ACC Latin America Conference 2017

MEXICO CITY
JUNE 22 - 24, 2017

GLOBAL EXPERTS, LOCAL LEARNING
Arrhythmias and Clinical EP
Contemporary Management of Anticoagulant Therapies

Samuel Asirvatham, MD & Ivan Mendoza, MD
Saturday, June 24, 2017
11:15 a.m. to 12 p.m.
Disclosures

Relevant financial relationship(s) with industry
• I receive royalties for work licensed through Mayo Clinic to a privately held company for contributions related to the use of nerve signal modulation to treat central, autonomic and peripheral nervous system disorders, including pain. Mayo Clinic receives royalties and owns equity in this company. The company does not currently license or manufacture any drug or device in the medical field.
• Co-patent holder for technique to minimize coagulum formation during radiofrequency ablation
• Products or techniques related to the above disclosures are not being discussed in this presentation
• Pertains to inventions/startup companies that include Nevro, Aegis and the Phoenix Corp

Honoraria/Speakers
• Abiomed, Atricure, Biotronik, Blackwell Futura, Boston Scientific, Medtronic, Medtelligence Sanofi-aventis, Spectranetics, St. Jude, Zoll

Consulting
• Aegis, ATP, Nevro, Sanovas, Sorin Medical, FocusStart
Warfarin Use in AF Patients With an Indication
How are We Doing in Practice?

Piccini et al: Curr Opin Cardiol 25:312, 2010
Targets in Anticoagulation Cascade for Novel Anticoagulants

Fibrinogen → Fibrin

IX → IXa

X → Xa

Tissue factor → VIIa → IIa

Rivaroxaban → Apixaban

Dabigatran

Cove/Hylek: J Am Heart Assoc 2013:e000136 DOI: 10.1161/JAHA.113.000136
## Phase III AF Trials

<table>
<thead>
<tr>
<th></th>
<th>RE-LY</th>
<th>ROCKET AF</th>
<th>ARISTOTLE</th>
<th>ENGAGE AF-TIMI 48</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug</strong></td>
<td>Dabigatran</td>
<td>Rivaroxaban</td>
<td>Apixaban</td>
<td>Edoxaban</td>
</tr>
<tr>
<td><strong>Dose (mg)</strong></td>
<td>150, 110</td>
<td>20 (15*)</td>
<td>5 (2.5*)</td>
<td>60*, 30*</td>
</tr>
<tr>
<td><strong>freq</strong></td>
<td>BID</td>
<td>QD</td>
<td>BID</td>
<td>QD</td>
</tr>
<tr>
<td><strong>No.</strong></td>
<td>18,113</td>
<td>14,266</td>
<td>18,206</td>
<td>&gt;21,000</td>
</tr>
<tr>
<td><strong>Design</strong></td>
<td>PROBE</td>
<td>2 x blind</td>
<td>2 x blind</td>
<td>2 x blind</td>
</tr>
<tr>
<td><strong>AF criteria</strong></td>
<td>AF x 1</td>
<td>AF x 2</td>
<td>AF or AFI x 2</td>
<td>AF x 1</td>
</tr>
<tr>
<td></td>
<td>&lt;6 mo</td>
<td>(≥1 in &lt;30d)</td>
<td>&lt;12 mo.</td>
<td>&lt;12 mo.</td>
</tr>
<tr>
<td><strong>VKA naïve (%)</strong></td>
<td>50</td>
<td>38</td>
<td>43</td>
<td>Goal 40</td>
</tr>
</tbody>
</table>

*Dose adjusted in pt with ↓drug clearance: **Max of 10% with CHADS<sub>2</sub> score = 2 and no stroke/TIA/SEE: PROBE = prospective, randomized, open-label, blinded end point evaluation: VKA = vitamin K antagonist*
New Anticoagulant Therapies Compared to Warfarin
Stroke or Systemic Embolism

Dabigatran 150 mg BID
Dabigatran 110 mg BID
Rivaroxaban 20 mg o.d.
Abixaban 5 mg BID

Intracerebral Hemorrhage
The Worst Complication of Antithrombotic Therapy

• >10% of intracerebral hemorrhages (ICH) occur in patients on antithrombotic therapy

• Aspirin increases the risk by ~40%

• Warfarin (INR 2-3) doubles the risk to 0.3-0.6%/year

• ICH during anticoagulation is catastrophic (~50% mortality in most studies)

• In anticoagulated patients with AF, concomitant antiplatelet therapy is the most important modifiable independent risk factor for ICH
New Anticoagulant Therapies Compared to Warfarin
Gastrointestinal Bleeding

Dabigatran 150 mg BID
Dabigatran 110 mg BID
Rivaroxaban 20 mg o.d.
Abixaban 5 mg BID

Does Warfarin Predispose to Bleeding

Theoretical explanation

Increased expression of tissue factor in the cerebral cortex

Factor VII

Hemostasis

Sites of Action of Warfarin

XII

XI

IX

VIII

VII

Warfarin

X

V

II

I

Fibrin clot

Theoretical explanation:

- Factor VII
- Hemostasis

Sites of Action of Warfarin:

