Novel Oral Anticoagulants
Analyzing Clinical Trial Findings of the Efficacy and Safety Profiles of Novel Anticoagulants for the Treatment of Atrial Fibrillation and Prevention of Stroke

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Highlights

• Prevalence and incidence of AF
• Risk stratification for stroke and bleeding
• New oral anticoagulants
• Review of relevant clinical trials
• Guidelines
• Practical considerations for choosing an anticoagulant
Atrial Fibrillation — Profiling Afib

• Atrial fibrillation (Afib) affects about 1% of the population or about 2.3 million people in the United States
• Prevalence increases with age — affecting roughly 10% of population age 80 or older
• Afib is associated with a four- to five-fold increase in risk of stroke
AF responsible for 1/6 of all strokes

Warfarin reduces stroke in AF by 64%
- significant increase in intracranial and other hemorrhage
- Difficult to use

Only 50% of eligible patients receive warfarin

An alternative treatment is needed
### Prevalence of Diagnosed AF

**Stratified by Age and Sex**

Men surpass women in every age range.

- **x-axis = %**
- **y-axis = # of men/women**

<table>
<thead>
<tr>
<th>Age</th>
<th># Women</th>
<th># Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;55</td>
<td>530</td>
<td>1529</td>
</tr>
<tr>
<td>55-59</td>
<td>310</td>
<td>634</td>
</tr>
<tr>
<td>60-64</td>
<td>566</td>
<td>934</td>
</tr>
<tr>
<td>65-69</td>
<td>896</td>
<td>1426</td>
</tr>
<tr>
<td>70-74</td>
<td>1498</td>
<td>1907</td>
</tr>
<tr>
<td>75-79</td>
<td>1572</td>
<td>1886</td>
</tr>
<tr>
<td>80-84</td>
<td>1291</td>
<td>1374</td>
</tr>
<tr>
<td>&gt; 85</td>
<td>1132</td>
<td>759</td>
</tr>
</tbody>
</table>

# Incidence of AF

## Lifetime Risk for AF at Selected Index Ages by Sex

<table>
<thead>
<tr>
<th>Index Age, yrs</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>40</td>
<td>26.0% (24.0 – 27.0)</td>
<td>23.0% (21.0 – 24.0)</td>
</tr>
<tr>
<td>50</td>
<td>25.9% (23.9 – 27.0)</td>
<td>23.2% (21.3 – 24.3)</td>
</tr>
<tr>
<td>60</td>
<td>25.8% (23.7 – 26.9)</td>
<td>23.4% (21.4 – 24.4)</td>
</tr>
<tr>
<td>70</td>
<td>24.3% (22.1 – 25.5)</td>
<td>23.0% (20.9 – 24.1)</td>
</tr>
<tr>
<td>80</td>
<td>22.7% (20.1 – 24.1)</td>
<td>21.6% (19.3 – 22.7)</td>
</tr>
</tbody>
</table>

**1 in 4**

**Men & women >40 Years will develop AF**

**Lifetime risk if currently free of AF**

Risk stratification for stroke
Scoring Systems in Atrial Fibrillation

- Given that anticoagulant therapy has both risks (principally bleeding) and benefits (a reduced risk of thrombosis) many authors have attempted to produce scoring systems which estimate the risks of these outcomes.
- No one scoring system is universally accepted or highly predictive (in individual patients).
Scoring Systems in Stroke Risk

- A variety of systems have been published
- All use selected clinical characteristics to predict the risk of stroke
- Most widely used is the CHADS2 score
- All scores provide a rough estimate of risk of thrombosis in a population at similar risk as patient being reviewed
## CHADS2: Risk of Stroke

