A New Era of Oral Anticoagulant Therapy

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Disclosures: Consultant for Ortho McNeil; Bristol Myers Squibb; Boehringer Ingelheim; Daiichi
Anticoagulants – Highlights in Development

- **Oral**
  - Spilled Sweet Clover
  - Dicoumarol Discovered
  - Warfarin Clin Use
  - Warf / Vit K Mechanism
  - Hi / Low Dose Warf / INR
  - Warf Clin Trials

- **Parenteral**
  - Heparin Discovered
  - Hep Clin Use
  - Cont Hep Infusion / aPTT
  - LMWH Discovered
  - LMWH Clin Trials

- **New Oral Xa & IIa Inhibitors**
  - Direct thrombin inhibitors
  - Pentasacch Clin Trials
Anticoagulants Commonly Used Today

- Unfractionated Heparin
- Low Molecular Weight Heparin
- Fondaparinux
- Warfarin

XII → XI → IX → VIII → VII → X → V → II → I → Fibrin Clot
Problems with current therapy

For Prevention

- Parenteral agents – no simple oral agent
- Expensive
- 2 drug regimen for selected indications (inpatient/outpatient)
- Side effects (e.g. HIT)

For Treatment

- 2 drug regimen: parenteral followed by oral agent
- Hospitalization often required
- Monitoring required
- Complex, burdensome therapy for both patient and doctor
- High rate of adverse events
- Under use of therapy
A New Era in Anticoagulants

New Oral IIa Inhibitors
- Ximelagatran
- Dabigatran etexilate

New Oral Xa Inhibitors
- Rivaroxaban
- Apixaban
- Edoxaban
- Betrixaban
- YM150

Unfractionated Heparin
Low Molecular Weight Heparin
Warfarin
Fibrin Clot
Factor IIa Inhibitors

- Dabigatran etexilate

Pro Drug

- Dabigatran

Factor Xa Inhibitors

- Rivaroxaban

- Apixaban

IIa

Xa
## Comparative Features of Warfarin and New Oral Anticoagulants

<table>
<thead>
<tr>
<th></th>
<th>Warfarin</th>
<th>Dabigatran etexilate</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target</strong></td>
<td>Vit K epox reduc</td>
<td>Thrombin</td>
<td>Factor Xa</td>
<td>Factor Xa</td>
</tr>
<tr>
<td><strong>Oral bioavailability</strong></td>
<td>99%</td>
<td>6-7%</td>
<td>60-80%</td>
<td>80%</td>
</tr>
<tr>
<td><strong>T (max)</strong></td>
<td>72-96 h</td>
<td>2 h</td>
<td>2.5-4 h</td>
<td>3 h</td>
</tr>
<tr>
<td><strong>Half-life</strong></td>
<td>40 h</td>
<td>14-17 h</td>
<td>5-9 h healthy, 9-13 h elderly</td>
<td>8-15 h</td>
</tr>
<tr>
<td><strong>Monitoring</strong></td>
<td>INR-adjusted</td>
<td>Not needed</td>
<td>Not needed</td>
<td>Not needed</td>
</tr>
<tr>
<td><strong>Administration</strong></td>
<td>OD</td>
<td>OD or BID</td>
<td>QD or BID</td>
<td>BID</td>
</tr>
<tr>
<td><strong>Metabolism / Elimination</strong></td>
<td>Cytochrome P450</td>
<td>80% renal, 20% biliary</td>
<td>66% renal, 33% biliary</td>
<td>25% renal 75% biliary</td>
</tr>
<tr>
<td><strong>Antidote or treatment of bleeding</strong></td>
<td>Vitamin K + FFP, APCC, or recFVIIa</td>
<td>Standard of Care (plasma or factor replacement; rVIIa)</td>
<td>Standard of Care (plasma or factor replacement; rVIIa) (Xa derivative)</td>
<td>Standard of Care (plasma or factor replacement; rVIIa) (Xa derivative)</td>
</tr>
<tr>
<td><strong>Assay</strong></td>
<td>PT/INR</td>
<td>Ecarin clotting time</td>
<td>Anti-factor Xa, PiCT®, HepTest®</td>
<td>Anti-factor Xa</td>
</tr>
<tr>
<td><strong>Drug Interactions</strong></td>
<td>CYP 2C9, 1A2, and 3A4</td>
<td>Potent P-gp inhibitors/inducers; PPIs decrease absorp</td>
<td>Potent P-gp inhibitors/inducers; CYP3A4 inhibitors</td>
<td>Potent P-gp inhibitors/inducers; CYP3A4 inhibitors</td>
</tr>
</tbody>
</table>
# Development Programs of New Oral Anticoagulants

