New oral anticoagulants and antiplatelets: Where do they fit?

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Objectives

- Describe the mechanisms of action for novel oral anticoagulants
- Discuss the advantages and disadvantages with the novel oral anticoagulants and antiplatelets
- Identify therapeutic options for reversal of oral anticoagulants
Ideal Anticoagulant

- Administered orally, once daily
- Highly effective in reducing thromboembolic events
- Predictable dose response and kinetics
- Low rate of bleeding
- No routine monitoring
- Wide therapeutic window
- No dose adjustment required
- Little interaction with food or other drugs
- Low, nonspecific plasma protein binding
- Reversible
FDA approved oral anticoagulants

- Dabigatran (Pradaxa®)
- Rivaroxaban (Xarelto®)
- Warfarin (Coumadin®)
Mechanism of Action

Inhibited by Rivaroxaban

Inhibited by Dabigatran

Inhibited by Warfarin
Dabigatran (Pradaxa®)

- A direct thrombin inhibitor and prodrug that is rapidly converted to an active moiety by hydrolysis via nonspecific esterases in the plasma and urine

- FDA Indication
  - Stroke prevention in non-valvular atrial fibrillation
    - Approved in Europe and Canada for prevention of VTE after hip and knee replacement

- Contraindications
  - Serious hypersensitivity to dabigatran
  - Active pathological bleeding
## Pharmacokinetics

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Absorption-Bioavailability</strong></td>
<td>3-7%</td>
<td>100%</td>
</tr>
<tr>
<td><strong>Cmax</strong></td>
<td>1-4hrs</td>
<td>4hr</td>
</tr>
<tr>
<td><strong>Steady State</strong></td>
<td>2-5 days</td>
<td>3-4 days</td>
</tr>
<tr>
<td><strong>Distribution</strong></td>
<td>Vd= 50-70L</td>
<td>Vd=0.14L/kg</td>
</tr>
<tr>
<td></td>
<td>35% protein bound</td>
<td>99% protein bound</td>
</tr>
<tr>
<td><strong>Metabolism</strong></td>
<td>Hepatic, plasma esterases Not metabolized through CYP450</td>
<td>Extensively metabolized through CYP450</td>
</tr>
<tr>
<td><strong>Elimination</strong></td>
<td>Urine: primarily $t_{1/2} : 14-17$hrs</td>
<td>Urine: 92% $t_{1/2} : 37-89$hrs</td>
</tr>
</tbody>
</table>
Dosing

- Stroke prevention in Nonvalvular Atrial Fibrillation
  - Est CrCl > 30mL/min
    - 150mg capsule orally, twice daily
  - Est CrCl 15-30mL/min
    - 75mg capsule orally, twice daily
    - Dose based on pharmacokinetic research, patients were excluded from RE-LY with CrCl < 30mL/min
  - Est CrCl < 15mL/min
    - No dosage recommendations
Administration

- Do not break, chew, or open capsules
  - Manipulation of product can cause a 75% increase in absorption and potentially serious adverse reactions
- Administer with water
- Can be taken without regard to meals
- Dosage Forms
  - 75mg and 150mg capsules
Drug Interactions

- **P-glycoprotein (P-gp) inducers**
  - Avoid use with rifampin; may reduce dabigatran bioavailability

- **P-gp inhibitors**
  - **Amiodarone**
    - Avoid use in patients with severe renal impairment (CrCl 15-30mL/min); may increase dabigatran levels
  - **Dronedarone and Ketoconazole**
    - Dosage reduction should be considered if CrCl 30-50mL/min, avoid use if CrCl 15-30mL/min; may increase dabigatran levels
Adverse Reactions

- Most commonly reported side effect
  - Gastrointestinal upset (11% of patients) and bleeding

- Most common complication
  - Bleeding
  - Risk factors for bleeding include:
    - Concomitant antiplatelets
      - Low dose aspirin was permitted in RE-LY, subgroup analyses of bleeding risk, not yet available
    - Chronic use of non-steroidal anti-inflammatories (NSAIDs)
Monitoring and Reversal

