Thrombosis and atherosclerosis, focus on new anticoagulants: Perspective of a Stroke Neurologist.

Faculty of Consulting Physicians of South Africa Annual Meeting

Capetown, SA
May 18, 2012
Disclosures and Acknowledgements

- **Grant-in-Aid**
- **Salary Award**
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- **Salary Award**

**Speaker’s / Advisory Board Honoraria**
- Boeringher Ingelheim
- Bayer
- BMS
- Octapharma

**Logos**
- Heart & Stroke Foundation
- Alberta Innovates Health Solutions
- Canada Research Chairs
- CIHR IRSC
- University Hospital Foundation
South African Connections

KwaZulu Natal 1996

Alberta, 2012
Outline

1. Rapid Diagnosis of Stroke/TIA

2. Approach to Secondary Stroke/TIA Prevention

3. Antithrombotic Options in Cardioembolic and Non-cardioembolic Stroke
Case History

- 58 year old male with a history of hypertension and smoking complains of headache and nausea to his office co-workers. One minute later, he develops left sided facial droop and falls to his left.

- EMS is called and he is brought to your ED. BP is 195/100, HR is 90 BPM and he is in NSR.
Stroke Diagnosis Requires Brain Scan

Patient 1

Patient 2

Time is Brain!
Who Needs Brain Imaging?

• Patients with **focal** neurological deficits
  – Weakness
  – Speech problems

• Our Patient: Symptoms resolve en route to hospital.
  – Does he require imaging?
Is Imaging Required?

YES!

57 year old male with transient dysarthria and sensory symptoms (left)
The TIA-Minor Stroke Continuum: (Acute Cerebrovascular Syndrome)

50% of TIA Patients Have MRI Lesions
Early Recurrent Stroke After TIA/Minor Stroke

Cumulative % of patients readmitted with stroke

Days after TIA

Gladstone, D. J. et al. CMAJ 2004;170:1099-1104
Mechanisms of Ischemic Stroke

Lacunar Infarcts (LACI)

Cortical Infarcts (PACI)

Lipohyalinosis

Artery-artery Embolism

Cardioembolism
Limitations of Clinical Localization in Acute Stroke Patients

Cortical

Sub-cortical

Asdaghi et al, Stroke, 2011
Secondary Prevention Strategies

**Lipohyalinosis**

**Artery-artery Embolism**

**Cardioembolism**

**Medical Optimization**
- **Antiplatelet agents**
- **Antihypertensives (SBP <140 mmHg/130 mmHg if diabetic)**
- **LDL <2 mmol/L**

**Surgical/Interventional**
- **Urgent CEA IF symptomatic stenosis >70%**
- **Carotid Stent if medically unstable**

**Anticoagulation**
Cortical Ischemic Stroke

Normal Carotid Arteries

Next Investigation?
Echocardiography Options

Transthoracic Echocardiogram

Transesophageal Echocardiogram
Left Atrial Appendage: Invisible to TTE
Higher Yield Cardiac Investigation

Holter Monitor

% of Patients with Paroxysmal Atrial Fibrillation (this changes management!)

Future: External/Implantable Loop Recorders

Number of Imaging Identified Infarcts
81 M, Transient Leg Weakness

CT: Camrose (Telestroke Site)

Doppler: 90% stenosis left ICA and 85% of right ICA
MRI at University Hospital

Cardioembolic Pattern of Infarction
(PAF later confirmed by Holter)
Cardio-embolic Stroke

Atrial Fibrillation
Typical Cardio-embolic Infarcts
Worse Prognosis Following Cardioembolic Stroke

One Year Risk of Death

- Small Vessel: 1.4%
- Large Vessel: 8%
- Cardioembolic: 30%

Atrial Fibrillation
Major Risk Factor for Stroke

- Independent risk factor for stroke - increases the risk of stroke by 5-fold\(^1,\,2,\,3\)

- Accounts for approximately 15-20% of all strokes nationally\(^1,\,4\) …likely under-estimated due to paroxysmal AF

- Risk of stroke in AF patients increases with age
  - 1.5% in 50–59 year olds
  - 23.5% in 80–89 year olds