### National Registry of Atrial Fibrillation Participants (NRAF)

<table>
<thead>
<tr>
<th>CHADS2 Score</th>
<th># Patients (n = 1733)</th>
<th># Strokes (n = 94)</th>
<th>NRAF Crude Stroke Rate per 100 Patient-yrs</th>
<th>NRAF Adjusted Stroke Rate (95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>120</td>
<td>2</td>
<td>1.2</td>
<td>1.9 (1.2-3.0)</td>
</tr>
<tr>
<td>1</td>
<td>463</td>
<td>17</td>
<td>2.8</td>
<td>2.8 (2.0-3.8)</td>
</tr>
<tr>
<td>2</td>
<td>523</td>
<td>23</td>
<td>3.6</td>
<td>4.0 (3.1-5.1)</td>
</tr>
<tr>
<td>3</td>
<td>337</td>
<td>25</td>
<td>6.4</td>
<td>5.9 (4.6-7.3)</td>
</tr>
<tr>
<td>4</td>
<td>220</td>
<td>19</td>
<td>8.0</td>
<td>8.5 (6.3-11.1)</td>
</tr>
<tr>
<td>5</td>
<td>65</td>
<td>6</td>
<td>7.7</td>
<td>12.5 (8.2-17.5)</td>
</tr>
<tr>
<td>6</td>
<td>5</td>
<td>2</td>
<td>44.0</td>
<td>18.2 (10.5-27.4)</td>
</tr>
</tbody>
</table>

**Scoring:**
1 point: Congestive heart failure, HTN, < 75 years, and DM
2 points: Stroke history or transient ischemic attack
† Expected stroke rate per 100 pt-yrs from the exponential survival model, assuming aspirin not taken

### ACCP Guidelines

For patients with Nonrheumatic AF, including those with Paroxysmal AF

<table>
<thead>
<tr>
<th>Level of Risk</th>
<th>ACCP Recommendation</th>
<th>Alternative*</th>
<th>Not Recommended</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Risk (CHADS2 = 0)</td>
<td>No Therapy</td>
<td>Aspirin</td>
<td>Oral anticoagulation or combination therapy with aspirin and clopidogrel</td>
</tr>
<tr>
<td>Intermediate Risk</td>
<td>Oral anticoagulation</td>
<td>Aspirin with clopidogrel</td>
<td>Aspirin</td>
</tr>
<tr>
<td>(CHADS2 = 1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High Risk (CHADS2 = 2)</td>
<td>Oral anticoagulation (dabigatran 150 mg b.i.d. vs. VKA**)</td>
<td>Aspirin with clopidogrel</td>
<td>Aspirin</td>
</tr>
</tbody>
</table>

*For patients with AF unsuitable for, or who refuse, oral anticoagulant (for reasons other than concerns about major bleeding)

**VKA = adjusted-dose vitamin K antagonist

Advantages of Old Anticoagulants

- Familiarity
- No unexpected side effects
- Demonstrated use in multiple clinical areas
Disadvantages of Warfarin

- Drug interactions
- Food interactions
- Variable metabolism
- Frequent monitoring
Optimal Candidates for Warfarin

Patients who:
• Have (borderline) renal insufficiency
• Are taking stable dose of warfarin and do not find INR testing burdensome
• Have access to self-testing machine
• Are concerned about the lack of an evidence-based reversal strategy
Novel oral anticoagulants
New Anticoagulants

- Two Classes
  - Thrombin inhibitors
  - Anti-Xa inhibitors
Optimal Candidates for New Drugs

Patients who:
• Find INR testing burdensome
• Despite adherence to provider recommendations, have low ‘time-in-range’
• Can afford (or arrange to get) the new drugs
• Have normal renal function
DTI

- Parental
  - Argatroban
  - Lepirudin
  - Bivalirudin
- Oral
  - Ximelagatran
  - Dabigatran
Direct Thrombin Inhibitors

Thrombin is key step in thrombosis
  
  Turns fibrinogen into clot
  
  Activates platelets
  
  Activates clotting factors
Coagulation

TF + VII
IX + VIII
X + V

II

CLOT
Dabigatran : PRADAXA

- Oral Thrombin Inhibitor
- Bioavailability: 6.5%
- Onset of action: 2-3 hours
- Half-life: 12-14 hours
- Renal excretion: 80%
- Drug interactions: p-glycoprotein
  - Rifampin
RE-LY Study Overview

• In a large, randomized trial, two doses of the direct thrombin inhibitor dabigatran were compared with warfarin in patients who had atrial fibrillation and were at risk for stroke.
• At 2 years, the 110-mg dose of dabigatran was found to be noninferior, and the 150-mg dose superior, to warfarin with respect to the primary outcome of stroke or systemic embolism.
RE-LY: Study Design

Atrial fibrillation
≥1 Risk Factor
Absence of contra-indications
951 centers in 44 countries

Blinded Event Adjudication.

