Target-Specific Oral Anticoagulants (TSOACs): Clinical Aspects

Quest Diagnostics Nichols Institute
Case-Oriented Symposium on Bleeding & Thrombosis
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Full disclosures for Adam Cuker

- Research support
  - NIH
  - FDA
  - Stago

- Consultant/Advisory Board
  - Baxter
  - Bayer
  - Daiichi Sankyo
  - Sanofi/Genzyme

- Patents
  - Laboratory assays for HIT

- Off-label use
  - Dabigatran and Apixaban are not labeled for VTE
A Brief History of Oral Anticoagulation

Warfarin

1. Efficacious
2. Experience (FDA approved in 1954)
3. Cheap

1. Bleeding risk
2. Requires monitoring
3. Drug-drug interactions
4. Food interactions
5. Slow onset/offset

Outline

- Pharmacology
- Indications, Efficacy & Safety
  - Atrial fibrillation
  - VTE
  - Safety
- Special situations
  - Perioperative management
  - Management of bleeding
- Pros and Cons (vs. warfarin)
Mechanism of Action

Cabral KP et al., Nat Rev Cardiol 2012;9:385

Dabigatran

Dabigatran etexilate Dabigatran

Rivaroxaban & Apixaban
Pharmacology

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran etexilate</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target</td>
<td>Thrombin</td>
<td>FXa</td>
<td>FXa</td>
</tr>
<tr>
<td>Bioavailability</td>
<td>6%</td>
<td>80%</td>
<td>60%</td>
</tr>
<tr>
<td>Peak activity ($t_{max}$)</td>
<td>1-3 hr</td>
<td>1-3 hr</td>
<td>1-3 hr</td>
</tr>
<tr>
<td>Half-life</td>
<td>14-17 hr</td>
<td>7-11 hr</td>
<td>12 hr</td>
</tr>
<tr>
<td>Protein binding</td>
<td>35%</td>
<td>92-95%</td>
<td>84%</td>
</tr>
<tr>
<td>Renal clearance</td>
<td>80%</td>
<td>66%</td>
<td>25%</td>
</tr>
<tr>
<td>Drug interactions</td>
<td>P-glycoprotein</td>
<td>CYP3A4</td>
<td>CYP3A4</td>
</tr>
</tbody>
</table>

Eikelboom JW et al., Circulation 2010;121:1023

Drug-Drug Interactions

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of interaction</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verapamil</td>
<td>P-gp competition; CYP3A4 inhibition</td>
<td>Yellow</td>
<td>Yellow</td>
<td>Yellow</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>P-gp competition</td>
<td>Yellow</td>
<td>Yellow</td>
<td>Yellow</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>P-gp competition</td>
<td>Yellow</td>
<td>Yellow</td>
<td>Yellow</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>P-gp competition; CYP3A4 inhibition</td>
<td>Red</td>
<td>Red</td>
<td>Red</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>P-gp competition; CYP3A4 inhibition</td>
<td>Red</td>
<td>Red</td>
<td>Red</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>P-gp competition; CYP3A4 inhibition</td>
<td>Red</td>
<td>Red</td>
<td>Red</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>P-gp competition; CYP3A4 induction</td>
<td>Yellow</td>
<td>Yellow</td>
<td>Yellow</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>P-gp competition; CYP3A4 inducer</td>
<td>Yellow</td>
<td>Yellow</td>
<td>Yellow</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>P-gp competition; CYP3A4 inducer</td>
<td>Yellow</td>
<td>Yellow</td>
<td>Yellow</td>
</tr>
<tr>
<td>St. John’s wort</td>
<td>P-gp competition; CYP3A4 inducer</td>
<td>Yellow</td>
<td>Yellow</td>
<td>Yellow</td>
</tr>
</tbody>
</table>

Adapted from Heidbuchel H et al., Eur Heart J 2013;34:2094

Environmental Interactions

<table>
<thead>
<tr>
<th>Drug</th>
<th>Interaction with food</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivaroxaban</td>
<td>Food increases plasma concentration 39%</td>
<td>Take with food</td>
</tr>
<tr>
<td>Apixaban</td>
<td>None</td>
<td>Take with or without food</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>None</td>
<td>Take with or without food</td>
</tr>
</tbody>
</table>