Risk Stratification: CHADS$_2$ Score

- 1 point for Congestive Heart Failure
- 1 point for Hypertension
- 1 point for Age $\geq 75$ years
- 1 point for Diabetes Mellitus
- 2 points for Prior Stroke or TIA

CHADS$_2$ Score* | Stroke rate
--- | ---
0 | 1.9 (1.2 - 3.0)
1 | 2.8 (2.0 - 3.8)
2 | 4.0 (3.1 - 5.1)
3 | 5.9 (4.6 - 7.3)
4 | 8.5 (6.3 - 11.1)
5 | 12.5 (8.2 - 17.5)
6 | 18.2 (10.5 - 17.4)

*Score 0: Patients can be administered aspirin
*Score 1: Patients can be on aspirin and anticoagulant therapy
*Score $\geq 2$: Patients should be on anticoagulant therapy

29 year old male, lone AF

Warfarin Prevents Ischemic Stroke in Atrial Fibrillation Patients

Adjusted dose warfarin compared with placebo or control

AFSAK I
SPAF I
BAATAF
CAFA
SPINAF
EAFT

All trials ($n = 6$)

Relative Risk Reduction (95% CI)

Favors Warfarin

Favors Placebo or Control

AFSAK I = Copenhagen Atrial Fibrillation, Aspirin and Anticoagulation Study
SPAF I = Stroke Prevention in Atrial Fibrillation Study
BAATAF = Boston Area Anticoagulation Trial doe Atrial Fibrillation
CAFA = Canadian Atrial Fibrillation Anticoagulation
SPINAF = Stroke Prevention in Nonrheumatic Atrial Fibrillation
EAFT = European Atrial Fibrillation Trial

About 15-20% of all stroke is due to AF
INR Control and Stroke Risk

Does ASA Have a Role?

<table>
<thead>
<tr>
<th>Comparison</th>
<th>No. trials</th>
<th>No. pts</th>
<th>RRR stroke 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjusted–dose warfarin vs control</td>
<td>6</td>
<td>2900</td>
<td>64% (49,74)</td>
</tr>
<tr>
<td>Antiplatelets vs control</td>
<td>8</td>
<td>4876</td>
<td>22% (6,35)</td>
</tr>
<tr>
<td>Adjusted–dose warfarin vs antiplatelets</td>
<td>12</td>
<td>12,963</td>
<td>39% (27,49)</td>
</tr>
</tbody>
</table>

Hart RG and Aguilar MI. J Thromb Thrombolysis 2008;25:26–32

ASA reserved for true lone AF patients (CHADS=0), and patients with ABSOLUTE contraindications to anticoagulation
ACTIVE-W: Clopidrogel Plus Aspirin Versus Warfarin

Hemorrhagic complication rates were comparable in both groups

RR=1.44 (1.18–1.76), p=0.0003
ASA and Clopidogrel: Bilateral Subdural Hemorrhages
Clopidogrel and ASA: Not a Benign Combination

- Danish registry (n=82,854); patients discharged from hospital on Warfarin, Aspirin or Clopidogrel
- Bleeding requiring admission

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patient Years</th>
<th>Bleed rate (%/year)</th>
<th>RR (95% CI)</th>
<th>NNH/Year (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>93,492</td>
<td>3.9</td>
<td>1 (reference)</td>
<td>1 (reference)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>72,146</td>
<td>3.7</td>
<td>0.96 (0.95-0.96)</td>
<td>217 (151-388)</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>1,865</td>
<td>5.6</td>
<td>1.45 (1.22-1.66)</td>
<td>619 (288-4102)</td>
</tr>
<tr>
<td>C + A</td>
<td>1,264</td>
<td>7.4</td>
<td>1.91 (1.59-2.21)</td>
<td>28 (20-48)</td>
</tr>
<tr>
<td>W + A</td>
<td>17,712</td>
<td>6.9</td>
<td>1.75 (1.71-1.79)</td>
<td>34 (30-39)</td>
</tr>
<tr>
<td>W + C</td>
<td>496</td>
<td>13.9</td>
<td>3.57 (2.88-4.22)</td>
<td>10 (8-14)</td>
</tr>
<tr>
<td>W + C + A</td>
<td>408</td>
<td>15.7</td>
<td>4.03 (3.22-4.78)</td>
<td>8 (7-12)</td>
</tr>
</tbody>
</table>

