Efficacy and Safety of the NOAC’s

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Disclosures

- **Medical Advisory Board**
  - Boston Scientific
  - The Medicines Company

- **Speakers Bureau**
  - Bristol-Myers Squibb
  - Pfizer
  - Daiichi Sankyo
NVAF Is Associated With Significant Morbidity and Mortality

Morbidity
- The risk of stroke is increased ~5-fold in NVAF patients vs those without NVAF\(^1,2\)

Incidence of Stroke According to Presence of NVAF (Framingham Heart Study)

Mortality
- Stroke patients with NVAF are at increased risk of death vs those without AF\(^3\)

Rate of Death

\(\begin{array}{c|c}
\text{Without AF (n=2661)} & \text{With NVAF (n=674)} \\
\hline
\text{30-Day Mortality} & 16.2\% & 34.7\%
\hline
\text{1-Year Mortality} & 27.1\% & 52.4\%
\end{array}\)

* \(P<0.001\).
AF=atrial fibrillation.
The CHADS₂ and CHA₂DS₂-VASc Scoring Systems Assess Stroke Risk in Patients With NVAF

### CHADS₂ Stroke Risk Index¹,²

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive heart failure</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>Age ≥75 years</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
</tr>
<tr>
<td>Stroke or TIA (prior)</td>
<td>2</td>
</tr>
</tbody>
</table>

*Maximum score: 6*

### CHA₂DS₂-VASc* Stroke Risk Index²,³

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive heart failure/LVD</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>Age ≥75 years</td>
<td>2</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
</tr>
<tr>
<td>Stroke, TIA, or thromboembolism (prior)</td>
<td>2</td>
</tr>
<tr>
<td>Vascular disease†</td>
<td>1</td>
</tr>
<tr>
<td>Age 65 to 74 years</td>
<td>1</td>
</tr>
<tr>
<td>Sex category (ie, female gender)</td>
<td>1</td>
</tr>
</tbody>
</table>

*Maximum score: 9*

* A patient’s CHA₂DS₂-VASc score can either be the same as or higher than the CHADS₂ score; it cannot be lower.
† Prior myocardial infarction, peripheral artery disease, or aortic plaque
LVD=left ventricular dysfunction; TIA=transient ischemic attack.

Stroke Risk Increases With Higher CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VASc Scores in Patients With NVAF

### Stroke Risk in National Registry of NVAF Patients by CHADS<sub>2</sub> Score (N=1733)<sup>1,2</sup>

<table>
<thead>
<tr>
<th>CHADS&lt;sub&gt;2&lt;/sub&gt; Score</th>
<th>Adjusted Stroke Rate* (%)/year (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.9 (1.2–3.0)</td>
</tr>
<tr>
<td>1</td>
<td>2.8 (2.0–3.8)</td>
</tr>
<tr>
<td>2</td>
<td>4.0 (3.1–5.1)</td>
</tr>
<tr>
<td>3</td>
<td>5.9 (4.6–7.3)</td>
</tr>
<tr>
<td>4</td>
<td>8.5 (6.3–11.1)</td>
</tr>
<tr>
<td>5</td>
<td>12.5 (8.2–17.5)</td>
</tr>
<tr>
<td>6</td>
<td>18.2 (10.5–27.4)</td>
</tr>
</tbody>
</table>

* The adjusted stroke rate is the expected stroke rate per 100 patient-years from the exponential survival model, assuming that aspirin was not taken.

- As CHADS<sub>2</sub> score increases, so does the risk of stroke<sup>1,2</sup>

### Risk of Stroke in NVAF Patients by CHA<sub>2</sub>DS<sub>2</sub>-VASc Score (N=7329)<sup>2,3</sup>

<table>
<thead>
<tr>
<th>CHA&lt;sub&gt;2&lt;/sub&gt;DS&lt;sub&gt;2&lt;/sub&gt;-VASc Score</th>
<th>Adjusted Stroke Event Rate, %/year†</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>1.3</td>
</tr>
<tr>
<td>2</td>
<td>2.2</td>
</tr>
<tr>
<td>3</td>
<td>3.2</td>
</tr>
<tr>
<td>4</td>
<td>4.0</td>
</tr>
<tr>
<td>5</td>
<td>6.7</td>
</tr>
<tr>
<td>6</td>
<td>9.8</td>
</tr>
<tr>
<td>7</td>
<td>9.6</td>
</tr>
<tr>
<td>8</td>
<td>6.7</td>
</tr>
<tr>
<td>9</td>
<td>15.2</td>
</tr>
</tbody>
</table>

† Theoretical event rates without therapy; assuming that oral anticoagulation provides a 64% reduction in risk.