- Factor XII
- Factor XI
- Factor IX
- Factor VIII
- Factor VII
- Factor X
- Factor V
- Factor II
- Factor I

Increased expression of tissue factor in the cerebral cortex.
Indirect Comparison of Efficacy and Safety

Comparable Primary Efficacy Endpoints on Stroke or Systemic Embolism

Comparative HR (95% CI)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Comparative HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>dabigatran 150 mg B.I.D.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>dabigatran 110 mg B.I.D.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>rivaroxaban 20 mg Q.D.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>apixaban 5 mg B.I.D.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

De Caterina, JACC 2012

Comparable Primary Safety Endpoints of Major Bleeding

Comparative HR (95% CI)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
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<td></td>
</tr>
<tr>
<td>apixaban 5 mg B.I.D.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Which Agent?

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Largest RRR of ischemic stroke:</td>
<td><strong>dabigatran</strong></td>
</tr>
<tr>
<td>Largest renal elimination:</td>
<td><strong>dabigatran</strong></td>
</tr>
<tr>
<td>One daily dosing:</td>
<td><strong>rivaroxaban / edoxaban</strong></td>
</tr>
<tr>
<td>Well established dosing for high risk patients with modest renal insufficiency:</td>
<td><strong>rivaroxaban</strong></td>
</tr>
<tr>
<td>Single dose with reduction in stroke and reduction in major bleeding:</td>
<td><strong>apixaban</strong></td>
</tr>
<tr>
<td>Least expensive:</td>
<td><strong>warfarin</strong></td>
</tr>
</tbody>
</table>
Risk of major bleeding in the elderly: meta-analysis of all major RCTs

Dabigatran 150mg

Rivaroxaban

Apixaban

Edoxaban 60mg

← Favors DOAC  Favors warfarin →

Manuj Sharma et al. Circulation. 2015
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## Renal Function and Dabigatran

Estimated Pharmacokinetic Parameters of Dabigatran by Renal Function

<table>
<thead>
<tr>
<th>Renal function</th>
<th>CrCl mL/min</th>
<th>Increase in AUC</th>
<th>Increase in C&lt;sub&gt;max&lt;/sub&gt;</th>
<th>T&lt;sub&gt;1/2&lt;/sub&gt; hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>80</td>
<td>1x</td>
<td>1x</td>
<td>13</td>
</tr>
<tr>
<td>Mild</td>
<td>50</td>
<td>1.5x</td>
<td>1.1x</td>
<td>15</td>
</tr>
<tr>
<td>Moderate</td>
<td>30</td>
<td>3.2x</td>
<td>1.7x</td>
<td>18</td>
</tr>
</tbody>
</table>

Dabigatran FDA package insert
Renal Function and Novel Drugs

- RE-LY, ROCKET excluded patients with eGFR<30, ARISTOTLE eGFR <25
- Dabigatran is 80% renally eliminated; riva, apixaban and edoxaban are around 30%
- Renal impairment is independent risk factor for stroke, for bleeding, for death
- 150 mg bid of dabigatran should be used cautiously in elderly (>80 y/o) and with renal impairment (< ~40 ml/min)
- Riva should be used at 15 mg/d with CrCL <50
- Apixaban should be used at 2.5 mg
**Recommendations**

<table>
<thead>
<tr>
<th>Class</th>
<th>Level</th>
<th>Details</th>
</tr>
</thead>
</table>
| IIa   | B     | Where dabigatran is prescribed, a dose of 150 mg bid should be considered for most patients in preference to 110 mg bid with the latter dose recommended in:  
  • Elderly patients, age ≥80  
  • Concomitant use of interacting drugs (eg verapamil)  
  • High bleeding risk (HAS-BLED score ≥3)  
  • Moderate renal impairment (CrCl 30-49 mL/min) |
| IIa   | C     | Where rivaroxaban is being considered, a dose of 20 mg od should be considered for most patients in reference to 15 mg o.d. with the latter dose recommended in:  
  • High bleeding risk (HAS-BLED score ≥3)  
  • Moderate renal impairment (CrCl 30-49 mL/min) |
| IIa   | B     | Baseline and subsequent regular assessment of renal function by (CrCl) is recommended in patients following initiation of any NOAC, which should be done annually but more frequently in those with moderate renal impairment where CrCl should be assessed 2-3 times per year. |
| III   | A     | NOACs (dabigatran, rivaroxaban and apixaban) are not recommended in patients with severe renal impairment (CrCl <30 mL/min). |
Dabigatran

- Gut
- Esterase-mediated hydrolysis
- No CYP450
- Bio-availability: 3–7%
- Dabigatran etexilate
- P-gp
- t½ = 12-17h

Rivaroxaban

- Gut
- CYP3A4
- Bio-availability: 66% (without food)
- 100% (with food)
- Rivaroxaban
- P-gp
- t½ = 5-9h (young)
- 11-13h (elderly)
- CYP2C9
- Bio-availability: ~35%