Arch Intern Med 2010;170(16):1433-1441.
Issues with Warfarin

• 79 year old male
• PMHx: AF x 6 years; on warfarin; INR checked **monthly**
• Presents with mild dysphasia and right upper extremity weakness
• INR 1.7
Issues with Warfarin continued

- Discharged on warfarin; INR checks q weekly
- One year later: patient presents with ‘confusion’
  INR 1.8
Primary Intracerebral Hemorrhage

3 h

6 h
Anticoagulant Associated ICH Expansion

11h
INR = 2.4

24h

Hematoma Growth is 8 x more likely with anticoagulation
Desirable Qualities of a New Anticoagulant

- Prevents embolic stroke as / more effectively than warfarin
- Hemorrhage rates similar to / lower than warfarin
- Oral
- Predictable effect
- No anticoagulation monitoring
- Minimal food and drug interactions
- Rapid onset and offset of action
Thrombin (IIa)

Intrinsic (contact)

Extrinsic (tissue factor)

Prothrombin

Fibrinogen

Fibrin

Novel Oral Anticoagulants

Rivaroxaban
Apixaban
Edoxaban

Dabigatran etexilate
# Key Features of New Oral Anticoagulants

<table>
<thead>
<tr>
<th></th>
<th><strong>Dabigatran</strong>&lt;sup&gt;1,2,3&lt;/sup&gt;</th>
<th><strong>Rivaroxaban</strong>&lt;sup&gt;3,4&lt;/sup&gt;</th>
<th><strong>Apixaban</strong>&lt;sup&gt;3,5&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mechanism of action</strong></td>
<td>Direct thrombin inhibitor</td>
<td>Direct Xa inhibitor</td>
<td>Direct Xa inhibitor</td>
</tr>
<tr>
<td><strong>Prodrug</strong></td>
<td>Prodrug</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Routine Monitoring</strong></td>
<td>Not required</td>
<td>Not required</td>
<td>Not required</td>
</tr>
<tr>
<td><strong>Bioavailability</strong></td>
<td>6 %</td>
<td>&gt; 80 %</td>
<td>66 %</td>
</tr>
<tr>
<td><strong>Tmax</strong></td>
<td>2 hrs</td>
<td>2-4 hrs</td>
<td>3 hrs</td>
</tr>
<tr>
<td><strong>Half-life</strong></td>
<td>14-17 hours</td>
<td>7-11 hours</td>
<td>8-15 hours</td>
</tr>
<tr>
<td><strong>Dosing Frequency</strong></td>
<td>BID</td>
<td>QD</td>
<td>BID</td>
</tr>
<tr>
<td><strong>Excretion</strong></td>
<td>Renal (80%), Fecal (20%)</td>
<td>66% renal; 28% fecal/biliary</td>
<td>55% fecal; 25% renal&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Food</strong></td>
<td>Delayed absorption</td>
<td>No dietary restrictions</td>
<td>Not reported</td>
</tr>
<tr>
<td><strong>Drug-drug</strong></td>
<td>P-glycoprotein</td>
<td>CYP3A4 and P-glycoprotein</td>
<td>CYP3A4 and P-glycoprotein</td>
</tr>
</tbody>
</table>

## AF Trials: Key Features

<table>
<thead>
<tr>
<th></th>
<th>Re-LY</th>
<th>ROCKET-AF</th>
<th>ARISTOTLE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug</strong></td>
<td>Dabigatran</td>
<td>Rivaroxaban</td>
<td>Apixaban</td>
</tr>
<tr>
<td><strong>Dose (mg) Freq</strong></td>
<td>150, 110 BID</td>
<td>20 (15*) QD</td>
<td>5 (2.5*) BID</td>
</tr>
<tr>
<td><strong>N</strong></td>
<td>18,113</td>
<td>14,266</td>
<td>18,206</td>
</tr>
<tr>
<td><strong>Design</strong></td>
<td>PROBE</td>
<td>2x blind</td>
<td>2x blind</td>
</tr>
<tr>
<td><strong>% VKA naive</strong></td>
<td>50%</td>
<td>38%</td>
<td>43%</td>
</tr>
</tbody>
</table>

*Dose adjusted in patients with ↓ drug clearance. **Max of 10% with CHADS-2 score = 2 and no stroke/TIA/SEE