Patients were eligible if they had atrial fibrillation documented on electrocardiography performed at screening or within 6 months beforehand and at least one of the following characteristics:

1. Previous stroke or transient ischemic attack
2. A left ventricular ejection fraction of less than 40%
3. New York Heart Association class II or higher heart-failure symptoms within 6 months before screening
4. An age of at least 75 years or an age of 65 to 74 years plus diabetes mellitus, hypertension, or coronary artery disease

Warfarin
adjusted (INR 2.0-3.0)
N=6000

Dabigatran Etexilate
110 mg BID
N=6000

Dabigatran Etexilate
150 mg BID
N=6000

Cumulative Hazard Rates for the Primary Outcome of Stroke or Systemic Embolism, According to Treatment Group

Factor Xa Inhibitors

- Xa creates thrombin
- Blocking prevents amplification of coagulation
Factor Xa Inhibitors

- Rivaroxaban
- Apixaban
- Endobaxiban
- Betrixaban
Rivaroxaban

- Oral Xa Inhibitor
- Bioavailability: 80-100%
- Onset of action: 2.5-4 hours
- Half-life: 5-9 hours
- Renal excretion: ~66%
- Drug interactions: CYP 3A4
Rocket AF Study Design

Atrial Fibrillation

- Rivaroxaban
  - 20 mg daily
  - 15 mg for Cr Cl 30-49 ml/min
- Warfarin
  - INR target - 2.5
    - (2.0-3.0 inclusive)

Randomize Double Blind / Double Dummy
(n ~ 14,000)

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

At least 2 or 3 required*

Monthly Monitoring
Adherence to standard of care guidelines

Primary Endpoint: Stroke or non-CNS Systemic Embolism

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

Rocket AF Investigators, AHA 2010
Apixaban

- Oral Xa Inhibitor
- Bioavailability: 66%
- Onset of action: 1-3 hours
- Half-life: 8-15 hours
- Renal excretion: 25%
- Drug interactions: CYP 3A4
  - Multiple other pathways
Atrial Fibrillation with at Least One Additional Risk Factor for Stroke

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

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

**Warfarin** (target INR 2-3)

**Inclusion risk factors**
- Age ≥ 75 years
- Prior stroke, TIA, or SE
- HF or LVEF ≤ 40%
- Diabetes mellitus
- Hypertension

**Primary outcome:** stroke or systemic embolism

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

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

Stroke (ischemic or hemorrhagic) or systemic embolism

P (non-inferiority)<0.001

Apixaban 212 patients, 1.27% per year
Warfarin 265 patients, 1.60% per year

HR 0.79 (95% CI, 0.66–0.95); P (superiority)=0.011

21% RRR
Major Bleeding

ISTH definition

Apixaban  327 patients, 2.13% per year
Warfarin  462 patients, 3.09% per year

HR 0.69 (95% CI, 0.60–0.80); P<0.001

No. at Risk
Apixaban  9088  8103  7564  6365  5365  3048  1515
Warfarin  9052  7910  7335  5196  2956  1491

31% RRR
EDOXABAN : Savaysa
Study Design

21,105 PATIENTS
AF on electrical recording within last 12 m
CHADS2 ≥2

1:1:1 randomization is stratified by CHADS2 score 2–3 versus 4–6
and need for edoxaban dose reduction*

Double-blind, Double-dummy

Warfarin (INR 2.0–3.0)

High-dose Edoxaban 60* mg QD

Low-dose Edoxaban 30* mg QD

1º Efficacy EP = Stroke or SEE
2º Efficacy EP = Stroke or SEE or CV mortality
1º Safety EP = Major Bleeding (ISTH criteria)

