
<td>rFVIIa</td>
<td>Complete reversal of lab parameters in most studies in animal and human in vitro studies</td>
<td>Reduced bleeding in baboon model (Gruber 2009), and rat (Perszborn 2008, 2013)</td>
<td></td>
</tr>
<tr>
<td>aPCC</td>
<td>Complete reversal of lab parameters in most studies in animal and human in vitro studies</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Legend:**
- **Not effective**
- **Mixed Results**
- **Effective**
- **No studies**
### Apixaban reversal studies

<table>
<thead>
<tr>
<th>Reversal Agent</th>
<th>Lab Assay</th>
<th>Animal Bleeding</th>
<th>Human Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activated Charcoal</td>
<td>Healthy volunteers, up to 6 hours post dose (Wang 2014)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rat/Dog in vivo study (Zhang 2013)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemo dialysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4F-PCC</td>
<td>Partial to complete correction of coagulation parameters (Martin 2013, Escolar 2013)</td>
<td>Reduced blood loss in rat model (Jeske 2013)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Did not reduce blood loss in rabbit model (Martin 2013)</td>
<td></td>
</tr>
<tr>
<td>rFVIIa</td>
<td>Partial to complete correction of coagulation parameters (Martin 2013, Escolar 2013)</td>
<td>Did not reduce blood loss in rabbit model (Martin 2013)</td>
<td></td>
</tr>
<tr>
<td>aPCC</td>
<td>Partial to complete reversal of lab parameters (Blomback 2011, 2012)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Legend:**

- **Not effective**
- **Mixed Results**
- **Effective**
- **No studies**
Summary 2a

- **Direct thrombin inhibitors**
  - Activated charcoal: within 2 hours post ingestion
  - Hemodialysis: within 4-8 hours post ingestion
  - Coagulation factor replacement
    - Probably effective - Activated PCC
    - Equivocal efficacy - Non-activated PCC
    - Probably not effective - Recombinant activated Factor VII
Summary 2b

- **Direct Factor Xa Inhibitor**
  - Activated charcoal: within 2-3 hours post ingestion
  - Hemodialysis: no data, probably NOT effective
  - Coagulation factor replacement
    - Possibly effective - Activated PCC
    - Equivocal efficacy - Non-activated PCC
    - Possibly not effective - Recombinant activated Factor VII
NOAC reversal recommendations

Manufacturers

Experts

Guidelines
Precautions to Prevent Initial Bleeding on NOACs

- Patient selection
  - Older patients
  - Chronic renal disease
  - Other co morbidities

- Bleeding risk assessment
Principles of Reversal

- Do all bleeding require intervention?
- Can we estimate/quantify the anticoagulation effect of NOAC?
- Are there drug-specific intervention?
WHO bleeding severity

- Grade 0 – no evidence of bleeding
- Grade I – mild or asymptomatic
- Grade II – moderate, not requiring transfusion
- Grade III – severe blood loss requiring transfusion
- Grade IV – severe life-threatening or bleeding into a closed space, requiring major urgent interventions and transfusions
# NOAC Effect on Clotting Assay

<table>
<thead>
<tr>
<th>Drug</th>
<th>Peak NOAC Effect</th>
<th>Drug-specific Test</th>
<th>Preferred Assay</th>
<th>Alternative Assay</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ECT</td>
<td>TT</td>
<td>Anti-FXa Activity</td>
<td>PT</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>++</td>
<td>++</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>-</td>
<td>-</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Apixaban</td>
<td>-</td>
<td>-</td>
<td>++</td>
<td>++</td>
</tr>
</tbody>
</table>

Legend:
ECT – Ecarin Clotting Time
TT – Thrombin Time
PT – Prothrombin Time
PTT – Partial Thromboplastin Time

## Dabigatran reversal studies vs recommendations

<table>
<thead>
<tr>
<th>Reversal Agent</th>
<th>Lab Assay</th>
<th>Animal Bleeding</th>
<th>Human Bleeding</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activated Charcoal</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td><strong>NA</strong></td>
</tr>
<tr>
<td>Hemo dialysis</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>++</td>
</tr>
<tr>
<td>4F-PCC</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>+</td>
</tr>
<tr>
<td>rFVIIa</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>+</td>
</tr>
<tr>
<td>aPCC</td>
<td>**</td>
<td>**</td>
<td>**</td>
<td>+</td>
</tr>
</tbody>
</table>

