Anticoagulation Task Force
Newest Recommendations

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THE DRUGS
THE PERFECT ANTICOAGULANT

- Oral administration
- Once daily dosing to increase adherence
- Rapid anticoagulant effect
- Predictable dose-response relationship
- No drug interactions
- No requirement for laboratory monitoring
- No increased bleeding
- Rapid-acting antidote
THE HISTORY

• The first oral anticoagulant
  • Karl Paul Link and Wilhelm Schoeffel
  • Dicoumarol discovery and introduction to therapy - 1940 to 1941
  • Warfarin introduced as rat poison in 1948
  • The 1951 suicide attempt leading to...
  • The launch of Coumadin™ in 1954 as an oral anticoagulant
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WARFARIN’S PLACE

• Valvular atrial fibrillation
  • Chronic oral anticoagulation with warfarin for patients at high risk for stroke (CHA\_2DS\_2-VASc of 2 or greater) and acceptably low risk for hemorrhagic complications

• Mechanical prosthetic cardiac valves
  • Warfarin and low-dose aspirin in patients who have received an aortic mechanical prosthetic valve (with or without risk factors) or any mitral mechanical prosthetic valve
    • Variable INR targets depending on valve position and/or risk factors

Source: 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation
• The “second” oral anticoagulant
  • Ximelagatran (Exanta™), a direct thrombin inhibitor
  • Rapid oral absorption with peak at 2 to 3 hours after administration
  • Poor bioavailability and major dependence on renal excretion
  • Predictable pharmacokinetics
  • No CYP-based interactions
  • Fixed dosing and no monitoring
  • Approved in 12 countries and then...
THE HISTORY

• The “third” oral anticoagulant
  • Dabigatran (Pradaxa™), a direct thrombin inhibitor
  • Approved October 19, 2010 for prevention of stroke in patients with nonvalvular atrial fibrillation
  • February 2011- American College of Cardiology adds dabigatran to the guidelines for management of nonvalvular atrial fibrillation with a class I recommendation
THE HISTORY

• The “fourth” oral anticoagulant
  • Rivaroxaban (Xarelto™), a Factor Xa inhibitor
  • Discovered through high-output screening of approximately 200,000 compounds
  • Approved by the FDA on July 1, 2011 for deep vein thrombosis prophylaxis
  • Approved by the FDA on November 4th of the same year for stroke prevention in people with nonvalvular atrial fibrillation
THE PERFECT ANTICOAGULANT?

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ORAL ANTICOAGULATION

- Vitamin K antagonists
  - Warfarin sodium (Coumadin™)
- Direct thrombin inhibitors
  - Dabigatran (Pradaxa™)
- Direct Factor Xa Inhibitors
  - Apixaban (Eliquis™)
  - Edoxaban (Savaysa™)
  - Rivaroxaban (Xarelto™)
DIRECT ANTICOAGULATION

- Right to the action site
  - NOAC (New oral anticoagulants)
  - NOAC (Novel oral anticoagulants)
  - DOAC (Direct acting oral anticoagulants)
  - TSOAC (Target Specific Oral Anticoagulants)
    - Apixaban (Eliquis™)
    - Dabigatran (Pradaxa™)
    - Edoxaban (Savaysa™)
    - Rivaroxaban (Xarelto™)
DOACs- HOW THEY DO THAT

• Direct thrombin inhibitors (e.g., dabigatran)
  • Drug molecule occupies site on thrombin preventing formation of fibrin

• Direct Factor Xa inhibitors (e.g., rivaroxaban)
  • Bind directly and reversibly to Factor Xa via the S1 and S4 pockets
  • Inhibits both free and clot-bound Factor Xa to interrupt the clotting cycle
DOAC COMPARISON

- Pharmacokinetics

<table>
<thead>
<tr>
<th>DRUG</th>
<th>PEAK</th>
<th>HALF-LIFE</th>
<th>METABOLISM</th>
<th>CYP EFFECT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban</td>
<td>1 to 3 hours</td>
<td>9 to 14 hours</td>
<td>Hepatic</td>
<td>15%</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>1.5 to 3 hours</td>
<td>12 to 17 hours</td>
<td>Hepatic</td>
<td>-</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>1 to 2 hours</td>
<td>10 to 14 hours</td>
<td>Hepatic</td>
<td>3%</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>2 to 4 hours</td>
<td>5 to 9 hours</td>
<td>Hepatic</td>
<td>30%</td>
</tr>
</tbody>
</table>
DOAC COMPARISON