PROBE = prospective, randomized, open-label, blinded end point evaluation

VKA = Vitamin K antagonist
The new OAC agents are consistently associated with a numerically lower risk for stroke or systemic embolism compared to warfarin.†

<table>
<thead>
<tr>
<th>TRIAL</th>
<th>OAC Agent</th>
<th>Relative Risk (95% CI)</th>
</tr>
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<tbody>
<tr>
<td>RE-LY</td>
<td>Dabigatran 150mg b.i.d.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dabigatran 110mg b.i.d.</td>
<td></td>
</tr>
<tr>
<td>ROCKET-AF</td>
<td>Rivaroxaban 20mg o.d.</td>
<td></td>
</tr>
<tr>
<td>ARISTOTLE</td>
<td>Apixaban* 5mg b.i.d.</td>
<td></td>
</tr>
</tbody>
</table>

† Not intended as cross-trial comparison
*Not approved in Canada for stroke prevention in AF patients

Data obtained from intention-to-treat analysis
New Anticoagulants vs Warfarin
Intracranial Hemorrhage

The new OAC agents are consistently associated with a significantly lower risk for intracranial hemorrhage compared to warfarin.†

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<tr>
<td>RE-LY</td>
<td>Dabigatran 150mg b.i.d.</td>
<td>0.1</td>
</tr>
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<td></td>
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<td></td>
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</table>

No ↑ GI Bleed Rate

† New Anticoagulant Better

Apixaban*: 5mg b.i.d.
Rivaroxaban: 20mg o.d.
Dabigatran: 110mg b.i.d., 150mg b.i.d.

Bleeding Complications in RELY

<table>
<thead>
<tr>
<th></th>
<th>Warfarin (n=6015)</th>
<th>Dabigatran 110 bid (n=6076)</th>
<th>Dabigatran 150 bid (n=6022)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td>477 (100)</td>
<td>397 (100)</td>
<td>486 (100)</td>
</tr>
<tr>
<td><strong>Intracranial</strong></td>
<td>88 (18.4)</td>
<td>31 (7.8)</td>
<td>38 (7.8)</td>
</tr>
<tr>
<td><strong>Subdural</strong></td>
<td>41 (8.6)</td>
<td>13 (3.3)</td>
<td>23 (4.7)</td>
</tr>
<tr>
<td><strong>Intraparenchymal</strong></td>
<td>45 (9.4)</td>
<td>16 (4.0)</td>
<td>15 (3.1)</td>
</tr>
<tr>
<td><strong>GI</strong></td>
<td>139 (29.1)</td>
<td>154 (39.8)</td>
<td>218 (44.9)</td>
</tr>
</tbody>
</table>
Canadian 2012 Recommendations: Anticoagulation for Stroke Prevention in AF Patients

Stratify all patients for risk of stroke (CHADS$_2$) and risk of bleeding

- CHADS$_2$ = 0
  - ASA
  - No antithrombotic may be appropriate in selected young patients with no stroke risk factor

- CHADS$_2$ = 1
  - OAC*
  - Based on individual risk/benefit considerations, ASA is a reasonable alternative for some

- CHADS$_2$ ≥ 2
  - OAC*

*Apixaban (not yet available), dabigatran and rivaroxaban are preferred oral anticoagulants over warfarin in most patients.
### The Anticoagulant Battleground

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Dabigatran 110 mg (N=6015)</th>
<th>Dabigatran 150 mg (N=6076)</th>
<th>Warfarin (N=6022)</th>
<th>P-value Dabigatran 110 mg vs. Warfarin</th>
<th>P-value Dabigatran 150 mg vs. Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial Infarction (%/year)</td>
<td>98 (0.82)</td>
<td>97 (0.81)</td>
<td>75 (0.64)</td>
<td>0.09</td>
<td>0.12</td>
</tr>
</tbody>
</table>

- **DABIGATRAN**
  - Superior ischemic stroke protection (150 BID dose)

- **RIVAROXABAN**
  - Once daily dosing

- **APIXABAN**
  - No increase in cardiac events

**FEWER GI BLEEDS**

**Less Renal Clearance**
The new OAC agents are consistently associated with a numerically lower risk for all-cause mortality compared to warfarin.†

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<td>ARISTOTLE</td>
<td>Apixaban* 5mg b.i.d.</td>
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† New Anticoagulants vs Warfarin All-Cause Mortality

Summary

• Stroke/TIA are medical emergencies
  – Rapid investigation is required to prevent early recurrence

• Atrial Fibrillation is the most important risk factor for stroke in individual patients

• The novel oral anticoagulants are all at least as effective as warfarin in preventing ischemic stroke and all are safer with respect to intracranial bleeding
Arguments Against NOAC

- Cost
- Reversal
Cost in Perspective

All of these are approximately 3.00 CDN per day
What Caused this ICH?