**Legend:**
- M=Manufacturer
- E=Experts
- G=Guidelines

- Not effective
- Mixed Results
- Effective
- No studies
### Rivaroxaban reversal studies vs recommendations

<table>
<thead>
<tr>
<th>Reversal Agent</th>
<th>Lab Assay</th>
<th>Animal Bleeding</th>
<th>Human Bleeding</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activated Charcoal</td>
<td></td>
<td></td>
<td></td>
<td>NA ++ ++</td>
</tr>
<tr>
<td>Hemo dialysis</td>
<td></td>
<td></td>
<td></td>
<td>- - -</td>
</tr>
<tr>
<td>4F-PCC</td>
<td></td>
<td>+</td>
<td>++</td>
<td>++ ++ ++</td>
</tr>
<tr>
<td>rFVIIa</td>
<td></td>
<td>-/+</td>
<td>+</td>
<td>-/+ ++</td>
</tr>
<tr>
<td>aPCC</td>
<td></td>
<td>-/+</td>
<td>+</td>
<td>++</td>
</tr>
</tbody>
</table>

**Legend:**
- M=Manufacturer
- E=Experts
- G=Guidelines
- **Not effective**
- **Mixed Results**
- **Effective**
- No studies
## Apixaban reversal studies vs recommendations

<table>
<thead>
<tr>
<th>Reversal Agent</th>
<th>Lab Assay</th>
<th>Animal Bleeding</th>
<th>Human Bleeding</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activated Charcoal</td>
<td></td>
<td></td>
<td></td>
<td>+ ++ ++</td>
</tr>
<tr>
<td>Hemo dialysis</td>
<td></td>
<td></td>
<td></td>
<td>- - -</td>
</tr>
<tr>
<td>4F-PCC</td>
<td></td>
<td></td>
<td></td>
<td>+ ++ +</td>
</tr>
<tr>
<td>rFVIIa</td>
<td></td>
<td></td>
<td></td>
<td>+ + -/+</td>
</tr>
<tr>
<td>aPCC</td>
<td></td>
<td></td>
<td></td>
<td>+ + +</td>
</tr>
</tbody>
</table>

**Legend:**
- **M**=Manufacturer
- **E**=Experts
- **G**=Guidelines

**Legend Colors:**
- **Red** = Not effective
- **Yellow** = Mixed Results
- **Green** = Effective
- **White** = No studies
## Safety of Reversal Agents

<table>
<thead>
<tr>
<th>Drugs available in the US</th>
<th>4-Factor Prothrombin Complex Concentrate</th>
<th>Recombinant activated Factor VII</th>
<th>Anti-Inhibitor Coagulant Complex</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thromboembolic events in selected trials, registries and post marketing surveillance</td>
<td>1.4% (Leissinger 2008) 0-2.4% (Franchini 2010) 1.8% (Dentali 2011) 3.8% (Majeed 2012) 3.9% (Sarode 2013) 3.2/100,000 infusion (Hanke 2013)</td>
<td>9%, 5.5% arterial (Levi 2010)</td>
<td>0.36% (Coppola 2012)</td>
</tr>
<tr>
<td>Pertinent observation</td>
<td>PE predominant ischemic event</td>
<td>Acute stroke predominant ischemic event</td>
<td>Myocardial infarction predominant ischemic event</td>
</tr>
</tbody>
</table>
Future Direction
# Antidote Development

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
<th>Preclinical Data</th>
<th>Human Trial</th>
<th>Stage of Drug Development</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct Thrombin Inhibitor Antidote</td>
<td>Fab (Anti-Dabigatran Antibody fragment)</td>
<td>Rapid, dose-dep, sustained decrease in blood loss</td>
<td>Phase I-Complete, sustained reversal of DTI inhibition Safe</td>
<td>Phase II planned</td>
</tr>
<tr>
<td>Factor Xa Inhibitor Antidote</td>
<td>Andexanet Alфа (PRT064445)</td>
<td>Rapid, dose-dep, sustained decrease in blood loss</td>
<td>Phase I-Temp (bolus) or sustained (infusion) reversal of FXa inhibition Safe</td>
<td>Phase II ongoing Designated breakthrough therapy 2013</td>
</tr>
<tr>
<td>Universal Antidote</td>
<td>Aripazine (PER977)</td>
<td>Rapid, dose-dep, sustained decrease in blood loss</td>
<td>Phase 1- Dose dependent reversal of anticoagulation due to DTI, FXa-I, UFH, LMWH Safe</td>
<td>Phase II planned</td>
</tr>
</tbody>
</table>
Summary: General Measures