<table>
<thead>
<tr>
<th>Condition</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hip Replacement</td>
<td>Phase III</td>
<td>Phase III</td>
<td>Phase III</td>
</tr>
<tr>
<td>Knee Replacement</td>
<td>Phase III</td>
<td>Phase III</td>
<td>Phase III</td>
</tr>
<tr>
<td>Stroke Prev in AF</td>
<td>Phase III</td>
<td>Phase III</td>
<td>Phase III</td>
</tr>
<tr>
<td>Medically Ill</td>
<td>----</td>
<td>Phase III</td>
<td>Phase III</td>
</tr>
<tr>
<td>ACS</td>
<td>Phase II</td>
<td>Phase III</td>
<td>Phase III</td>
</tr>
<tr>
<td>VTE Treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute</td>
<td>Phase III</td>
<td>Phase III</td>
<td>Phase III</td>
</tr>
<tr>
<td>Chronic</td>
<td>Phase III</td>
<td>Phase III</td>
<td>Phase III</td>
</tr>
<tr>
<td>Hip Fracture</td>
<td>----</td>
<td>----</td>
<td>----</td>
</tr>
<tr>
<td>Oncology</td>
<td>----</td>
<td>----</td>
<td>Phase II</td>
</tr>
</tbody>
</table>
Treatment of Acute DVT

**Dabigatran vs Warfarin: RE-COVER Study**

2539 patients with acute DVT treated initially with UFH/LMWH for a mean of 10 days randomized to dabigatran, 150 mg BID vs warfarin (double blind); treatment for 6 months; **Non-Inferiority Study** (Abstract #1)

- **Dx of VTE**
- **Random, double-blind assignment**
- **Primary Efficacy**: Recurrent, symptomatic VTE
- **Primary Safety**: Major bleeding

- **Routine therapy with UFH or LMWH**
- **Dabigatran 150 mg BID x 6 months**
  - Follow-up 1 month

- **Routine therapy with UFH or LMWH**
- **Warfarin INR 2.0 – 3.0 x 6 months**
  - Follow-up 1 month

Dabigatran etexilate = Pradaxa

Schulman et al. NEJM 2009;361:2342
## Treatment of Acute DVT

### Dabigatran vs Warfarin: RE-COVER Study

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>#</td>
<td>1,273</td>
<td>1,266</td>
</tr>
<tr>
<td>DVT only</td>
<td>69%</td>
<td>69%</td>
</tr>
<tr>
<td>PE only</td>
<td>21%</td>
<td>21%</td>
</tr>
<tr>
<td>Cancer</td>
<td>5%</td>
<td>5%</td>
</tr>
<tr>
<td>Previous VTE</td>
<td>26%</td>
<td>25%</td>
</tr>
<tr>
<td>Parenteral AC pre-rand (days)</td>
<td>2.8 d</td>
<td>2.8 d</td>
</tr>
<tr>
<td>LMWH Rx</td>
<td>89%</td>
<td>91%</td>
</tr>
<tr>
<td>Time in Range</td>
<td>-</td>
<td>60 %</td>
</tr>
</tbody>
</table>

