The Great Debate: Is Warfarin Obsolete?

Supporter’s View

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Limitations of Warfarin

- Slow onset/offset
- Dosing difficulties
- Narrow therapeutic index
- Food/drug interactions
- High bleeding rates
- Burden for patients/system of care

Failure to use
Failure to achieve treatment goals

ACTIVE-W: Warfarin vs ASA + Clopidogrel
Outcome Based on Quality of INR Control

Warfarin Therapy in AF
INR Control vs Outcome
Current Question

- It is time to offer a safer and easier-to-use anticoagulant to our patients?

New Anticoagulants

- Oral, synthetic, non-peptide direct thrombin inhibitor (DTI)
- Highly polar zwitterionic molecule → not absorbed orally
- Formulated into dabigatran etexilate (prodrug)
- Hydrolyzed to active form by esterases in plasma

Pharmacokinetics of Dabigatran

- Bioavailability: 7%
  - Rapidly absorbed & converted to active drug
  - peak levels (Cmax) within 2 hrs
- Protein binding: 35%
- Linear PK profile
  - Plasma conc. increases with dose increase
- T 1/2 = 12–14 hours

Dabigatran (Pradaxa®)

- Oral, synthetic, non-peptide direct thrombin inhibitor (DTI)
- Highly polar zwitterionic molecule → not absorbed orally
- Formulated into dabigatran etexilate (prodrug)
- Hydrolyzed to active form by esterases in plasma

Pharmacokinetics of Dabigatran

- Metabolism / Elimination
  - 80% excreted unchanged by kidney
  - 20% conjugation with glucoronic acid
  - Not metabolised by and do not influence CYP450 enzymes
  - Substrates of P-glycoprotein
    - Drug interaction with P-glycoprotein inhibitors

**RE-LEY: A Noninferiority Trial**

- Atrial Fibrillation with ≥1 Risk Factor for Stroke
- Absence of Contraindications
- Conducted in 951 centers in 44 countries

Blinded Event Adjudication

- Open
- Warfarin
  - Adjusted INR 2.0 – 3.0
  - N=6000
- Dabigatran etexilate
  - 110 mg BID
  - N=6000
- Dabigatran etexilate
  - 150 mg BID
  - N=6000

Blinded Event Adjudication

- Open
- Warfarin
- Dabigatran etexilate 110 mg
- Dabigatran etexilate 150 mg


**Major bleeding rates**

<table>
<thead>
<tr>
<th>Drug</th>
<th>% per year</th>
<th>RR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>2.71</td>
<td>1</td>
<td>0.69–0.93</td>
<td>p=0.003 (sup)</td>
</tr>
<tr>
<td>D110 mg BID</td>
<td>3.11</td>
<td>1</td>
<td>0.81–1.07</td>
<td>p=0.31 (sup)</td>
</tr>
<tr>
<td>D150 mg BID</td>
<td>3.36</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Time to first stroke / SSE**

- RR 0.91 (95% CI: 0.74–1.11) p=0.34 (Sup)

**Time to first intra-cranial bleed**

- RR 0.31 (95% CI: 0.20–0.47) p<0.001 (Sup)

**Summary of Dabigatran**

- Simple PK/PD → easy to use
- Fix dosing, no need for INR tests
- The 1st drug to beat warfarin
  - 110 mg BID → less bleeding, same efficacy
  - 150 mg BID → less stroke, same bleeding
- ADRs
  - GI effects, slightly more cases of MI
  - Benefit may still far outweigh the risk

**Oral Direct Factor Xa Inhibitors Currently in Development**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Half-life (Hours)</th>
<th>Bioavailability</th>
<th>Elimination (%)</th>
<th>Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban</td>
<td>12</td>
<td>50</td>
<td>25</td>
<td>75</td>
</tr>
<tr>
<td>Betrixaban</td>
<td>19</td>
<td>47</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>6–12</td>
<td>100%</td>
<td>62</td>
<td>35</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>5–9</td>
<td>80</td>
<td>33</td>
<td>67</td>
</tr>
<tr>
<td>YM150</td>
<td>18–20</td>
<td>25–82</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>
Stroke Prevention Trials in AF

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>Treatment Arms</th>
<th>Primary End Point(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROCKET-AF</td>
<td>14,000</td>
<td>Rivaroxaban 20 mg qd vs warfarin</td>
<td>Stroke and systemic embolism</td>
</tr>
<tr>
<td>ARISTOTLE</td>
<td>18,000</td>
<td>Apixaban 5 mg bid vs warfarin</td>
<td>Stroke and systemic embolism</td>
</tr>
<tr>
<td>AVERROES</td>
<td>5600</td>
<td>Apixaban 5 mg bid vs aspirin</td>
<td>Stroke and systemic embolism</td>
</tr>
<tr>
<td>ENGAGE AF – TIMI 48</td>
<td>16,500</td>
<td>Edoxaban 30 mg qd vs warfarin</td>
<td>Stroke and systemic embolism</td>
</tr>
</tbody>
</table>

www.clinicaltrials.gov

Tecafarin (ATI-5923)

- New VKORC1 antagonist
  - Structural analogue of warfarin
  - Single enantiomer
- No CYP450 involvement
  - Metabolized by carboxyesterase
  - T ½ of 120 hours (5 days)
- Phase II study suggested improvement of TTR compared to warfarin

The Great Debate: Is Warfarin Obsolete?