- Initial assessment and management
  - Hemodynamic stability
    - Volume resuscitation/support
    - Blood product transfusion for specific additional condition
      - RBC-anemia
      - Plt – thrombocytopenia
  - Source of bleeding
    - Local control/surgical evaluation
  - Time since last dose/specific drugs
  - Renal function/Coagulation testing
Specific Measures: DTI

- Direct thrombin inhibitors: Dabigatran
  - Determine need for reversal
    - Normal PTT, likely no need for reversal
  - Within 2 hours post ingestion
    - Activated charcoal 100 gram once
  - Within 4-8 hours post ingestion/Renal disease
    - Hemodialysis with or without carbon hemoperfusion
- Coagulation factor replacement
  - *Activated PCC 80 IU/kg IV once
  - Non-activated PCC 50 IU/kg IV once
  - rFVIIa 120 mcg/kg once (NB: high thrombotic risk)

*Preferred by experts
Specific Measures: FXa-I

- **Direct Factor Xa Inhibitors: Rivaroxaban/Apixaban**
  - Determine need for reversal
    - Normal PT, likely no need for reversal
  - Within 2-3 hours post ingestion
    - Activated charcoal 100 gram once
  - Coagulation factor replacement
    - Activated PCC 80 IU/kg IV once
    - *Non-activated PCC 50 IU/kg IV once
    - rFVIIa 120 mcg/kg once (NB: high thrombotic risk)

*Preferred by experts*
Thank You
Potential Future Uses of the New Oral Anti-Coagulants

Mitchell S.V. Elkind, MD, FAAN, FAHA
Professor of Neurology and Epidemiology
Columbia University, New York, NY
Disclosure Information

FUNDING SOURCES:
NINDS R01 NS 48134, R01 NS 50724, R37 NS 29993
NINDS P50 NS 49060, R01 NS55809, R01 NS62820,
LeDucq; diaDexus, Inc.; BMS-Sanofi Partnership

FINANCIAL DISCLOSURES
Boehringer-Ingelheim (dabigatran)
BMS-Pfizer (apixaban)
Daiichi-Sankyo (edoxaban)
Janssen (rivaroxaban)
BMS-Sanofi Partnership; Biogen IDEC;
Jarvik Heart; diaDexus, Inc.; Novartis/Organon; Merck
Potential Future Uses of the New Oral Anti-Coagulants

1. Cryptogenic stroke/Embolic stroke of undetermined source
   • Occult AF
   • “Atriopathy”
2. Intracranial atherosclerotic disease
3. Lacunar infarcts
4. Hypercoagulable states
5. Venous thromboembolism
Cryptogenic stroke

57 year old man with left arm and hand weakness and numbness
**Embolic stroke of undetermined source (ESUS)**

Requires full evaluation to establish the following:

- Non-lacunar stroke detected by CT or MRI
- Absence of extracranial or intracranial atherosclerosis causing $\geq 50\%$ luminal stenosis in arteries supplying territory
- No major-risk cardioembolic source of embolism based on TTE and $\geq 24$ hr monitoring (AF/flutter, prosthetic valve, LVEF $< 30\%$, etc.)
- No other specific cause identified (dissection, vasculitis, spasm, etc.)

Warfarin-Aspirin Recurrent Stroke Study Primary Endpoint

Kaplan-Meier Analyses of the Time to Recurrent Ischemic Stroke or Death According to Treatment Assignment