Age 85
Blood Pressure = 175/85
Taking warfarin; INR = 2.8
INR Correction Required for Hemostasis in ICH

% coagulation Factors

INR and Coagulation Reversal

zone of normal hemostasis

zone of anticoagulation

INR 3.1: Management Options?

1. Vitamin K 5 mg PO
2. FFP 1 unit IV – INR not re-checked

3 hours later: patient now hemiplegic, GCS 15
Management Continued

FFP 2 units IV -- INR 2.8

4 hours later
Management Continued

Transfer to tertiary centre
FFP 4 units IV -- INR 1.0
Prothrombin Complex Concentrate (PCC)

- Blood Product
- Factors II, VII, IX, X
- Indicated for Vitamin K Antagonist associated hemorrhage

Octaplex available in Alberta:
40 mL octaplex® and Vitamin K 10 mg IV; re-check INR in 15 min

IF unavailable, use FFP 15 ml/Kg and Vitamin K 10 mg IV
CT to Needle Time: 59 minutes

16:11, INR=3.3

PCC at 17:10, repeat INR=1.4

23 hour f/u scan
Poor Prognosis in Warfarin-Associated Intracranial Hemorrhage Despite Anticoagulation Reversal

Dar Dowlatshahi, MD, PhD; Kenneth S. Butcher, MD, PhD; Negar Asdaghi, MD, MSc; Susan Nahiriak, MD; Manya L. Bernbaum, BSc; Antonio Giulivi, MD; Jason K. Wasserman, PhD; Man-Chiu Poon, MD; Shelagh B. Coutts, MD; on behalf of the Canadian PCC Registry (CanPro) Investigators*

**Background and Purpose**—Anticoagulant-associated intracranial hemorrhage (aaICH) presents with larger hematoma volumes, higher risk of hematoma expansion, and worse outcome than spontaneous intracranial hemorrhage. Prothrombin complex concentrates (PCCs) are indicated for urgent reversal of anticoagulation after aaICH. Given the lack of randomized controlled trial evidence of efficacy, and the potential for thrombotic complications, we aimed to determine outcomes in patients with aaICH treated with PCC.

**Methods**—We conducted a prospective multicenter registry of patients treated with PCC for aaICH in Canada. Patients were identified by local blood banks after the release of PCC. A chart review abstracted clinical, imaging, and laboratory data, including thrombotic events after therapy. Hematoma volumes were measured on brain CT scans and primary outcomes were modified Rankin Scale at discharge and in-hospital mortality.

**Results**—Between 2008 and 2010, 141 patients received PCC for aaICH (71 intraparenchymal hemorrhages). The median age was 78 years (interquartile range, 14), 59.6% were male, and median Glasgow Coma Scale was 14. Median international normalized ratio was 2.6 (interquartile range, 2.0) and median parenchymal hematoma volume was 15.8 mL (interquartile range, 31.8). Median post-PCC therapy international normalized ratio was 1.4: 79.5% of patients had international normalized ratio correction (<1.5) within 1 hour of PCC therapy. Patients with intraparenchymal hemorrhage had an in-hospital mortality rate of 42.3% with median modified Rankin Scale of 5. Significant hematoma expansion occurred in 45.5%. There were 3 confirmed thrombotic complications within 7 days of PCC therapy.

**Conclusions**—PCC therapy rapidly corrected international normalized ratio in the majority of patients, yet mortality and morbidity rates remained high. Rapid international normalized ratio correction alone may not be sufficient to alter prognosis after aaICH. *(Stroke. 2012;43:00-00.)*

**Key Words:** acute care ■ acute Rx ■ anticoagulation ■ emergency medicine ■ hemorrhag ■ intrac. ■ intracerebral hemorrhage
Be Wary of....