Supporter’s View

REBUTTAL

Issues To Consider

- Benefit of warfarin depends on INR control
- Ability to achieve such control in all patients is questionable
- Current data of new agents are encouraging at least for AF, VTE
- Patient’s preference on choice of therapy

Warfarin Problems in Asia

- Patient factors
  - Genetic factors
  - Level of patient education
  - Patient’s behavior & socioeconomic status
- Drug factors
  - Drug product quality
  - System of care
  - Accessibility & quality of care system

Resources Consumed to Improve INR Control

- Human resources
  - Anticoagulation clinic
- Cost of laboratory monitoring
  - Usual lab, patient self-testing
- Cost of genetic testing
- Cost of complications from warfarin
- Cost to healthcare system
- Cost to patients
Current Question

- It is time to offer a safer and easier-to-use anticoagulant to our patients?

**YES!!!**

Benefit of New Agents

- To provide treatment for patients needing anticoagulant but unable to use warfarin
- To improve outcome for patients failing to achieve good INR control
- To reduce morbidity & mortality associated with warfarin therapy
- To empower patient the right to choose tx

Candidate for New Agents

- Pts not deemed to be candidate for warfarin
- Pts experiencing difficulty in controlling their INR despite the best effort available
- Pts who are at high risk for warfarin complications
- Pts who are at high risk for drug interactions
- Pts who prefer a drug that is not interfering with lifestyle

ACTIVE W Trial

**VKA vs dual antiplatelet Rx**

*Minimum threshold TTR necessary to realize benefit of warfarin: ≥ 58%*

Comparison of Outcomes Among Patients Randomized to Warfarin According to Anticoagulant Control

**Results From SPORTIF III and V**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>TTR &lt; 60%</th>
<th>TTR 60-75%</th>
<th>TTR &gt;75%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality, %</td>
<td>4.2</td>
<td>1.84</td>
<td>1.69</td>
</tr>
<tr>
<td>Major Bleed, %</td>
<td>3.85</td>
<td>1.96</td>
<td>1.58</td>
</tr>
<tr>
<td>Stroke/SEE, %</td>
<td>2.10</td>
<td>1.34</td>
<td>1.07</td>
</tr>
</tbody>
</table>

Hazes of Anticoagulant Medications

- #1 in 2003 and 2004 in the number of mentions of "deaths for drugs causing adverse effects in therapeutic use"\(^1\)
- Warfarin-6% of 702,000 ADEs treated in ED per year; 17% require hospitalization\(^2\)
- 21 million warfarin prescriptions in 1998-31 million in 2004\(^2\)
- The incidence AC-related intracranial hemorrhage quintupled during this time period\(^2\)


Most common adverse events

<table>
<thead>
<tr>
<th>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>9.3</td>
<td>9.7</td>
</tr>
<tr>
<td>Dizziness</td>
<td>8.1</td>
<td>8.3</td>
<td>5.4</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

Rivaroxaban: Pharmacokinetics

- Bioavailability: 80% - 100% (10 mg)
- Rapidly absorbed; Cmax in 2 - 4 hours
- Protein binding: 92-95%
- T ¼ : 7-11 hr
- Metabolism / Elimination
  - 2/3 metabolized (50% liver / 50% kidney)
  - CYP3A4, CYP2J2 and CYP-independent mechanisms
  - 1/3 excreted unchanged via kidney

Net clinical benefit and components

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Dabi 110 mg</th>
<th>Dabi 150 mg</th>
<th>Warfarin</th>
<th>P-value 110 vs. W</th>
<th>P-value 150 vs. W</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients (n)</td>
<td>6015</td>
<td>6076</td>
<td>6022</td>
<td>0.10</td>
<td>0.04</td>
</tr>
<tr>
<td>Net Clinical Benefit</td>
<td>7.09</td>
<td>6.91</td>
<td>7.64</td>
<td>0.0005</td>
<td>0.0005</td>
</tr>
<tr>
<td>- Stroke / SSE</td>
<td>3.13</td>
<td>3.11</td>
<td>3.16</td>
<td>&lt;0.0001 (NI)</td>
<td>&lt;0.0001 (NI)</td>
</tr>
<tr>
<td>- Death</td>
<td>3.75</td>
<td>3.64</td>
<td>4.13</td>
<td>0.034 (adj)</td>
<td>&lt;0.0001 (adj)</td>
</tr>
<tr>
<td>- MI</td>
<td>2.71</td>
<td>3.11</td>
<td>3.36</td>
<td>0.003</td>
<td>0.31</td>
</tr>
<tr>
<td>- PE</td>
<td>0.12</td>
<td>0.15</td>
<td>0.09</td>
<td>0.56</td>
<td>0.21</td>
</tr>
</tbody>
</table>