Schulman et al. NEJM 2009;361:2342
Treatment of Acute DVT

Dabigatran vs Warfarin: RE-COVER Study

- **Recurrent Symptomatic VTE**
  - **Dabigatran**: 2.4%
  - **Warfarin**: 2.1%
  - HR 1.10; P < 0.001 for NI

- **Major Bleed**
  - **Dabigatran**: 1.6%
  - **Warfarin**: 1.9%
  - HR 0.82; p = NS

- **Major or CRNM Bleed**
  - **Dabigatran**: 5.6%
  - **Warfarin**: 8.8%
  - HR 0.63; P = 0.002

INR in range 60% of time; above range 19%; below range 21%

Schulman et al. NEJM 2009;361:2342
3,449 patients with acute DVT treated for 3 - 12 months with either rivaroxaban or enoxaparin followed by warfarin (open label).

**Rivaroxaban vs Standard Rx: EINSTEIN DVT**

- **Dx of VTE in 3,449 patients Randomized to Rivaroxaban vs Standard Rx**
- **Enoxaparin 1 mg/kd BID ≥ 5 d, then warfarin with INR 2 – 3 x 3, 6 or 12 months (1,718)**
- **Rivaroxaban, 15 mg BID x 21 days then 20 mg QD x 3, 6 or 12 months (1,731)**

Random, double-blind assignment

Primary Efficacy: Recurrent, symptomatic VTE
Primary Safety: Major bleeding

rivaroxaban = Xarelto

Buller et al. ESC 2010; Session 708007 - 708008
# Treatment of Acute DVT

*Rivaroxaban vs Standard Rx: EINSTEIN DVT*

<table>
<thead>
<tr>
<th></th>
<th>Rivaroxaban</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>#</td>
<td>1,731</td>
<td>1,718</td>
</tr>
<tr>
<td>Age (mean)</td>
<td>55.8</td>
<td>56.4</td>
</tr>
<tr>
<td>Unprovoked DVT</td>
<td>61%</td>
<td>63%</td>
</tr>
<tr>
<td>Previous VTE</td>
<td>19%</td>
<td>19%</td>
</tr>
<tr>
<td>Parenteral AC pre-random</td>
<td>73%</td>
<td>71%</td>
</tr>
<tr>
<td>Duration Pre Rx</td>
<td>4% &gt;1 day</td>
<td>4% &gt;1 day</td>
</tr>
<tr>
<td>Time in Range</td>
<td>-</td>
<td>58%</td>
</tr>
</tbody>
</table>

Buller et al. ESC 2010
**Treatment of Acute DVT**

*Rivaroxaban vs Standard Rx: EINSTEIN DVT*

- **Rec Symptomatic VTE**: Rivaroxaban 2.1%, Standard Rx 3.0%
- **Rec DVT**: Rivaroxaban 0.8%, Standard Rx 1.6%
- **Non Fatal PE**: Rivaroxaban 1.2%, Standard Rx 1.0%
- **Major Bleed**: Rivaroxaban 0.8%, Standard Rx 1.2%
- **Major & CRNM Bleed**: Rivaroxaban 8.1%, Standard Rx 8.1%

*P < 0.0001 for NI
P = 0.076 for Sup*

Buller et al. ESC 2010
Long-Term Treatment of DVT
*Rivaroxaban vs Placebo EINSTEIN-Extension*

1197 patients with acute DVT treated for 6 - 12 mon with standard Rx or rivaroxaban and then randomized to rivaroxaban 20 mg QD vs placebo (double blind) and treated for 6 - 12 months; Superiority Study

- **Primary Efficacy:** Recurrent, symptomatic VTE
- **Primary Safety:** Major bleeding

- Rivaroxaban, 20 mg QD x 6 - 12 months (mean duration 190 d)
- Placebo x 6 - 12 months (mean duration 190 d)

Buller et al. Blood 2009;114:
Long-Term Treatment of DVT
Rivaroxaban vs Placebo EINSTEIN-Extension