- Better identifies low-risk patients with AF<sup>2</sup>

CI=confidence interval.

What Does CHADS2 Really Tell Us?

Atrial Fibrillation CHADS(2) Score for Stroke Risk

Select Criteria:
- Diagnosed heart failure, past or current (1 point)
- Hypertension treated or untreated (1 point)
- Age >= 75 years (1 point)
- Diabetes Mellitus (1 point)
- Secondary prevention in patients with prior ischemic stroke, TIA or thromboembolism (2 points)

Results:
Total Criteria Point Count: 0

Stroke Risk per 100 Person Years/ Warfarin Rx Interpretation

- 0 Points: 0.25 ON Rx; 0.49 NO Rx
- 1 Point: 0.72 ON Rx; 1.52 NO Rx
- 2 Points: 1.27 ON Rx; 2.50 NO Rx
- 3 Points: 2.20 ON Rx; 5.27 NO Rx
- 4 Points: 2.35 ON Rx; 6.02 NO Rx
- 5-6 Points: 4.60 ON Rx; 6.88 NO Rx


## CHADS2 Risk Calculator in Clinical Practice

Event Rate (per 100 person-years) – 95% Confidence Interval

<table>
<thead>
<tr>
<th>CHADS2 Score</th>
<th>Taking Warfarin</th>
<th>Not Taking Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (2557)</td>
<td>0.25 (0.11-0.55)</td>
<td>0.49 (0.30-0.78)</td>
</tr>
<tr>
<td>1 (3662)</td>
<td>0.72 (0.50-1.03)</td>
<td>1.52 (1.19-1.94)</td>
</tr>
<tr>
<td>2 (2955)</td>
<td>1.27 (0.94-1.72)</td>
<td>2.50 (1.98-3.15)</td>
</tr>
<tr>
<td>3 (1555)</td>
<td>2.20 (1.61-3.01)</td>
<td>5.27 (4.15-6.70)</td>
</tr>
<tr>
<td>4 (556)</td>
<td>2.35 (1.44-3.83)</td>
<td>6.02 (3.90-9.29)</td>
</tr>
<tr>
<td>5 or 6 (241)</td>
<td>4.60 (2.72-7.76)</td>
<td>6.88 (3.42-13.84)</td>
</tr>
</tbody>
</table>

64% reduction on warfarin vs no antithrombotic therapy
2/3 of strokes on warfarin were at an INR <2

Aristotle – Efficacy of Apixaban vs Warfarin

Stroke / Systemic Embolism Rates

<table>
<thead>
<tr>
<th>Event Rate (%/year)</th>
<th>Apixaban</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.6%</td>
<td>265</td>
<td>212</td>
</tr>
<tr>
<td>1.27%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Apixaban superior, p=0.01
HR (95% CI)
0.79 (0.66-0.95)
21% RRR

n=9081
n=9120
ARISTOTLE – Major Bleeding Episodes

Major Bleeding Episodes

<table>
<thead>
<tr>
<th>Event Type</th>
<th>Warfarin, n=9052</th>
<th>Apixaban, n=9088</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracranial</td>
<td>0.82% (0.30-0.57)</td>
<td>0.33% (0.30-0.57)</td>
</tr>
<tr>
<td>GI</td>
<td>0.93% (0.70-1.14)</td>
<td>0.89% (0.70-1.14)</td>
</tr>
<tr>
<td>Fatal</td>
<td>0.27% (0.13-0.53)</td>
<td>0.06% (0.13-0.53)</td>
</tr>
<tr>
<td>Intraocular</td>
<td>1.42% (0.83-2.45)</td>
<td>0.21% (0.83-2.45)</td>
</tr>
</tbody>
</table>