- Application
  - Nonvalvular atrial fibrillation

<table>
<thead>
<tr>
<th>DRUG</th>
<th>DOSING</th>
<th>DOSE ADJUSTMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban</td>
<td>5 mg twice a day</td>
<td>2.5 mg twice a day (SCr 1.5 mg/dL or greater AND...)</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>150 mg twice a day</td>
<td>75 mg twice a day (CrCl 15-30 ml/min)</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>60 mg once daily</td>
<td>30 mg once a day (CrCl 15-30 ml/min)</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>20 mg once daily</td>
<td>15 mg once a day (CrCl 15-0 ml/min)</td>
</tr>
</tbody>
</table>
DOAC PIPELINE

• Betrixaban
  • Oral, once daily direct Factor Xa inhibitor
  • Hepatic elimination that may address issues other DOACs have with renal impairment
  • Manufacturer granted Fast Track designation for agent for extended duration prevention of venous thromboembolism in acute medically ill patients
• EXPLORE-Xa study
  • Evaluation of the safety and tolerability compared to warfarin in patients with atrial fibrillation
DOAC- WHAT’S GOOD?

- Kinetics and dynamics
  - Rapid onset and stop of activity
  - Fewer dietary and drug interactions compared to warfarin
  - Fixed dosing due to wide therapeutic window
  - No need for routine laboratory monitoring

- Patient factors
  - Patient satisfaction and better convenience

- Improved safety profile
DOAC- WHAT’S GOOD?

• Efficacy
  • Compared with warfarin, DOACs are associated with significantly fewer strokes and systemic embolism events
  • Lower event rate of stroke/systemic embolism by 19%, driven mainly by 51% fewer hemorrhagic strokes
  • DOACs and warfarin were *similarly* effective in preventing ischemic stroke and myocardial infarction
DOACs- WHAT’S NOT SO GOOD?

• Kinetics and dynamics
  • Requirement for dose adjustment for renal function
  • Short half lives means strict compliance, i.e., no missed doses

• Monitoring
  • One size fits all?

• Limited reversal agent availability

• Limited approved indications
  • No approved use with valves, acute coronary syndrome, etc.
DOACs- GOOD OR BAD?

- Cost effectiveness
  - Eliminate warfarin’s repeated laboratory tests, frequent office or clinic visits, cost of adverse events, etc.

<table>
<thead>
<tr>
<th>DRUG</th>
<th>DOSING</th>
<th>30 DAY ESTIMATED COST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban</td>
<td>5 mg twice a day</td>
<td>$400</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>150 mg twice a day</td>
<td>$400</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>60 mg once daily</td>
<td>$350</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>20 mg once daily</td>
<td>$400</td>
</tr>
<tr>
<td>Warfarin</td>
<td>5 mg once daily</td>
<td>$20</td>
</tr>
</tbody>
</table>

*Pricing data is a representative average wholesale price from a single manufacturer of the brand and/or generic product, respectively
THE BLEEDING RISK
DOACs - THE BLEEDING RISKS

• A “class effect”?
  • Lower major bleeding rates than warfarin except for gastrointestinal bleeding risk where lower rates of bleeding seen with warfarin

<table>
<thead>
<tr>
<th>DRUG</th>
<th>STUDY</th>
<th>MAJOR BLEEDING RISK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>RE-LY</td>
<td>3.11%</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>RELY-ABLE</td>
<td>3.74%</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>ROCKET</td>
<td>3.6%</td>
</tr>
<tr>
<td>Apixaban</td>
<td>ARISTOTLE</td>
<td>2.13%</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>ENGAGE-AF TIMI 48</td>
<td>2.75%</td>
</tr>
</tbody>
</table>
DOACs- THE BLEEDING RISKS

• A “class effect”?  
  • Pooled analysis of all DOACs for all indications together demonstrate no significant difference between DOACs and comparators for risk of major bleeding  
  • No significant difference found between DOACs  
  • Bleeding risk varies with indications

• Reduced risk compared to warfarin  
  • Reduced risk of fatal intracranial bleeding with DOACs  
  • No difference in fatal major bleeding in all other sites
DOACs- THE BLEEDING RISK

- DOACs (compared to warfarin)
  - Lower rate of hemorrhagic stroke
  - Higher rate of gastrointestinal bleeding
- Increasing the risk

<table>
<thead>
<tr>
<th>RISK FACTORS FOR MAJOR BLEEDING</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Older age</td>
<td>History of smoking</td>
</tr>
<tr>
<td>Mild anemia</td>
<td>Prior use of aspirin</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td></td>
</tr>
<tr>
<td>History of prior gastrointestinal bleeding</td>
<td></td>
</tr>
<tr>
<td>Baseline diastolic blood pressure of 90 mm Hg or greater</td>
<td></td>
</tr>
<tr>
<td>History of chronic obstructive pulmonary disease</td>
<td></td>
</tr>
</tbody>
</table>
THE RESCUE
DOACs- REVERSAL