- 87 year old female with Chronic Renal Failure
- 50 kg
- Cr 90-96
- eGFR (MDRD) = 48
- eGFR (Cockcroft-Gault) =
- Rx: Dabigatran 75 mg BID
Reversal of Rivaroxaban/Apixaban?

Intrinsic Hemostasis (XII, XI)

Extrinsic Hemostasis (Tissue factor)

Fibrinogen ➔ (XIII) Fibrin

Thrombin (IIa)

II

X

IXa

VIIa

Xa

Va

IX

VII
FEIBA (Activated PCC)

Contains Factors II, IX, and X, mainly non-activated, and Factor VII mainly in the activated form.
56 M, AF, Hypertension, CHF, INR=2.6: Re-anticoagulate?
Predicting ICH Recurrence

- 1.8-5.3 %/year overall
- OR increased 3x with warfarin

Location

Lobar recurrence up to 13.6%


Age

Risk Stratification with MRI

GRE/SWI:
Do NOT Anticoagulate

GRE/SWI:
Anticoagulate?
Our Patient: Dabigatran 110 BID
# Resumption of Anticoagulation

<table>
<thead>
<tr>
<th>Condition</th>
<th>Hold Period</th>
<th>Resumption</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanical Valve</td>
<td>1 week</td>
<td>IV heparin followed by VKA (no ASA)</td>
</tr>
<tr>
<td>Atrial Fibrillation-lobar hematoma</td>
<td>Discontinue permanently</td>
<td>ASA 81 mg</td>
</tr>
<tr>
<td>Atrial Fibrillation-deep hematoma</td>
<td>1 week</td>
<td>DABIGATRAN, particularly if INR &gt; 4.0; otherwise ASA 81 mg</td>
</tr>
</tbody>
</table>
Dabigatran
Mechanism of Action

Prothrombin

- Thrombin
- Fibrinogen
- Fibrin

Clot bound Thrombin

Amplification

Dabigatran
Study Design

Atrial Fibrillation

Rivaroxaban
- 20 mg daily
- 15 mg for Cr Cl 30-49 ml/min
- Randomize Double Blind / Double Dummy (n ~ 14,000)

Warfarin
- INR target - 2.5 (2.0-3.0 inclusive)

Monthly Monitoring Adherence to standard of care guidelines

Primary Endpoint: Stroke or non-CNS Systemic Embolism

Risk Factors
- CHF
- Hypertension
- Age ≥ 75
- Diabetes
- Stroke, TIA or Systemic embolus

At least 2 or 3 required*

* Enrollment of patients without prior Stroke, TIA or systemic embolism and only 2 factors capped at 10%
## Primary Efficacy Outcome

**Stroke and non-CNS Embolism**

<table>
<thead>
<tr>
<th></th>
<th>Rivaroxaban</th>
<th>Warfarin</th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>On Treatment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N= 14,143</td>
<td>1.70</td>
<td>2.15</td>
<td>0.79 (0.65, 0.95)</td>
<td>0.015</td>
</tr>
<tr>
<td><strong>ITT</strong></td>
<td>2.12</td>
<td>2.42</td>
<td>0.88 (0.74, 1.03)</td>
<td>0.117</td>
</tr>
</tbody>
</table>

Event Rates are per 100 patient-years

Based on Safety on Treatment or Intention-to-Treat thru Site Notification populations
<table>
<thead>
<tr>
<th>Major bleeding, no. (%)</th>
<th>CrCI 30–49 ml/min</th>
<th>CrCI ≥50 ml/min</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GI (upper, lower, and rectal)</strong></td>
<td>Riva 15 mg (N = 1474)</td>
<td>Warfarin (N=1476)</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>2.88</td>
<td>1.77</td>
<td></td>
</tr>
<tr>
<td><strong>Intracranial</strong></td>
<td>0.71</td>
<td>0.88</td>
<td>0.54</td>
</tr>
<tr>
<td><strong>Macroscopic haematuria</strong></td>
<td>0.05</td>
<td>0.18</td>
<td>0.22</td>
</tr>
<tr>
<td><strong>Bleeding associated with non-cardiac surgery</strong></td>
<td>0.24</td>
<td>0.42</td>
<td>0.31</td>
</tr>
<tr>
<td><strong>Intra-articular</strong></td>
<td>0.00</td>
<td>0.23</td>
<td>0.99</td>
</tr>
<tr>
<td><strong>Epistaxis</strong></td>
<td>0.19</td>
<td>0.09</td>
<td>0.40</td>
</tr>
</tbody>
</table>