All data represents %/year

**Cumulative Incidence of Major Bleeding in the First Year Among Patients Newly Starting Warfarin by Age**

**Risk of Stopping Therapy in the First Year Among Patients Newly Starting Warfarin by Age**

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

**Net clinical benefit and components**

**Rivaroxaban: Pharmacokinetics**

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**Special Populations/Warnings**

- Renal impairment
  - Used with caution in CrCl 15-29 mL/min
  - Contraindicated in CrCl < 15 mL/min
- Pregnancy/lactation
  - Avoid pregnancy, reproductive toxicity shown in animal models
  - Secreted into milk → avoid lactation

**Drug Interactions**

- Not recommended to be used with potent inhibitors / inducers of CYP3A4 & P-glycoprotein
  - Inhibitors:
    - Azole-antimycotics & HIV protease inhibitors
  - Inducers:
    - Rifampicin, phenytoin, carbamazepine, phenobarbital

**Future of Anticoagulants**

- Warfarin and heparins will slowly disappear
- New anticoagulants with simple PK/PD are emerging
  - Mainly oral (or long-acting s.c.) compounds
  - No distinction between initial and longterm therapy
  - Great majority of patients treated out of hospital

**Drug Interactions**

- P-glycoprotein inducers:
  - Rifampicin may reduce systemic exposure of dabigatran, caution is advised.
  - Pantoprazole decrease dabigatan’s AUC by 30%. However, pantoprazole and other PPIs was used with dabigatran in clinical trials with no effects on bleeding or efficacy.

**Key features of new oral anticoagulants**

<table>
<thead>
<tr>
<th>Dabigatran etexilate</th>
<th>Apixaban and Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral direct thrombin inhibitors</td>
<td></td>
</tr>
<tr>
<td>Prolong rapid biotransformation to active drug</td>
<td></td>
</tr>
<tr>
<td>Inhibit free and fibrin-bound FIIa activity</td>
<td></td>
</tr>
<tr>
<td>Fixed dosing - no coagulation monitoring required</td>
<td></td>
</tr>
<tr>
<td>Max inhibition of FIIa after 1-4 h</td>
<td></td>
</tr>
<tr>
<td>12-13 h</td>
<td></td>
</tr>
<tr>
<td>Few food/drug interactions</td>
<td></td>
</tr>
<tr>
<td>Renal excretion: 80%</td>
<td></td>
</tr>
<tr>
<td>Oral direct FXa inhibitors</td>
<td></td>
</tr>
<tr>
<td>Directly acting compound - no biotransformation</td>
<td></td>
</tr>
<tr>
<td>Inhibit free and fibrin-bound FXa activity, and prothrombinase</td>
<td></td>
</tr>
<tr>
<td>Fixed dosing - no coagulation monitoring required</td>
<td></td>
</tr>
<tr>
<td>Max inhibition of FXa after 1-4 h</td>
<td></td>
</tr>
<tr>
<td>12 h</td>
<td></td>
</tr>
<tr>
<td>Few food/drug interactions</td>
<td></td>
</tr>
</tbody>
</table>
| Renal excretion: 25%, 60%, resp.

**Phase III AF trials**

- Dabigatran etexilate: RE-LY
- Apixaban: ARISTOTLE, AVEROSES
- Rivaroxaban: ROCKET

**Phase II ACS trials**

- Dabigatran: RE-DREEM
- Apixaban: APPRAISE
- Rivaroxaban: ATLAS
Limitations of Current Anticoagulants

**Heparins**
- Parenteral administration
- Indirect action
- Low bioavailability
- Unable to inhibit clot-bound thrombin
- Heparin-induced thrombocytopenia

**Vitamin K antagonists**
- Slow onset / offset
- Narrow therapeutic window
- Interactions with co-medications
- Require monitoring and individual dosing
- Dietary restrictions

Indirect vs Direct Thrombin Inhibitors

**Indirect**
- Heparin
  - LMWH

**Direct**
- Parenteral
  - Hirudin
  - Argatroban
  - Bivalirudin
- Oral
  - Ximelagatran
  - Dabigatran
  - ete oxide