Event Rates (%/year)

HR (95% CI)

- Intracranial: 0.41 (0.30-0.57)
- GI: 0.89 (0.70-1.14)
- Fatal: 0.27 (0.13-0.53)
- Intraocular: 1.42 (0.83-2.45)

Major bleeding: fatal bleeding, critical site bleeding, Hb decrease >=2 g/dl, transfusion >=2 units packed red cells.
Clinically Relevant Non-major Bleeding

CRNM: Does not meet criteria for major bleeding and leads to hospital admission or physician guided medical or surgical treatment for bleeding or results in a change in antithrombotic therapy.

HR (95% CI): 0.70 (0.60-0.80)

p<0.0001
RE-LY Trial – Reduction in Stroke with Dabigatran

**Number of Events**

<table>
<thead>
<tr>
<th>Event Type</th>
<th>Warfarin (n=6022)</th>
<th>Dabigatran (n=6076)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>186</td>
<td>122</td>
</tr>
<tr>
<td>Ischemic Stroke</td>
<td>134</td>
<td>103</td>
</tr>
<tr>
<td>Hemorrhagic Stroke</td>
<td>45</td>
<td>12</td>
</tr>
<tr>
<td>Systemic Embolism</td>
<td>21</td>
<td>13</td>
</tr>
</tbody>
</table>

HR: 0.64 95% CI (0.51-0.81)  
HR: 0.75 95% CI (0.58-0.97)  
HR: 0.26 95% CI (0.14-0.49)  
HR: 0.64 95% CI (0.51-0.81)

RE-LY Trial – Bleeding Rates

RE-LY – Intracranial Hemorrhages

Event Rates Per 100 Patient Years

<table>
<thead>
<tr>
<th>Intracranial Hemorrhages</th>
<th>Warfarin (n=6022)</th>
<th>Dabigatran (n=6076)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>90 (0.8%)</td>
<td>38 (0.3%)</td>
</tr>
</tbody>
</table>

HR 0.41 (95% CI: 0.28-0.60)

ROCKET AF Trial - Outcomes

Primary composite endpoint vs warfarin: HR (95% CI): 0.88 (0.74, 1.03)

ROCKET AF – Bleeding Rates

Warfarin (n=7125)
- HR 95% CI: 1.03 (0.96, 1.11)

Rivaroxaban (n=7111)
- HR 95% CI: 1.04 (0.90, 1.20)

Major and Nonmajor Clinically Relevant
- Warfarin: 1449
- Rivaroxaban: 1475

Major
- Warfarin: 386
- Rivaroxaban: 395

Nonmajor Clinically Relevant
- Warfarin: 1151
- Rivaroxaban: 1185

TIMI 48 Study – Event Rates with Edoxaban

### First stroke or SEE
- **Warfarin (n=7012):** 232
- **Edoxaban 60 mg (n=7012):** 182

- **97.5% CI:** 0.79 (0.63, 0.99)
- **P:** 0.017

### Ischemic Stroke
- **Warfarin (n=7012):** 144
- **Edoxaban 60 mg (n=7012):** 135

- **95% CI:** 0.94 (0.75, 1.19)

### Hemorrhagic Stroke
- **Warfarin (n=7012):** 75
- **Edoxaban 60 mg (n=7012):** 39

- **95% CI:** 0.52 (0.36, 0.77)

### Systemic Embolism
- **Warfarin (n=7012):** 13
- **Edoxaban 60 mg (n=7012):** 8

- **95% CI:** 0.62 (0.26, 1.50)

ROCKET AF – Major Bleeding

- Bleeding Into a Critical Organ
  - Warfarin (n=7125): 133
  - Rivaroxaban (n=7111): 91

- Fatal Bleeding
  - Warfarin: 55
  - Rivaroxaban: 27

- Transfusion
  - Warfarin: 149
  - Rivaroxaban: 183

- GI Bleeding
  - Warfarin: 140
  - Rivaroxaban: 221

Meta Analysis

![Bar chart showing outcomes for different conditions and therapies.]