*Event rates per 100 pt-ys of follow-up*
Atrial Fibrillation with at Least One Additional Risk Factor for Stroke

Randomize double blind, double dummy \( (n = 18,201) \)

- Inclusion risk factors
  - Age \( \geq 75 \) years
  - Prior stroke, TIA, or SE
  - HF or LVEF \( \leq 40\%
  - Diabetes mellitus
  - Hypertension

- Major exclusion criteria
  - Mechanical prosthetic valve
  - Severe renal insufficiency
  - Need for aspirin plus thienopyridine

Apixaban 5 mg oral twice daily
(2.5 mg BID in selected patients)

Warfarin (target INR 2-3)

Warfarin/warfarin placebo adjusted by INR/sham INR based on encrypted point-of-care testing device

Primary outcome: stroke or systemic embolism

Hierarchical testing: non-inferiority for primary outcome, superiority for primary outcome, major bleeding, death

Duke Clinical Research Institute
## Efficacy Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Apixaban (N=9120) Event Rate (%/yr)</th>
<th>Warfarin (N=9081) Event Rate (%/yr)</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke or systemic embolism*</td>
<td>1.27</td>
<td>1.60</td>
<td>0.79 (0.66, 0.95)</td>
<td>0.011</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.19</td>
<td>1.51</td>
<td>0.79 (0.65, 0.95)</td>
<td>0.012</td>
</tr>
<tr>
<td>Ischemic or uncertain</td>
<td>0.97</td>
<td>1.05</td>
<td>0.92 (0.74, 1.13)</td>
<td>0.42</td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td>0.24</td>
<td>0.47</td>
<td>0.51 (0.35, 0.75)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systemic embolism (SE)</td>
<td>0.09</td>
<td>0.10</td>
<td>0.87 (0.44, 1.75)</td>
<td>0.70</td>
</tr>
<tr>
<td>All-cause death*</td>
<td>3.52</td>
<td>3.94</td>
<td>0.89 (0.80, 0.998)</td>
<td>0.047</td>
</tr>
<tr>
<td>Stroke, SE, or all-cause death</td>
<td>4.49</td>
<td>5.04</td>
<td>0.89 (0.81, 0.98)</td>
<td>0.019</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0.53</td>
<td>0.61</td>
<td>0.88 (0.66, 1.17)</td>
<td>0.37</td>
</tr>
</tbody>
</table>

*Part of sequential testing sequence preserving the overall type I error*
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Apixaban (N=9088) Event Rate (%)/yr</th>
<th>Warfarin (N=9052) Event Rate (%)/yr</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary safety outcome: ISTH major bleeding*</td>
<td>2.13</td>
<td>3.09</td>
<td>0.69 (0.60, 0.80)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Intracranial</td>
<td>0.33</td>
<td>0.80</td>
<td>0.42 (0.30, 0.58)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>0.76</td>
<td>0.86</td>
<td>0.89 (0.70, 1.15)</td>
<td>0.37</td>
</tr>
<tr>
<td>Major or clinically relevant non-major bleeding</td>
<td>4.07</td>
<td>6.01</td>
<td>0.68 (0.61, 0.75)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>GUSTO severe bleeding</td>
<td>0.52</td>
<td>1.13</td>
<td>0.46 (0.35, 0.60)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TIMI major bleeding</td>
<td>0.96</td>
<td>1.69</td>
<td>0.57 (0.46, 0.70)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Any bleeding</td>
<td>18.1</td>
<td>25.8</td>
<td>0.71 (0.68, 0.75)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* Part of sequential testing sequence preserving the overall type I error
Assessing the Anticoagulant Effect of Dabigatran
(General Guidance Based on Expert consensus)

Setting requiring assessment of dabigatran effect:
- Emergency Dept
- Perioperative
- Renal impairment
- Bleeding

1. Verify last dose of dabigatran
2. Measure aPTT

Is aPTT prolonged?