1197 patients with DVT treated for 6-12 months randomized to rivaroxaban, 20 mg QD vs placebo (double blind); mean duration of Rx 190 days

- Symp Rec DVT, fatal/non-fatal PE
  - Rivaroxaban: 1.3%
  - Placebo: 7.1%
  - HR 0.18; \( P<0.0001 \)

- Major Bleed
  - Rivaroxaban: 0.7%
  - Placebo: 0%
  - \( P=0.106 \)

- CRNM Bleed
  - Rivaroxaban: 5.4%
  - Placebo: 1.2%
  - \( P<0.01 \)

Buller et al. Blood 2009;114:
Long-Term Treatment of DVT
Rivaroxaban vs Placebo EINSTEIN-Extension

Number needed to treat to prevent 1 primary efficacy outcome ± 15

Number needed to harm: approximately 139

Rivaroxaban: 602 590 583 573 552 503 482 171 138 132 114 92 81
Placebo: 594 582 570 554 521 467 444 164 138 133 110 93 85

Time to event (days)

ITT population

Buller et al. Blood 2009;114:
8,101 hospitalized patients with medical illness from 52 countries at risk for VTE treated for 35 ± 4 days with rivaroxaban vs enoxaparin (10 ± 4 d) followed by placebo. Ultrasound at d 10 ± 4 and d 35 ± 4.

**Primary Efficacy:** asymptomatic/symptomatic DVT, non-fatal PE, and VTE-related death at 10 and 35 days

**Primary Safety:** Major and CRNM bleeding

Approximately 45% acute infectious disease; 33% heart failure; 28% acute respiratory insufficiency; only 7% active cancer

Cohen et. al. ACC 2011; abstract
Primary Post-Hospital Prophylaxis of VTE
Rivaroxaban vs Enoxaparin/Placebo: MAGELLAN

Primary efficacy at d 10 non-inferiority and at d 35 superiority

Cohen et al. ACC 2011; abstract
Stroke Prevention in Atrial Fibrillation

*Dabigatran etexilate vs warfarin (RE-LY)*

Non-valvular atrial fibrillation at moderate to high risk of stroke or systemic embolism (at least one high-risk factor)

- **Dabigatran Etexilate**
  - 110 mg b.i.d.
  - N=6000
  - Blinded

- **Dabigatran Etexilate**
  - 150 mg b.i.d.
  - N=6000
  - Blinded

- **Warfarin**
  - 1 mg, 3mg, 5 mg (INR 2.0-3.0)
  - N=6000
  - Open Label

- Open label trial; blinded adjudication
- Primary objective: Noninferiority to warfarin
- Minimum 1 year follow-up, maximum of 3 years and mean of 2 years of follow-up
- Primary end point: Stroke + systemic embolism

Connolly et al. NEJM 2009;361:1139
### Stroke Prevention in Atrial Fibrillation

*Dabigatran etexilate vs warfarin (RE-LY)*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Dabigatran 110 mg BID (# 6,015)</th>
<th>Dabigatran 150 mg BID (# 6,076)</th>
<th>Warfarin (# 6,022)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean)</td>
<td>71.4</td>
<td>71.5</td>
<td>71.6</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>64%</td>
<td>63%</td>
<td>63%</td>
</tr>
<tr>
<td>CHADS$_2$ (mean)</td>
<td>2.1</td>
<td>2.2</td>
<td>2.1</td>
</tr>
<tr>
<td>Warfarin Naive</td>
<td>50%</td>
<td>50%</td>
<td>49%</td>
</tr>
<tr>
<td>Time in Range</td>
<td>-</td>
<td>-</td>
<td>64%</td>
</tr>
<tr>
<td>Use of ASA (continuously)</td>
<td>21%</td>
<td>20%</td>
<td>21%</td>
</tr>
</tbody>
</table>

Connolly et al. NEJM 2009;361:1139
Stroke Prevention in Atrial Fibrillation

*Dabigatran etexilate vs warfarin (RE-LY)*

18,113 patients; Dabigatran BID; CHADS Score: ~1/3rd 0-1, 2, 3-6; AF = ~1/3rd each w/ persistent; parox; permanent