- Monitoring
  - No routine monitoring is required
  - aPTT may be useful to indicate excessive anticoagulant effects
    - aPTT > 80 sec was associated with higher bleeding risk in literature

- Reversal
  - Antidote?
    - None yet, monoclonal antibody in the pipeline
  - Hemodialysis may be utilized to remove up to 60% of drug over 2 to 3 hours

- Supportive Care
  - May consider FFP, RBC’s, and/or recombinant factor VIIa.
  - PCC not effective in small study
### Surgical Considerations

<table>
<thead>
<tr>
<th>Estimated Renal Function (CrCl)</th>
<th>Recommended timing for discontinuation of dabigatran prior to surgery or invasive procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High Risk of Bleeding *</td>
</tr>
<tr>
<td>CrCl &gt; 50mL/min</td>
<td>2 to 4 days</td>
</tr>
<tr>
<td>CrCl 30 to 50 mL/min</td>
<td>4 days</td>
</tr>
<tr>
<td>CrCl &lt; 30 mL/min</td>
<td>&gt; 5 days</td>
</tr>
<tr>
<td></td>
<td>Standard Risk of Bleeding</td>
</tr>
<tr>
<td></td>
<td>24 hours</td>
</tr>
<tr>
<td></td>
<td>&gt; 2 days (48 hours)</td>
</tr>
<tr>
<td></td>
<td>2 to 5 days</td>
</tr>
</tbody>
</table>

* Examples of high risk bleeding include: cardiac surgery, neurosurgery, abdominal surgery, and surgeries involving a major organ. Spinal anesthesia may require complete hemostasis and is therefore considered high risk. Other determinants of bleeding risk include advanced age, comorbidities and concomitant use of antiplatelet therapy.

Rivaroxaban (Xarelto®)

- Direct factor Xa inhibitor (antithrombin independent)

- FDA indication
  - Stroke prevention in nonvalvular atrial fibrillation
  - Prophylaxis of DVT in patients undergoing knee or hip replacement surgery

- Contraindications
  - Hypersensitivity to rivaroxaban
  - Active pathological bleeding
# Pharmacokinetics

<table>
<thead>
<tr>
<th></th>
<th>Rivaroxaban</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Absorption-Bioavailability</strong></td>
<td>80-100%</td>
<td>100%</td>
</tr>
<tr>
<td><strong>Cmax</strong></td>
<td>3 hrs</td>
<td>4 hrs</td>
</tr>
<tr>
<td><strong>Steady State</strong></td>
<td>2-5 days</td>
<td>3-4 days</td>
</tr>
<tr>
<td><strong>Distribution</strong></td>
<td>Vd=50-58 L</td>
<td>Vd= 0.14L/kg</td>
</tr>
<tr>
<td></td>
<td>92-95% protein bound</td>
<td>99% protein bound</td>
</tr>
<tr>
<td><strong>Metabolism</strong></td>
<td>Renal (1/3 excreted unchanged)</td>
<td>Extensively metabolized through the CYP450 pathway.</td>
</tr>
<tr>
<td></td>
<td>Biliary/fecal</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hepatic (through CYP3A4)</td>
<td></td>
</tr>
<tr>
<td><strong>Elimination</strong></td>
<td>Urine: 66%</td>
<td>Urine: 92%</td>
</tr>
<tr>
<td></td>
<td>$T_{1/2}$: 5-12 hrs</td>
<td>$T_{1/2}$: 37-89 hrs</td>
</tr>
</tbody>
</table>
Dosing

- Nonvalvular atrial fibrillation
  - CrCl > 50 mL/min
    - 20mg tablet orally, once daily
  - CrCl 15-50 mL/min
    - 15mg tablet orally, once daily
  - Avoid use in Child Pugh B or C hepatic impairment

- DVT prophylaxis (hip and knee surgery)
  - CrCl > 30 mL/min
    - 10mg tablet orally, once daily
  - CrCl < 30mL/min
    - Avoid use
  - Avoid use in Child Pugh B or C hepatic impairment
Administration