- **Stroke or Systemic Embolism**:
  - Warfarin (n=29,285): 982
  - NOAC's (n=29,310): 778

- **Major Bleeding**:
  - Warfarin (n=29,285): 2815
  - NOAC's (n=29,310): 2587

- **Intracerebral Hemorrhage**:
  - Warfarin (n=29,285): 419
  - NOAC's (n=29,310): 199
Meta Analysis

Stroke or Systemic Embolism

- Warfarin (n=29,285)
- NOAC’s (n=29,310)
Meta Analysis

Major Bleeding Episodes

Warfarin (n=29,285)   NOAC's (n=29,310)
Meta Analysis

Intracerebral Hemorrhage

- Warfarin (n=29,285)
- NOAC’s (n=29,310)
Reversal Agents

- Indications
  - Life threatening bleeding
  - Uncontrolled bleeding
  - Emergency surgery
  - Urgent procedures
Coumadin prescribing information

Prothrombin complex concentrate (PCC), fresh frozen plasma, or activated Factor VII treatment may be considered if the requirement to reverse the effects of COUMADIN is urgent. A risk of hepatitis and other viral diseases is associated with the use of blood products; PCC and activated Factor VII are also associated with an increased risk of thrombosis. Therefore, these preparations should be used only in exceptional or life-threatening bleeding episodes secondary to COUMADIN overdosage.
Reversal Agents

Swedish Epic order set

<table>
<thead>
<tr>
<th>Indications</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase in HGB</td>
<td>A greater than or equal to 5 g/dL decrease in the hemoglobin concentration resulting in anticipated hemodynamic compromise.</td>
</tr>
<tr>
<td>Increase in HCT</td>
<td>A greater than or equal to 15% absolute decrease in the hematocrit resulting in anticipated hemodynamic compromise.</td>
</tr>
<tr>
<td>Compression of vital structures</td>
<td>Compression of vital structures clinically related to anticoagulation.</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>ICH is always considered a life threatening emergency.</td>
</tr>
</tbody>
</table>
Reversal Agents

Swedish Epic order set

Select the patient’s anticoagulation agent
Warfarin/Coumadin® (for any INR with serious or life-threatening bleeding) (Single Response)

Select the appropriate panel based on the patient’s INR.

May consider the INR 2-4 protocol for patients with INR 1.5 to less than 2. There are no guidelines for this INR level; consider the risks and benefits carefully.

Administer Vitamin K concurrently to patients receiving Kcentra for reversal of warfarin. Vitamin K is administered to maintain Vitamin K-dependent clotting factor levels once the effects of Kcentra have diminished.

Consider the following list of potential contraindications to Kcentra use: History of thrombotic or thromboembolic event in past 6 weeks (DVT/PE, ischemic stroke, ACS, acute venous/arterial ischemia, etc), known prothrombotic condition (malignancy, DIC, hypercoagulable condition, hepatic disease, polytrauma, HIT, etc). Weigh risk-benefit of Kcentra in these circumstances.
## Reversal Agents