- YES
  - Dabigatran effect is present
- NO
  - Dabigatran effect is NOT present

Median aPTT at peak is 2 times control (80 sec) and at trough is 1.5 times control (<65 sec)

Note: Normal PTT varies with reagents/kits; UAH = 25-37 s

- aPTT and thrombin time provide a qualitative assessment of dabigatran effect
- Hemoclot provides a quantitative assessment of dabigatran concentration

van Ryn Thromb Haemost 2010;103:1116
Pradaxa SPC EMEA
Using the Hemoclot Assay to Assess Dabigatran’s Effect
(General Guidance Based on Expert consensus)

Hemoclot® Thrombin Inhibitor assay:
• Sensitive assay that provides quantitative measure of dabigatran concentration in plasma
• There is a direct linear relationship between dabigatran concentration and clotting time (ranging from about 30 to 75 seconds)
• Website: http://www.aniara.com/Search/?q=hemoclot

Hemoclot® Thrombin Inhibitor assay:
• Sensitive dilute TT assay (1:8-1:20 ratio)
• Dabigatran level:
  • 30-50 ng/ml or less: Minimal level
  • >200 ng/ml, at trough after 150 mg bid (10-16 hrs after lastdose): increased risk of bleeding

Linear relationship between Hemoclot TT assay and dabigatran concentrations in healthy volunteers receiving 220 mg

van Ryn  Thromb Haemost 2010;103:1116
58 year old male; Right hemiplegia, global dysphasia

- PAF
- Dabigatran 150 mg BID
Treatment Options?

- aPTT = 22 (reference 25-37 sec)
- TT = 30.7 (reference 14.3-19.7 sec)
1 hour post IV tPA
Protect Your Patients

• 71 year old male, working, guardian of grandson
• AF
• Dabigatran 150 mg BID
• Stopped 14 days prior to Cardiac Surgery
• Day 10….
24 hour NCCT Scan (post tPA)
Post-Hemicraniectomy
Active Carotid Plaque in a ‘TIA’ Patient

50% of TIA patients have acute MRI lesions
Are all TIAs the Same?

ABCD² Score

A: age ≥ 60 years – 1 point

B: BP (systolic>140mmHg, diastolic>90 mmHg). Either 1 point. (max 1 point)

C: clinical – unilateral weakness =2, speech only = 1

D: Duration, ≥60 minutes =2, 10-59 =1, <10 =0

D²: Diabetes=1

ABCD² >5: 8% risk of stroke within 48 h

Potential Anti-thrombotic Options

- Warfarin
- ASA
- ASA+Clopidogrel
- Dabigatran
- Rivaroxaban
- Apixaban
**Most Common Adverse Event: Dyspepsia**

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Dabigatran 110 mg (%)</th>
<th>Dabigatran 150 mg (%)</th>
<th>Warfarin (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspepsia*</td>
<td>11.8</td>
<td>11.3</td>
<td>5.8</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>9.3</td>
<td>9.5</td>
<td>9.7</td>
</tr>
<tr>
<td>Dizziness</td>
<td>8.1</td>
<td>8.3</td>
<td>9.4</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>7.9</td>
<td>7.9</td>
<td>7.8</td>
</tr>
<tr>
<td>Fatigue</td>
<td>6.6</td>
<td>6.6</td>
<td>6.2</td>
</tr>
<tr>
<td>Cough</td>
<td>5.7</td>
<td>5.7</td>
<td>6.0</td>
</tr>
<tr>
<td>Chest pain</td>
<td>5.2</td>
<td>6.2</td>
<td>5.9</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>4.5</td>
<td>5.5</td>
<td>5.7</td>
</tr>
<tr>
<td>Back pain</td>
<td>5.3</td>
<td>5.2</td>
<td>5.6</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>5.6</td>
<td>5.4</td>
<td>5.6</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6.3</td>
<td>6.5</td>
<td>5.7</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>4.5</td>
<td>4.8</td>
<td>5.6</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>4.8</td>
<td>4.7</td>
<td>5.2</td>
</tr>
</tbody>
</table>

*Occurred more commonly on dabigatran p<0.001

Dabigatran etexilate is in clinical development and not licensed for clinical use in stroke prevention for patients with atrial fibrillation