- Dose $\geq 15$mg/day should be administered with food
  - 10mg/day may be administered without regard to meals
- Do not administer via a feeding tube that delivers rivaroxaban directly into the small intestine or colon (ie J-tube) due to a decrease in the max concentration
Drug Interactions

- **CYP3A4/P-gp inducers**
  - Avoid use with strong inducers (e.g. carbamazepine, phenytoin, rifampin, St. Johns wort); can decrease rivaroxaban levels

- **CYP3A4/P-gp inhibitors**
  - Avoid use with strong inhibitors (e.g. ketoconazole, itraconazole, ritonavir, conivaptan); can increase rivaroxaban levels
Adverse Reactions

- Most common side effect/complication
  - Bleeding
  - Increased LFT’s
Monitoring and Reversal

- Monitoring
  - In Phase I and II studies Factor Xa activity did not completely return to baseline within 24 hours for doses >5mg
  - Affects both the PT and aPTT in a dose dependent manner, although PT may be more sensitive

- Reversal
  - Antidote?
    - None available

- Supportive Care
  - Activated charcoal
    - Ideally within 2 hours of ingestion
  - Consider FFP, RBC’s, recombinant factor VIIa and PCC’s can also be considered
## Surgical Considerations

<table>
<thead>
<tr>
<th>Recommended timing for discontinuation of rivaroxaban prior to surgery or invasive procedure</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High Risk of Bleeding</strong>*</td>
<td><strong>Standard Risk of Bleeding</strong></td>
</tr>
<tr>
<td>24 to 48 hours (may be longer based on renal function)</td>
<td>Minimum of 24 hours</td>
</tr>
</tbody>
</table>

* Examples of high risk bleeding include: cardiac surgery, neurosurgery, abdominal surgery, and surgeries involving a major organ. Spinal anesthesia may require complete hemostasis and is therefore considered high risk. Other determinants of bleeding risk include advanced age, comorbidities and concomitant use of antiplatelet therapy.

** Neuraxial anesthesia: Avoid removal of epidural catheter for at least 18 hours following last rivaroxaban dose; avoid rivaroxaban administration for at least 6 hours following epidural catheter removal; if traumatic puncture occurs, avoid rivaroxaban for at least 24 hours.
**Comparison of agents for stroke prevention**

<table>
<thead>
<tr>
<th>Variable</th>
<th>ROCKET AF (n=14,264)</th>
<th>RE-LY (n=18,113)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Drug</td>
<td>Rivaroxaban 20mg/day (15mg/day for CrCl 30-49mL/min)</td>
<td>Dabigatran 150mg twice a day</td>
</tr>
<tr>
<td>Comparator Drug</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time in therapeutic range (mean)</td>
<td>Warfarin dosed to goal INR 2-3 55%</td>
<td>Warfarin dosed to goal INR 2-3 64%</td>
</tr>
<tr>
<td>Study population</td>
<td>AF and at least two stroke risk factors</td>
<td>AF and at least one stroke risk factor</td>
</tr>
<tr>
<td>CHADS2 score (mean)</td>
<td>Study drug</td>
<td>Comparator</td>
</tr>
<tr>
<td>Study drug</td>
<td>3.48</td>
<td>2.2</td>
</tr>
<tr>
<td>Comparator</td>
<td>3.46</td>
<td>2.1</td>
</tr>
<tr>
<td>History of TIA or stroke</td>
<td>Study drug</td>
<td>Comparator</td>
</tr>
<tr>
<td>Study drug</td>
<td>55%</td>
<td>20.3%</td>
</tr>
<tr>
<td>Comparator</td>
<td>55%</td>
<td>19.8%</td>
</tr>
<tr>
<td>Primary outcome (study drug vs comparator)</td>
<td>Stroke or non-CNS embolism: 2.12% vs 2.42%/yr (p=0.0017)</td>
<td>Stroke or systemic embolism: 1.11% vs 1.69%/yr (p&lt; 0.001)</td>
</tr>
<tr>
<td>Number needed to treat</td>
<td>333</td>
<td>172</td>
</tr>
<tr>
<td>Major Bleeding</td>
<td>3.6% vs 3.46%/yr (p=0.576)</td>
<td>3.11% vs 3.36%/ yr (p=0.31)</td>
</tr>
<tr>
<td>Intracranial Hemorrhage</td>
<td>0.49% vs 0.74%/yr (p=0.019)</td>
<td>0.3% vs 0.74%/yr (p&lt;0.001)</td>
</tr>
<tr>
<td>Clinically relevant nonmajor bleeding</td>
<td>11.8% vs 11.37%/yr (p=0.345)</td>
<td>N/A</td>
</tr>
<tr>
<td>Study Conclusion</td>
<td>Rivaroxaban is noninferior to warfarin without increasing the risk of major bleeding or intracranial hemorrhage</td>
<td>Dabigatran is superior to warfarin without increasing the risk of major bleeding or intracranial hemorrhage</td>
</tr>
</tbody>
</table>
Controversies