Connolly et al. NEJM 2009;361:1139
The Incidence of Stroke or Systemic Embolism Is Significantly Lower in Patients Treated With Dabigatran Etexilate 150 mg bid Than Patients Treated With Warfarin

Cumulative Hazard Rate for Primary Outcome of Stroke or Systemic Embolism

- Warfarin
- Dabigatran Etexilate 110 mg bid
- Dabigatran Etexilate 150 mg bid

RRR 34%

RR 0.66
(95% CI: 0.53-0.82)

p < 0.001

Stroke prevention in Atrial Fibrillation
Dabigatran vs warfarin (RE-LY)

Wallentin et al. Lancet 2010;376:975
Stroke Prevention in Atrial Fibrillation

*Dabigatran etexilate vs warfarin (RE-LY)*

Time to outcome in patients with previous stroke or TIA

![Graph showing cumulative hazard rates for different treatments](image)

**Number at risk**
- 110 mg dabigatran: 1195, 1159, 1131, 908, 573, 289
- 150 mg dabigatran: 1233, 1200, 1163, 938, 517, 321
- Warfarin: 1195, 1159, 1125, 895, 565, 251

Diener et al. Lancet Neurol 2010;9:1157
Stroke prevention in Atrial Fibrillation

*Rivaroxaban vs warfarin (ROCKET AF)*

**Primary Endpoint:** Stroke or non-CNS systemic embolism

Statistics: non-inferiority, >95% power, 2.3% warfarin event rate

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

At least 2 required

Atrial Fibrillation

Randomize

*Double blind / Double Dummy (n ~ 14,000)*

**Rivaroxaban**
- 20 mg daily
- 15 mg for Cr Cl 30-49

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

Monthly monitoring and adherence to standard of care guidelines

Mahaffey et al. AHA, Nov 2010
## Stroke prevention in Atrial Fibrillation

*Rivaroxaban vs warfarin (ROCKET AF)*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Rivaroxaban (# 7,081)</th>
<th>Warfarin (# 7,090)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>73</td>
<td>73</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>60%</td>
<td>60%</td>
</tr>
<tr>
<td>Creatinine Clearance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;50</td>
<td>79%</td>
<td>79%</td>
</tr>
<tr>
<td>30 - 50</td>
<td>21%</td>
<td>21%</td>
</tr>
<tr>
<td>CHADS$_2$ (mean)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 - 6</td>
<td>3.48</td>
<td>3.46</td>
</tr>
<tr>
<td>Warfarin Naive</td>
<td>28%</td>
<td>27%</td>
</tr>
<tr>
<td>Time in Range</td>
<td>-</td>
<td>57.8%</td>
</tr>
</tbody>
</table>

Mahaffey et al. AHA, Nov 2010
Stroke prevention in Atrial Fibrillation
*Rivaroxaban vs warfarin (ROCKET AF)*

<table>
<thead>
<tr>
<th>Event</th>
<th>Rivaroxaban</th>
<th>Warfarin</th>
<th>HR</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke &amp; SE</td>
<td>2.12</td>
<td>2.42</td>
<td>0.88</td>
<td>0.117</td>
</tr>
<tr>
<td>Stroke &amp; SE</td>
<td>1.7</td>
<td>2.25</td>
<td>0.79</td>
<td>0.015</td>
</tr>
<tr>
<td>Maj Bleed</td>
<td>3.6</td>
<td>3.45</td>
<td>1.04</td>
<td>0.576</td>
</tr>
<tr>
<td>ICH</td>
<td>0.49</td>
<td>0.74</td>
<td>0.67</td>
<td>0.019</td>
</tr>
</tbody>
</table>

Intention-to-Treat: HR 0.88; p = 0.117
On Treatment: HR 0.79; p = 0.015
Maj Bleed: HR 1.04; p = 0.576
ICH: HR 0.67; p = 0.019