Apixaban

- Gut
- P-gp
- Bio-availability: 50%
- Apixaban
- t½ = 12h

Edoxaban

- Gut
- P-gp
- Bio-availability: 62%
- Edoxaban
- t½ = 10-14h

Dabigatran as P-glycoprotein Substrate

**Intestinal lumen**

**Gut wall**

**Blood stream**

**Efflux transporter**

Dabigatran etexilate

Dabigatran etexilate

Dabigatran etexilate

Dabigatran etexilate

Dabigatran absolute bioavailability = ~5–7.5%

Absorption

P-glycoprotein

Dabigatran

Serum esterases

Dabigatran

Dabigatran etexilate

Dabigatran etexilate

Dabigatran etexilate

Dabigatran etexilate

Dabigatran etexilate
## Effect on NOAC Plasma Levels from D-D Interactions and Recommendations

<table>
<thead>
<tr>
<th>Dabigatran (%)</th>
<th>Apixaban</th>
<th>Edoxaban</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td>+18</td>
<td>No data</td>
<td>No effect</td>
</tr>
<tr>
<td>Digoxin</td>
<td>No effect</td>
<td>No data</td>
<td>No effect</td>
</tr>
<tr>
<td>Verapamil</td>
<td>+12-180 reduce dose take together</td>
<td>No data</td>
<td>+53 (SR) reduce dose</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>No effect</td>
<td>+40</td>
<td>No data</td>
</tr>
<tr>
<td>Quinidine</td>
<td>+50</td>
<td>No data</td>
<td>+80 reduce dose</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>+12-60</td>
<td>No data</td>
<td>No effect</td>
</tr>
<tr>
<td>Dronedarone</td>
<td>+70-100</td>
<td>No data</td>
<td>+88 reduce dose</td>
</tr>
</tbody>
</table>

### Notes
- **Not recommended/contraindicated**
- **Reduce dose if 2 factors or more**
- **Reduce dose**
- **No data yet**

# Transitioning Between Anticoagulants

## From warfarin to DOAC

<table>
<thead>
<tr>
<th>Anticoagulant</th>
<th>Apixaban</th>
<th>Rivaroxaban</th>
<th>Dabigatran</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stop warfarin &amp; start apixaban when</td>
<td><strong>INR &lt;2</strong></td>
<td>Stop warfarin &amp; start rivaroxaban when</td>
<td><strong>INR &lt;3</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stop warfarin &amp; start dabigatran when</td>
<td><strong>INR &lt;2</strong></td>
</tr>
</tbody>
</table>
Ischemic Stroke in an Obese Patient Receiving Dabigatran

Breuer: NEJM, 2014

Plasma level of Dabigatran (ng/mL)

Daytime hours (day 4)

Interquartile ranges

Peak plasma level at 2 hrs

Minimum plasma levels at 12 hrs

Dabigatran administration

Peak plasma level 50 ng/mL
How to Monitor

- Dabigatran
  - dTT
  - Ect

- Xa Inhibitors
  - Measurement of levels
    - Anti-Xa activity – STA-Rotachrom, Biochem
  - PT and aPTT prolonged
Managing Bleeding

- Novel OACs have less fatal bleeding than warfarin
- No specific antidote
  - Idarucizumab
  - Apirazine
- \textit{Not} dialyzable
  Protamine and Vitamin K does \textit{not} reverse
- Prothrombin complex concentrates reverse $\pm 30$-50\%

Management Decisions

Does procedure require anticoagulant discontinuation?

No

Yes

Mayo Approach:
Until we have more experience, we suggest **discontinuation of direct factor inhibitors** prior to *most invasive procedures*.
In Which Patients is Warfarin Preferred?

- Mechanical valves
- LV thrombi
- Rheumatic mitral valve disease

<table>
<thead>
<tr>
<th>Pt with severe renal impairment (CrCl &lt;30 mL/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stable INR and no bleeding</td>
</tr>
<tr>
<td>Easy access to anticoagulation clinic</td>
</tr>
<tr>
<td>and home INR monitoring</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Noncompliant pt</th>
</tr>
</thead>
<tbody>
<tr>
<td>INR as a monitoring tool</td>
</tr>
<tr>
<td>Adherence to bid dosing?</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncovered pt</td>
</tr>
<tr>
<td>Need for societal economic analyses</td>
</tr>
</tbody>
</table>

Noncompliant pt
Good Candidates for New Oral A/C

- Patients unwilling to take Warfarin after thorough discussion
- New patients naïve to Warfarin
  - Age <75 yrs
  - Compliant
  - Preserved renal function
- Compliant pts with unstable INR on Warfarin
- Patients not taking Dronedarone, Amiodarone, Verapmil, Quinidine
- Non-compliance is *not* an indication
Conclusions

• Compared to warfarin, the novel oral anticoagulants are at least as good at preventing stroke, have half the rate of ICH, have 10% lower mortality, and are easier to use.

• But many practical issues are important in their safe use, including:
  • Adjusting for renal dysfunction
  • Understanding how to measure their effect
  • Understanding how to manage procedures
  • Understanding how to manage bleeding
  • Avoiding aspirin without clear indication

• Having protocols in place to guide rational use of the novel drugs is a high priority.