Spirker SA et al., Circulation 2011;124:e209
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FDA-Approved Indications

<table>
<thead>
<tr>
<th>Drug</th>
<th>Non-valvular AF</th>
<th>Acute VTE (~3 mos)</th>
<th>Prevention of recurrent VTE (&gt;3 mos)</th>
<th>TKA/THA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Apixaban</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Other indications under study:
- Secondary prophylaxis after ACS
- Secondary prophylaxis after TIA/stroke
- Mechanical heart valves
- Heparin-induced thrombocytopenia
- Cardioversion
- DVT prophylaxis after hip fracture surgery
- Patent foramen ovale
- DVT prophylaxis in medical patients
- Prophylaxis in cancer patients
- Cardiac catheterization

Atrial Fibrillation (Phase III Trials)
TSOACs vs. Warfarin for AF

22% RR reduction in stroke and systemic embolism

Favors TSOAC
Favors Warfarin

Miller CS et al., Am J Cardiol 2012;110:453

TSOACs vs. Warfarin for AF

Mortality

RE-LY
ARISTOTLE
ROCKET-AF

Favors TSOAC
Favors Warfarin

TSOACs associated with a 12% risk reduction in mortality

Adam SS et al., Ann Intern Med 2012;157:798

Acute VTE (Phase III Trials)

Einstein Investigators, NEJM 2010;363:2499;
Agnelli G et al., NEJM 2013;369:799
Myocardial infarction (AF and VTE Pooled)

Dabigatran
FXa inhibitors

RR
(95% CI)
0.84
1.04
1.09
1.95

Favors TSOAC
Favors Warfarin

Adam SS et al., Ann Intern Med 2012;157:796

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Pros and Cons (vs. warfarin)

Elective surgery: When to stop...

Dabigatran

<table>
<thead>
<tr>
<th>CrCl (ml/min)</th>
<th>Standard risk surgery</th>
<th>High risk surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;80</td>
<td>24 h</td>
<td>48 h</td>
</tr>
<tr>
<td>50-80</td>
<td>36 h</td>
<td>72 h</td>
</tr>
<tr>
<td>30-50</td>
<td>48 h</td>
<td>96 h</td>
</tr>
<tr>
<td>15-30</td>
<td>4 days</td>
<td>6 days</td>
</tr>
</tbody>
</table>

Rivaroxaban and Apixaban

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<th>CrCl (ml/min)</th>
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<td>36 h</td>
<td>48 h</td>
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Heidbuchel H et al., Eur Heart J 2013;34:2094
Managing bleeding in patients on TSOACs

• No clinically available specific antidote
• Discontinuation of drug
• Supportive care (IVFs, pRBCs, etc.)
• Activated charcoal (if ingested in last 2 hours)
• Hemodialysis (dabigatran only)
• Consider PCC, APCC, or rFVIIa for organ- or life-threatening bleeding

Specific Reversal Agents

- Dabigatran
  - Anti-dabi Fab
- Rivaroxaban & Apixaban
  - PRT0464445
    - Recombinant form of FXa
    - Lacks catalytic and membrane-binding activity
    - Retains ability to bind FXa inhibitors

Both agents show correction of in vitro clotting times and reduction of bleeding in animal injury models.

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TSOACs vs. Warfarin: Pros & Cons

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<thead>
<tr>
<th></th>
<th>Warfarin</th>
<th>TSOACs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy</td>
<td>+</td>
<td>+ (+ AF)</td>
</tr>
<tr>
<td>Bleeding</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Need for monitoring</td>
<td>- (+)</td>
<td>+ (-)</td>
</tr>
<tr>
<td>Use in ESRD</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Drug interactions</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Dietary interactions</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Onset/offset</td>
<td>- (+)</td>
<td>+ (-)</td>
</tr>
<tr>
<td>Reversibility</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Long-term safety</td>
<td>+</td>
<td>?</td>
</tr>
<tr>
<td>Familiarity to clinicians</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Cost</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>

Take-home points

- The TSOACs provide an increasing number of options for patients with thromboembolic disorders
- Clinicians should be familiar with their pharmacology
- Selection of an agent should take into consideration patient characteristics, drug characteristics, and cost
- Warfarin will not go away anytime soon (ESRD, mechanical heart valves, uncertain compliance, stable on warfarin)