No. At Risk

<table>
<thead>
<tr>
<th>Days after Randomization</th>
<th>Warfarin</th>
<th>Aspirin</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1,103</td>
<td>1,103</td>
</tr>
<tr>
<td>90</td>
<td>1,047</td>
<td>1,057</td>
</tr>
<tr>
<td>180</td>
<td>1,013</td>
<td>1,032</td>
</tr>
<tr>
<td>210</td>
<td>998</td>
<td>1,004</td>
</tr>
<tr>
<td>360</td>
<td>972</td>
<td>984</td>
</tr>
<tr>
<td>450</td>
<td>956</td>
<td>974</td>
</tr>
<tr>
<td>540</td>
<td>939</td>
<td>951</td>
</tr>
<tr>
<td>630</td>
<td>924</td>
<td>932</td>
</tr>
<tr>
<td>720</td>
<td>885</td>
<td>900</td>
</tr>
</tbody>
</table>

n = 2,206

### WARSS: outcome by initial stroke subtype

<table>
<thead>
<tr>
<th></th>
<th>Probability of event at 2 yrs</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>#</td>
<td>Warfarin</td>
<td>Aspirin</td>
<td></td>
</tr>
<tr>
<td>Cryptogenic</td>
<td>576</td>
<td>15.0</td>
<td>16.5</td>
<td><strong>0.92</strong></td>
</tr>
<tr>
<td>Lacunar</td>
<td>1237</td>
<td>17.1</td>
<td>15.2</td>
<td><strong>1.15</strong></td>
</tr>
<tr>
<td>Large artery</td>
<td>259</td>
<td>18.8</td>
<td>15.7</td>
<td><strong>1.22</strong></td>
</tr>
<tr>
<td>Other</td>
<td>63</td>
<td>36.7</td>
<td>21.2</td>
<td>1.99</td>
</tr>
</tbody>
</table>

Primary outcome: ischemic stroke or death

WARSS tertiary analysis
Cryptogenic strokes

Interaction (Treatment * HTN) p=0.02

Proportion with event at 2 Years
(unadjusted for censoring)

<table>
<thead>
<tr>
<th></th>
<th>Warfarin</th>
<th>Aspirin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>21.1%</td>
<td>16.5%</td>
</tr>
<tr>
<td>No</td>
<td>7.9%</td>
<td>16.7%</td>
</tr>
</tbody>
</table>

RR=1.32  p=0.29
RR=0.45  p=0.04

RE-SPECT ESUS™

• To evaluate the efficacy and safety of Dabigatran for secondary stroke prevention in patients with an embolic stroke of undetermined source (ESUS)
• 6,000 patients who had an ESUS within six months prior to enrollment
• ASA 100 mg vs Dabigatran 150 mg BID or 110 mg BID for pts older than 75 or who have reduced renal function

Courtesy RL Sacco
Methods of detecting AF

- History
- ECG
- Hospital telemetry
- Holter
- Prolonged Holter
- External loop recorder
- Implantable loop recorder

Courtesy H. Kamel
## CRYSTAL AF

<table>
<thead>
<tr>
<th></th>
<th>Implantable cardiac monitor (n=221)</th>
<th>Standard care (n=220)</th>
<th>HR for detection of AF</th>
</tr>
</thead>
<tbody>
<tr>
<td>At 6 months</td>
<td>8.9%</td>
<td>1.4%</td>
<td>6.4 (1.9-21.7)</td>
</tr>
<tr>
<td>At 12 months</td>
<td>12.4%</td>
<td>2.0%</td>
<td>7.3 (2.6-20.8)</td>
</tr>
<tr>
<td>At 36 months</td>
<td>30%</td>
<td>3%</td>
<td>8.8 (3.5-22.2)</td>
</tr>
</tbody>
</table>

Bernstein RA et al. CRYptogenic STroke and underlying Atrial Fibrillation (CRYSTAL AF). ISC 2014.
“Atriopathies” as a cause of stroke

Atrial fibrillation
  Chronic AF
  Paroxysmal AF
  Occult AF

Other arrhythmias
Biomarkers of cardiac dysfunction
Enlarged left atrium
P wave abnormalities on EKG
Genetic markers of atrial fibrillation
Paroxysmal Supraventricular Tachycardia and the Risk of Ischemic Stroke

Deidentified data provided by states to AHRQ Healthcare Cost and Utilization Project (HCUP)

All non-federal hospitals in California for 2009
N= 4,806,830 eligible patients
N= 14,121 (0.29%) diagnosed with PSVT without AF
N=14,402 (0.30%) experienced stroke

Adj HR 2.10, 95% CI 1.69–2.62

Background

N-terminal pro-B-type natriuretic peptide (NT-proBNP)
• released by ventricles and atria in response to stretch and increased volume
• increased in heart failure, structural heart disease, and other situations of cardiac strain.