### Swedish Epic order set

<table>
<thead>
<tr>
<th>INR 2-4 (consider for INR 1.5 to less than 2)</th>
<th>25 Units/kg, Intravenous, ONE TIME For 1 Doses, STAT</th>
</tr>
</thead>
<tbody>
<tr>
<td>prothrombin clotting concentrate (PCC) (aka KCENTRA) in empty Viaflex container</td>
<td>25 Units/kg, Intravenous, PRN For 24 Hours, as indicated by anticoagulation reversal protocol</td>
</tr>
<tr>
<td>Anticoagulation Reversal Nursing Instructions</td>
<td>1. Hold Warfarin</td>
</tr>
<tr>
<td>2. Administer:</td>
<td></td>
</tr>
<tr>
<td>A. Prothrombin Complex Concentrate (PCC)</td>
<td></td>
</tr>
<tr>
<td>B. Vitamin K (phytonadione)</td>
<td></td>
</tr>
<tr>
<td>3. Order a stat protome (INR) to be drawn 15 minutes after the administration of the PCC. If this INR is greater than 1.5, repeat the PCC dose (see PRN tab) and 15 minutes post-dose INR as needed up to an additional two times (max PCC dose 2500 units).</td>
<td></td>
</tr>
<tr>
<td>4. If patient’s INR rises above 1.5 within the first 24 hours after the anticoagulation reversal protocol, administer the PRN dose of vitamin K (phytonadione). Call Provider.</td>
<td></td>
</tr>
<tr>
<td>5. Twenty-four hours after anticoagulation reversal protocol initiated, administer 24-hour scheduled dose of vitamin K (phytonadione).</td>
<td></td>
</tr>
<tr>
<td>phytonadione (aka AQUA-MEPHYTON) in NS (0.9% NaCl) INJ solution 50 mL</td>
<td>10 mg, Intravenous, ONE TIME, at 100 mL/hr, STAT</td>
</tr>
<tr>
<td>PROTIME WHOLE BLOOD</td>
<td>Routine, Q4HR, Starting today For 6 Occurrences, Lab Collect</td>
</tr>
</tbody>
</table>
### Reversal Agents

#### Swedish Epic order set

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>phytonadione (aka AQUA-MEPHYTON) in NS (0.9% NaCl) INJ solution 50 mL</td>
<td>10 mg, Intravenous, ONE TIME Starting H+24 Hours For 1 Doses, at 100 mL/hr, Routine</td>
</tr>
<tr>
<td>phytonadione (aka AQUA-MEPHYTON) in NS (0.9% NaCl) INJ solution 50 mL</td>
<td>10 mg, Intravenous, PRN For 24 Hours, at 100 mL/hr, Other, If INR increases above 1.5 after anticoagulation reversal protocol, Routine</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>INR 4-6</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>prothrombin clotting concentrate (PCC) (aka KCENTRA) in empty Viaflex container</td>
<td>35 Units/kg, Intravenous, ONE TIME For 1 Doses, STAT</td>
</tr>
<tr>
<td>prothrombin clotting concentrate (PCC) (aka KCENTRA) in empty Viaflex container</td>
<td>35 Units/kg, Intravenous, PRN For 24 Hours, as indicated by anticoagulation reversal protocol</td>
</tr>
</tbody>
</table>
Idarucizumab (Praxbind)

- Humanized monoclonal antibody fragment (Fab)
- Binds to dabigatran and its acylglucuronide metabolites
- Binding affinity higher to idarucizumab than to thrombin
- 5 gm dose
- Immediate reversal of anticoagulation due to dabigatran
Factor Xa Inhibition Reversal

- Andexanet alpha
- Portola Pharmaceuticals
- Recombinant modified human factor Xa decoy protein.
- Catalytically inactive
- Binds factor Xa inhibitors at their active site with high affinity
- Restores the activity of endogenous factor Xa
Anti Xa Agents Currently in Use

- Apixaban (eliquis)
- Rivaroxaban (xarelto)
- Edoxaban (savaysa)
- Low molecular weight heparin (lovenox)
- Fondaparinux (arixtra)
Factor Xa Inhibition Reversal

A Apixaban Study, Andexanet Bolus

End of bolus

Anti-Factor Xa Activity (ng/ml)

Placebo (N=9)
Andexanet (N=24)

Hours since Bolus

Factor Xa Inhibition Reversal

C Apixaban Study, Andexanet Bolus plus Infusion

End of bolus

End of infusion

Anti-Factor Xa Activity (ng/ml)

Placebo (N=8)

Andexanet (N=23)

Hours since Bolus

Factor Xa Inhibition Reversal

A Apixaban Study, Andexanet Bolus

End of bolus

Placebo (N=9)
Andexanet (N=24)

Preanticoagulant mean ± SD

Endogenous Thrombin Potential (nM-min)

Baseline

Hours since Bolus

Factor Xa Inhibition Reversal

C Apixaban Study, Andexanet Bolus plus Infusion

End of bolus
End of infusion

Placebo (N=8)
Andexanet (N=23)

Preanticoagulant mean ± SD

Endogenous Thrombin Potential (nM·min)

Baseline

Hours since Bolus