* Dose reduced by 50% if:
CrCl 30–50 mL/min
weight ≤60 kg
strong P-gp inhibitor

Non-inferiority
Upper 97.5% CI <1.38

Net Clinical Outcomes

**Edoxaban 60* mg QD vs warfarin**

**Edoxaban 30* mg QD vs warfarin**

Warfarin TTR 68.4%

**Hazard ratio (95% CI)**

- **Stroke, SEE, death, major bleeding**
  
  **Disabling stroke, life-threatening bleeding, death**

  **Stroke, SEE, life-threatening bleeding, death**

  *Dose reduced by 50% in selected pts*

  SEE = systemic embolic event

  edoxaban superior

  edoxaban inf

  P Value vs warfarin

  P = 0.003
  P < 0.001

  P = 0.008
  P < 0.001

  P = 0.003
  P = 0.007
Summary

Compared to well-managed warfarin (TTR 68.4%) once-daily edoxaban:

- Non-inferior for stroke/SEE (both regimens)
  - High dose ↓ stroke/SEE on Rx (trend ITT)
- Both regimens significantly reduced:
  - Major bleeding (20%/53%) - ICH (53%/70%)
  - Hem. stroke (46%/67%) - CV death (14%/15%)
- Superior net clinical outcomes

No excess in stroke or bleeding during transition → oral anticoagulant at end of trial
Pharmacokinetics of NOACs

<table>
<thead>
<tr>
<th></th>
<th>Apixaban</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct factor inhibition</td>
<td>Xa</td>
<td>IIa</td>
<td>Xa</td>
</tr>
<tr>
<td>Bioavailability (F_{rel})</td>
<td>80%</td>
<td>6%</td>
<td>80%</td>
</tr>
<tr>
<td>Peak action (t_{max})</td>
<td>1–3 hr</td>
<td>1–3 hr</td>
<td>1–3 hr</td>
</tr>
<tr>
<td>Protein binding</td>
<td>84%</td>
<td>35%</td>
<td>92–95%</td>
</tr>
<tr>
<td>Renal clearance</td>
<td>25%</td>
<td>80%</td>
<td>33%</td>
</tr>
<tr>
<td>Elimination half life with creatinine clearance &gt; 80 ml/min</td>
<td>15.1 hr</td>
<td>13.8 hr</td>
<td>8.3 hr</td>
</tr>
<tr>
<td>Elimination half life with creatinine clearance 50–79 ml/min</td>
<td>14.6 hr</td>
<td>16.6 hr</td>
<td>8.7 hr</td>
</tr>
<tr>
<td>Elimination half life with creatinine clearance 30–49 ml/min</td>
<td>17.6 hr</td>
<td>18.7 hr</td>
<td>9.0 hr</td>
</tr>
<tr>
<td>Elimination half life with creatinine clearance &lt; 30 ml/min</td>
<td>17.3 hr</td>
<td>27.5 hr</td>
<td>9.5 hr</td>
</tr>
</tbody>
</table>

Meta-analysis of Efficacy and Safety of New Oral Anticoagulants

Dabigatran, Rivaroxaban, Apixaban vs. Warfarin in AF patients

### All cause stroke/SEE

<table>
<thead>
<tr>
<th>Study</th>
<th>RR (95% CI)</th>
<th>n/N, NOA Therapy</th>
<th>n/N, Warfarin Therapy</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-LY</td>
<td>0.86 (0.66, 1.10)</td>
<td>336/396</td>
<td>402/462</td>
<td>28.57</td>
</tr>
<tr>
<td>ROCKET AF</td>
<td>0.88 (0.75, 1.03)</td>
<td>286/308</td>
<td>308/390</td>
<td>37.22</td>
</tr>
<tr>
<td>ARISTOTLE</td>
<td>0.67 (0.62, 0.72)</td>
<td>212/252</td>
<td>205/256</td>
<td>34.20</td>
</tr>
<tr>
<td>Subtotal (k^2 = 55.9%, p = 0.134)</td>
<td>0.78 (0.67, 0.92)</td>
<td>815/2227</td>
<td>773/2219</td>
<td>100.00</td>
</tr>
</tbody>
</table>