Cardiac troponin T (cTnT)
• Indicator of cardiac injury
• May be elevated with subclinical myocardial injury and structural heart disease.
• Highly-sensitive assay can detect concentrations >10 times lower than conventional assays used for the detection of acute cardiac ischemia.

Both NT-proBNP and cTnT:
• Associated with subclinical cardiac dysfunction
• May be associated with stroke risk through direct (embolism, impaired cerebral perfusion) and indirect (shared risk factors) mechanisms.

NT proBNP and incident ischemic stroke in the Cardiovascular Health Study (n= 4034) Adjusted for demographics, risk factors and potential mediators (AF, CHF, LVH)
WARSS/APPASS: Effect of warfarin vs aspirin on recurrent stroke/death among those with elevated NT-proBNP

NT-proBNP $\leq$ 750 pg/ml

NT-proBNP > 750 pg/ml

P wave abnormalities

Reflects left atrial structure and function

P-terminal Force in V1 = duration \times \text{amplitude (depth)} of the negative component of the P-wave in V1 (microvolt.millisecond)
MESA: P wave terminal force predicts ischemic stroke

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HR per 1-SD Increase (95% CI)</th>
<th>HR for ≥95% Percentile (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>P-wave terminal force, μV*ms</td>
<td>1.21 (1.02-1.44)</td>
<td>1.80 (1.01-3.21)</td>
</tr>
<tr>
<td>P-wave mean area, μV*ms</td>
<td>1.16 (0.98-1.39)</td>
<td>1.84 (0.98-3.43)</td>
</tr>
<tr>
<td>P-wave maximum area, μV*ms</td>
<td>1.16 (0.99-1.37)</td>
<td>1.36 (0.66-2.79)</td>
</tr>
<tr>
<td>P-wave mean duration, ms</td>
<td>1.11 (0.92-1.34)</td>
<td>1.33 (0.74-2.41)</td>
</tr>
<tr>
<td>P-wave maximum duration, ms</td>
<td>1.12 (0.93-1.35)</td>
<td>1.47 (0.84-2.57)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HR, hazard ratio; MESA, Multi-Ethnic Study of Atherosclerosis; SD, standard deviation.

*P-wave terminal force was defined as the duration of the downward deflection of the P-wave in lead V1 multiplied by the absolute value of its amplitude. Mean and maximum P-wave area and duration were calculated using all 12 leads.

Hazard ratios represent the output of separate Cox proportional hazards models assessing the independent association between each baseline P-wave variable and subsequent ischemic stroke. All models controlled for baseline age, sex, race, hypertension, diabetes, chronic kidney disease, left ventricular hypertrophy, and high- and low-density lipoprotein levels; in addition, incident AF was included as a time-varying covariate.
Refining a subgroup of patients MOST likely to benefit from NOACs

- Cryptogenic stroke?
  - May not have had full evaluation
- ESUS?
  - Includes arteriogenic emboli, PFO, strands, etc.
- Occult AF?
  - What do while waiting for monitoring results?
- Left atriopathy or abnormalities?
  - How can we best define this group?
Potential Future Uses of the New Oral Anti-Coagulants

1. Cryptogenic stroke/Embolic stroke of undetermined source
   - Occult AF
   - “Atriopathy”
2. Intracranial atherosclerotic disease
3. Lacunar infarcts
4. Hypercoagulable states
5. Venous thromboembolism
Cumulative probability of a primary endpoint by treatment
PTAS=percutaneous transluminal angioplasty and stenting.

Table 4. Post Hoc Analysis of On-Treatment, INR-Specific Rates of Major Hemorrhage, Ischemic Stroke, and Major Cardiac Events among Patients Randomly Assigned to Receive Warfarin.*