• Up to late 2015
  • Warfarin reversal with phytonadione, Kcentra™ (prothrombin complex concentrate)
  • Dabigatran reversal with FEIBA (anti-inhibitor coagulant complex)- off-label
  • Rivaroxaban reversal with Kcentra™ (prothrombin complex concentrate)- off-label

• Late 2015
  • Dabigatran reversal with idarucizumab (Praxbind™)
IDARUCIZUMAB (Praxbind™)

- A humanized monoclonal antibody fragment that binds specifically to dabigatran and its acylglucuronide metabolites
  - The affinity of dabigatran/idarucizumab is approximately 350 times greater than that of dabigatran/thrombin
  - Neutralization of the anticoagulant effect of dabigatran within minutes (approximately 15 minutes in animal models)
IDARUCIZUMAB (Praxbind™)

• Kinetics
  • Drug levels drop in biphasic manner
  • Initial half-life of approximately 45 minutes
  • Plasma concentration after 4 hours of 4% of peak
  • Effect sustained for 12 hours
  • Renal elimination
IDARUCIZUMAB (Praxbind™)

• Side effects
  • Mild such as headache, delirium, hypokalemia, hypersensitivity
  • Post-marketing/case reports- intracardiac thrombus, NSTEMI, acute ischemic stroke, deep vein thrombosis, pulmonary edema, pulmonary embolism...
IDARUCIZUMAB (Praxbind™)

- **Administration**
  - Single total dose of 5 g intravenously over 15 minutes or less (fastest, practical time)
  - Redosing for re-elevated coagulation parameters such as elevated aPTT or clinically relevant bleeding

- **Restricted use?**
  - Reversal of dabigatran-induced coagulopathy in patients with intracranial hemorrhage
  - Adult patients
IDARUCIZUMAB (Praxbind™)

• Cost considerations
  • Current average wholesale cost for a single 5 g dose is approximately $2100 per event
  • Alternatives such as FEIBA or Kcentra™ costs in excess of $5,000 to $10,000 per event

• And again
  • Due to its mechanism of action, reversal of dabigatran only
MARKET AND PRACTICE FORCES

- Usage patterns of DOACs and need for reversal agents
  - Rivaroxaban (Xarelto™) is the market leader followed by
  - Dabigatran (Pradaxa™) followed by
  - Apixaban (Eliquis™) but...

- Need for required reversal?

- Reversal of the direct Factor Xa inhibitors still unavailable
ANDEXANET ALFA

- A recombinant protein
- A modified form of factor Xa that is catalytically inactive but retains high-affinity binding to factor Xa inhibitors
  - ANNEXA-A/ ANNEXA-R trials showed reversal effects for both apixaban and rivaroxaban
  - ANNEXA-E trial to determine efficacy with edoxaban reversal
- Apixaban- anti-Factor Xa activity reduced by 94%
- Rivaroxaban- anti-Factor Xa activity reduced by 92%
ANDEXANET ALFA

• Kinetics
  • Normalization of coagulation parameters within 2 minutes after completion of IV bolus
  • Effects lasts 2 hours with IV bolus

• Administration
  • Appears to be an IV bolus dosing followed by infusion over 45 to 60 minutes

• Regulatory
  • FDA has accepted agent for priority review with action expected by mid-August 2016
A UNIVERSAL REMEDY?

• Aripazine (also known as ciraparantag)
  • Small, synthetic, water-soluble, cationic molecule
  • Binds to unfractionated heparin, low molecular weight heparins, fondaparinux, dabigatran and factor Xa inhibitors through hydrogen bonding and charge–charge interactions
• Issues
  • Studies only with edoxaban
  • Limited human studies but results “promising”
A UNIVERSAL REMEDY?

- Aripazine
  - Baseline hemostasis restored within 10 to 30 minutes after varying bolus doses of aripazine
  - Effect sustained for 24 hours
  - Additional Phase 2 studies are ongoing
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WHICH BRINGS US TO...

• For valvular atrial fibrillation, warfarin remains the mainstay therapy

• For atrial fibrillation *not* due to a valvular problem, DOACs represent a safe *alternative* to warfarin where there is a concern over intracranial bleeding
WHICH BRINGS US TO...

- Selection of a specific DOAC will depend on three factors none of which have to do with efficacy or safety
- Reversal of oral anticoagulants remains the same with a single exception for a third tier agent
WHICH BRINGS US TO...

- The fact that we still do not have the perfect oral anticoagulant
- But slowly but surely we may be getting as close as we ever will in the next 5 to 10 years