Mahaffey et al. AHA, Nov 2010
Stroke prevention in Atrial Fibrillation

*Apixaban vs warfarin (ARISTOTLE)*

Randomize

Double blind

(n = 15,000)

- Age ≥ 75 years
- Prior stroke, TIA or SE
- CHF or LVEF ≤ 40%
- Diabetes mellitus
- Hypertension

Apixaban

5 mg oral twice daily

+ Warfarin placebo

Warfarin daily

(target INR 2 – 3)

+ Apixaban placebo twice daily

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

**Primary outcome:** stroke and systemic embolism

**Other outcomes:** Death, MI, bleeding

Stratified by warfarin-naïve status
Stroke Prevention in Atrial Fibrillation

Apixaban vs ASA: AVERROES Study

Random, double-blind assignment

Apixaban
5 mg PO BID
2.5 mg BID in selected patients

ASA
81-324 mg/d

AF and ≥ 1 RF and demonstrated or expected unsuitable for VKA

5,600 patients with AF felt not to be suitable for VKA therapy
Terminated early; median follow up 1 year

Primary Efficacy: Stroke or Systemic Embolic Event
Primary Safety: Major bleeding

S Connolly. ESC 2010
## Stroke Prevention in Atrial Fibrillation

**Apixaban vs ASA: AVERROES Study**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Apixaban</th>
<th>ASA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized</td>
<td>2,809</td>
<td>2,791</td>
</tr>
<tr>
<td>Age (mean/SD)</td>
<td>70 ± 10</td>
<td>70 ± 10</td>
</tr>
<tr>
<td>Male</td>
<td>59%</td>
<td>58%</td>
</tr>
<tr>
<td>CHADS2 score (mean/SD)</td>
<td>2.1 ± 1.1</td>
<td>2.1 ± 1.1</td>
</tr>
<tr>
<td>0-1</td>
<td>36%</td>
<td>37%</td>
</tr>
<tr>
<td>2</td>
<td>37%</td>
<td>34%</td>
</tr>
<tr>
<td>3+</td>
<td>27%</td>
<td>29%</td>
</tr>
<tr>
<td>Prior stroke/TIA</td>
<td>14%</td>
<td>13%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>19%</td>
<td>20%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>86%</td>
<td>87%</td>
</tr>
<tr>
<td>CHF</td>
<td>40%</td>
<td>38%</td>
</tr>
<tr>
<td>Baseline ASA</td>
<td>76%</td>
<td>74%</td>
</tr>
</tbody>
</table>

S Connolly. ESC 2010
Stroke Prevention in Atrial Fibrillation

Apixaban vs ASA: AVERROES Study

- **Stroke or SE Stroke**: Apixaban 3.6%, ASA 1.5%
  - P < 0.001
- **Sys Emb Major Bleed CRNMB**
  - Apixaban: 1.4%
  - ASA: 1.2%
  - P = NS
- **ICH**
  - Apixaban: 3.0%
  - ASA: 2.6%
  - P = NS

P < 0.001
P < 0.001
P = 0.01
P = NS
P = NS
P = NS

---

S Connolly. ESC 2010
Stroke Prevention in AF
The value of new oral ACs

- Dabigatran offers 2 dose levels, one for patients with normal and one for patients with impaired renal function. Once again, it offers simple therapy without monitoring and the other drawbacks of warfarin. Most importantly, there appears to be superior efficacy with the higher dose and a decrease in ICH, but overall bleeding is the same.

- Rivaroxaban, (not yet approved), offers equivalent therapy as warfarin without the headache. There is also a decrease in ICH.

- Both drugs raise concern about compliance and rivaroxaban’s once daily dosing may offer advantages to dabigatran’s twice daily dosing.

- For patients deemed too risky for warfarin, apixaban (not yet approved), may be a good alternative, more effective, yet just as safe.