<table>
<thead>
<tr>
<th>INR Category†</th>
<th>No. of Patient-yr‡</th>
<th>Major Hemorrhage</th>
<th>Ischemic Stroke</th>
<th>Major Cardiac Event§</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Events</td>
<td>No. of Events per 100 Patient-yr (95% CI)</td>
<td>No. of Events per 100 Patient-yr (95% CI)</td>
<td>No. of Events per 100 Patient-yr (95% CI)</td>
</tr>
<tr>
<td>&lt;2.0</td>
<td>92.5</td>
<td>1</td>
<td>1.1 (0.03–6.0)</td>
<td>23</td>
</tr>
<tr>
<td>2.0–3.0</td>
<td>256.9</td>
<td>9</td>
<td>3.5 (1.6–6.6)</td>
<td>13</td>
</tr>
<tr>
<td>3.1–4.4</td>
<td>52.6</td>
<td>8</td>
<td>15.2 (6.6–30.0)</td>
<td>3</td>
</tr>
<tr>
<td>≥4.5</td>
<td>4.9</td>
<td>6</td>
<td>123.3 (45.3–268.4)</td>
<td>1</td>
</tr>
</tbody>
</table>

* The analysis did not include follow-up time or events while patients were not receiving study medication. The events not included were 3 of 27 major hemorrhages, 9 of 49 ischemic strokes, and 7 of 21 major cardiac events. INR denotes international normalized ratio, and CI confidence interval.
† The categories coincide with the prespecified target INR range (2.0 to 3.0) and critically high INR range (≥4.5).§
‡ The method assumed a linear interpolation to estimate INRs between consecutive INR tests. For example, if two consecutive INRs obtained a month apart were in the therapeutic range, the method assumed that the INR was in the therapeutic range for the entire month.
§ A major cardiac event was defined as myocardial infarction or sudden death.
Potential Future Uses of the New Oral Anti-Coagulants

1. Cryptogenic stroke/Embolic stroke of undetermined source
   • Occult AF
   • “Atriopathy”
2. Intracranial atherosclerotic disease
3. Lacunar infarcts (minor stroke/TIA/evolving stroke)
4. Hypercoagulable states
5. Venous Thromboembolism
Lacunar Infarct

Penetrating arteries

Middle cerebral artery
Pathophysiology of Lacunar Stroke

A. Lipohyalinosis

B. Microatheroma

C. Microembolism

D. Mural plaque

FIGURE 8.7 → Arterial pathologies that produce lacunes.
67 yo HTN AA woman with right arm>leg weakness

One week later acute increase in right hemiparesis
67 yo HTN AA woman with right arm > leg weakness

MRA

Oblique coronal contrast-enhanced T1 FLAIR (arterial wall image)
Testing the validity of the lacunar hypothesis: 25% of syndromic and radiological lacunes have a mechanism other than microvascular disease

Table 4 Distribution of final stroke mechanism

<table>
<thead>
<tr>
<th>Mechanism of infarction</th>
<th>Lacunar, n (%)</th>
<th>Atherosclerosis, n (%)</th>
<th>Cardioembolic, n (%)</th>
<th>Cryptogenic, n (%)</th>
<th>Others, n (%)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lacunar syndrome with radiologic lacune</td>
<td>147 (75)</td>
<td>17 (9)</td>
<td>10 (5)</td>
<td>17 (9)</td>
<td>4 (2)</td>
<td>195</td>
</tr>
<tr>
<td>PMH</td>
<td>55 (69)</td>
<td>11 (14)</td>
<td>6 (7)</td>
<td>7 (9)</td>
<td>1 (1)</td>
<td>80</td>
</tr>
<tr>
<td>PSS</td>
<td>15 (100)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>15</td>
</tr>
<tr>
<td>SMS</td>
<td>27 (69)</td>
<td>4 (10)</td>
<td>2 (5)</td>
<td>3 (8)</td>
<td>3 (8)</td>
<td>39</td>
</tr>
<tr>
<td>A-H</td>
<td>28 (72)</td>
<td>2 (5)</td>
<td>2 (5)</td>
<td>7 (18)</td>
<td>0 (0)</td>
<td>39</td>
</tr>
<tr>
<td>Other</td>
<td>22 (100)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>22</td>
</tr>
<tr>
<td>Nonlacunar syndrome or radiologically not lacune</td>
<td>21 (5)</td>
<td>80 (20)</td>
<td>116 (29)</td>
<td>166 (42)</td>
<td>13 (3)</td>
<td>396</td>
</tr>
<tr>
<td>Total</td>
<td>168 (28)</td>
<td>97 (16)</td>
<td>126 (23)</td>
<td>183 (31)</td>
<td>17 (3)</td>
<td>591</td>
</tr>
</tbody>
</table>

PMH = pure motor hemiparesis; PSS = pure sensory syndrome; SMS = sensorimotor syndrome; A-H = ataxic-hemiparesis.