### Ischemic and unspecified stroke

<table>
<thead>
<tr>
<th>Study</th>
<th>RR (95% CI)</th>
<th>n/N, NOA Therapy</th>
<th>n/N, Warfarin Therapy</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-LY</td>
<td>0.77 (0.61, 0.99)</td>
<td>116/127</td>
<td>142/122</td>
<td>27.29</td>
</tr>
<tr>
<td>ROCKET AF</td>
<td>0.80 (0.73, 1.13)</td>
<td>156/161</td>
<td>172/182</td>
<td>35.93</td>
</tr>
<tr>
<td>ARISTOTLE</td>
<td>0.62 (0.52, 1.14)</td>
<td>162/153</td>
<td>175/168</td>
<td>36.78</td>
</tr>
<tr>
<td>Subtotal (k^2 = 0.9%, p = 0.522)</td>
<td>0.87 (0.77, 0.98)</td>
<td>429/2227</td>
<td>482/2218</td>
<td>100.00</td>
</tr>
</tbody>
</table>

### Hemorrhagic stroke

<table>
<thead>
<tr>
<th>Study</th>
<th>RR (95% CI)</th>
<th>n/N, NOA Therapy</th>
<th>n/N, Warfarin Therapy</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-LY</td>
<td>0.36 (0.14, 0.96)</td>
<td>124/107</td>
<td>169/122</td>
<td>24.65</td>
</tr>
<tr>
<td>ROCKET AF</td>
<td>0.84 (0.47, 1.52)</td>
<td>70/106</td>
<td>80/118</td>
<td>34.94</td>
</tr>
<tr>
<td>ARISTOTLE</td>
<td>0.51 (0.34, 0.75)</td>
<td>49/126</td>
<td>78/168</td>
<td>40.50</td>
</tr>
<tr>
<td>Subtotal (k^2 = 52.2%, p = 0.124)</td>
<td>0.40 (0.31, 0.50)</td>
<td>81/2225</td>
<td>173/2218</td>
<td>100.00</td>
</tr>
</tbody>
</table>

## Reversal of NOACs

Suggestions for Reversal of New Oral Anticoagulants

<table>
<thead>
<tr>
<th>Method</th>
<th>Apixaban</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral activated charcoal</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Hemoperfusion with activated charcoal</td>
<td>Possible</td>
<td>Yes</td>
<td>Possible</td>
</tr>
<tr>
<td>Fresh frozen plasma</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Activated factor VIIa</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
</tr>
<tr>
<td>3-factor PCC</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
</tr>
<tr>
<td>4-factor PCC</td>
<td>Possible</td>
<td>Possible</td>
<td>Possible</td>
</tr>
</tbody>
</table>

Choosing an Anticoagulant: These patients are better off on Coumadin

- Patient already on Coumadin and is comfortable, with time in therapeutic range of at least 60%.
- No compliance issues
- Cost of medication
- Chronic Kidney disease with GFR < 30ml/min/1.73m2
- Contraindications to NOAT – like those on enzyme inducing antiepileptic drugs (Ex. Phenytoin) and patients who are on HAART therapy.

In the rest we prefer a NOAT.
Summary

- Warfarin in AF: ↓stroke 64% vs placebo
- Warfarin ↑bleeding and has well-known limitations
- All 4 NOACs at least as effective; ↓hem. stroke by 51%


AF=atrial fibrillation; CrCl=creatinine clearance; FXa=Factor Xa; NOAC=new oral anticoagulant; P-gp=p-glycoprotein
CONCLUSIONS: NOAT

CLASS EFFECTS

• All four novel anticoagulants are non-inferior to warfarin in reducing the risk of stroke and systemic embolization.

• All four agents reduce the risk of bleeding (fatal for Rivaroxaban, major for Apixaban, major at 110 mg for Dabigatran) and intracranial hemorrhage.

• The directionality and magnitude of the mortality reduction is consistent and approximates a RRR of 10% / year

DIFFERENTIATORS

• Dabigatran at a dose of 150 mg was associated with a reduction in ischemic stroke

• Rivaroxaban is a once a day drug associated with a lower rate of fatal bleeding

• Apixaban was associated with a reduction in all cause but not CV mortality