- Studies of apixaban and other agents are pending.
FDA Approves Dabigatran for Stroke Prevention in Atrial Fibrillation

**Indication**
Prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation

**Dosage forms**
75 mg and 150 mg

**Dosing**
150 mg BID for all patients except:
75 mg BID for Renal impairment: Clcr 15-30 mL/min
No dose adjustment for hepatic impairment

**Misc Guidelines**
Use without regard to meals
Monitoring: aPTT > 2.5 x control may indicate over anticoagulation
Instruct patients not to chew, break, or open capsules
Anticoagulant Options — Why the FDA Approved a Higher but Not a Lower Dose of Dabigatran

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On October 19, 2010, the Food and Drug Administration (FDA) approved dabigatran for the reduction of the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation considered safe and effective if studied alone in comparison with warfarin, although the noninferiority finding for the 110-mg dose is somewhat less compelling. But
Rationale for Selection of Dabigatran 75 mg Twice Daily in Patients With Renal Impairment

Data on file. Boehringer Ingelheim Pharmaceuticals, Inc.
Monitoring the effect of dabigatran

Van Ryn et al. Thromb Haemost 2010;103:1116
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Conversions

From parenteral AC to dabigatran:
  UFH: when continuous infusion stopped
  LMWH/Fondaparinux: 2 hr before next SQ dose

From dabigatran to parenteral AC:
  12 hours (Clcr > 30) or 24 hours (Clcr < 30) after last dabigatran dose

From warfarin to dabigatran:
  When the INR is < 2.0

From dabigatran to warfarin:
  Clcr > 50  start warfarin 3 days before dabigatran stopped
  Clcr 31-50 start warfarin 2 days before dabigatran stopped
  Clcr 15-30 start warfarin 1 day before dabigatran stopped
OVERDOSAGE
Accidental overdose may lead to hemorrhagic complications. There is no antidote to dabigatran etexilate or dabigatran.

In the event of hemorrhagic complications, initiate appropriate clinical support, discontinue treatment with PRADAXA, and investigate the source of bleeding.

Dabigatran is primarily excreted in the urine; therefore, maintain adequate diuresis. Dabigatran can be dialyzed (protein binding is low), with the removal of about 60% of drug over 2 to 3 hours; however, data supporting this approach are limited.

Consider surgical hemostasis or the transfusion of fresh frozen plasma or red blood cells. There is some experimental evidence to support the role of activated prothrombin complex concentrates (e.g., FEIBA), or recombinant Factor VIIa, or concentrates of coagulation factors II, IX or X; however, their usefulness in clinical settings has not been established.

Consider administration of platelet concentrates in cases where thrombocytopenia is present or long-acting antiplatelet drugs have been used. Measurement of aPTT or ECT may help guide therapy [see Clinical Pharmacology (12.2)].
Potential Drawbacks of New Oral Anticoagulants

- Cannot easily assess compliance without monitoring assay
- Cannot easily assess treatment failure without monitoring assay
- Cannot easily titrate dose to lower or higher level of anticoagulation without monitoring assay
- Cannot easily reverse anticoagulant affect
- Unclear how to treat major hemorrhage
- Cost may be a factor in utilization
Considerations in the next year

- Hospital formulary?
- Education of Emergency Department physicians?
- Treatment of overdoses?
- Treatment of major bleeding?
- Management of failure of therapy?
- Transitions of care:  - warfarin to new agent
  - new agent to warfarin
  - heparin to new agent
  - new agent to heparin
- Bridging for invasive procedures?
- Routine use of new AC in hospitalized patients?
What is the Future for Warfarin?

Vitamin K antagonists (warfarin and others) will not completely go away. Their use will continue in selected circumstances. For example -

1. Mechanical heart valves will be the last of the indications studied for new AC.
2. Patients who fail therapy on a new AC will likely be switched to a VKA.
3. When there is a question of compliance, a physician may prefer a monitored drug, i.e. VKA.
4. There may be some physician resistance to convert a stable patient to a new AC.