Recurrent Stroke Subtype:
Up to 50% of recurrent strokes after lacunar infarct are non-lacunar

Subtype of index stroke
Jackson C. et al. Brain;128:2507-2517, 2005
SPS3: Probability of the Primary Outcome

Efficacy of tPA by Stroke Subtype

Might more aggressive antithrombotic therapy play a role in evolving acute stroke?

**Oral Clopidogrel Load in Aspirin-Resistant Capsular Warning Syndrome**

*Christopher D. Fahey, Mark J. Alberts, and Richard A. Bernstein*

Ken and Ruth Davee Department of Neurology and Clinical Neurological Sciences, Feinberg School of Medicine of Northwestern University, Chicago, IL
**CHANCE**
Clopidogrel with Aspirin in Acute Minor Stroke or Transient Ischemic Attack
Probability of Survival Free of Stroke

Hazard ratio, 0.68 (95% CI, 0.57–0.81)
P<0.001

No. at Risk
Aspirin 2586 2307 2287 1906
Clopidogrel–aspirin 2584 2376 2361 1989

Results of Anticoagulation: Meta-analysis

- No significant difference in 2 week mortality
  - 8.5% in AC group vs 8.7% in control group
- Total new strokes identical between 2 treatment groups: 4.1%
- No evidence of heterogeneity among various studies or agents

AC, anticoagulation.
Trials being planned (clinicaltrials.gov)

- Apixaban Versus Dual-antiplatelet Therapy (Clopidogrel and Aspirin) in Acute Non-disabling Cerebrovascular Events (ADANCE)
- Treatment of Rivaroxaban Versus Aspirin for Non-disabling Cerebrovascular Events (TRACE)
- Others not publicly available
Potential Future Uses of the New Oral Anti-Coagulants

1. Cryptogenic stroke/Embolic stroke of undetermined source
   • Occult AF
   • “Atriopathy”
2. Intracranial atherosclerotic disease
3. Lacunar infarcts
4. Hypercoagulable states
5. Venous thromboembolism
Antiphospholipid antibodies and NOACs

- **Advantages**
  - INR monitoring is more difficult due to presence of antibodies
  - Decreased interactions with drugs in complicated patients with rheumatologic disease
- **Disadvantages**
  - NOAC trials vs VKA used INR 2.0-3.0
  - Patients with APL may require higher therapeutic ranges
Ongoing trial: Rivaroxaban in Antiphospholipid Syndrome (RAPS)

• Inclusion:
  – Patients with thrombotic APS, with or without SLE, who have had either a single episode of VTE while not on AC or recurrent episode off or on sub-therapeutic AC
  – Patients with a target INR 2.0–3.0
  – Treated with warfarin for a minimum period of three months since last VTE

• Exclusion:
  – H/o arterial events

• Outcome: Percent change in thrombin generation (non-inferiority)

• Sample size: 156
Dural sinus thrombosis

Randomized, open-label, noninferiority trial (n=4832) in patients with acute symptomatic PE

rivaroxaban

vs.

standard therapy with enoxaparin followed by VKA

P=0.003 for non-inferiority

P=0.23

P=0.003

Venous thromboembolism

- Trials of NOACs for VTE have not included patients with cerebral venous thrombosis
- Will we require RCT in Cerebral venous thrombosis/dural sinus thrombosis before use?
  - Risk of ICH?
RCT’s of anticoagulants in ischemic stroke versus in CVT

Cochrane review of anticoagulation for CVT

• Meta-analysis suggests anticoagulation is safe and may be beneficial…
• BUT there is no statistically significant evidence of benefit
• RRR 54% (-31% to 84%)
• ARR 13% (-30 to 3%)

• Stam J et al. Cochrane Database of Systemic Reviews.
Summary

• Many potential uses for the NOACs
  • Cryptogenic stroke/Embolic stroke of undetermined source
  • Intracranial atherosclerotic disease
  • Lacunar infarcts
  • Hypercoagulable states
  • Venous thromboembolism
  • Others

Questions:
• Can we define/refine subgroups of patients for treatment most likely to benefit?
• For uncommon diseases, what level of evidence will we require before we begin using NOACs for other indications?