- **Dabigatran**
  - Discovered after study closure, data re-analyzed
    - Increased rate of silent MI
  - Meta-analysis confirmed results that patients are at an increased risk of MI or ACS
    - Dabigatran grp 1.9% and control grp 0.79%

- **Rivaroxaban**
  - "Rebound" Effect
    - Related to lack of guidance at end of study for prescribers
    - Patients in rivaroxaban group were not transitioned from rivaroxaban to warfarin appropriately, putting them at risk for stroke
Summary

- Advantages
  - Predictable PK in patients with normal renal function
  - No monitoring
  - No food interactions

- Disadvantages
  - Limited experience
  - Knowledge gaps
  - Impaired renal function problematic with dosing
Oral Antiplatelet Agents

- Aspirin
- Aspirin/Dipyridamole
- Ticlopidine
- Clopidogrel (Plavix®)
- Prasugrel (Effient®)
- Ticagrelor (Brilinta®)
Mechanism of Action

Yousef O, Bhatt D. Nat. Rev. Cardiol. 2011
Clopidogrel Concerns

- Prodrug, that requires metabolism to active metabolites by the CYP P450 enzyme
  - Requires two separate CYP mediated steps
- Variability in antiplatelet response
  - Compliance issues
  - Variable metabolism
  - Genetic Variables
    - Polymorphisms of P2Y12 receptor
    - Polymorphisms of VYP3A system
      - Boxed Warning
        - Patients with one or more copies of the variant CYP2C19*2 and/or CYP2C19*3 alleles may have reduced conversion to active metabolite
Clopidogrel Concerns

- Drug Interactions
  - PPIs
    - Manufacturer recommendation
      - Avoidance of PPIs or use of a PPI with less potent CYP2C19 inhibition (i.e., pantoprazole)
    - ACCF/ACG/AHA
      - Patients with multiple risk factors for GI bleeding continue to use a PPI, regardless of degree of CYP2C19 inhibition
Clopidogrel Resistance?

- More appropriate term: Non-responder
  - Reported to vary between 4% and 44% among different populations
- VerifyNow® P2Y12
  - Point of care assay
  - Utilized to detect platelet reactivity
    - Used for both aspirin and clopidogrel reactivity
    - Test 5-7 days after starting clopidogrel 75mg daily OR 2-6 hours after a LD of clopidogrel
  - May be helpful in selection of medications for non-responders
**Pharmacokinetic Comparison**

<table>
<thead>
<tr>
<th></th>
<th>Max IPA</th>
<th>Peak plasma level* (hr)</th>
<th>Tmax IPA* (hr)</th>
<th>T(_{1/2}) (hr)</th>
<th>Offset of action (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clopidogrel</td>
<td>40-60%</td>
<td>1</td>
<td>4-8</td>
<td>6</td>
<td>5-7</td>
</tr>
<tr>
<td>Prasugrel</td>
<td>75-85%</td>
<td>0.5-1.5</td>
<td>2-4</td>
<td>7</td>
<td>5-7</td>
</tr>
<tr>
<td>Ticagrelor</td>
<td>85-95%</td>
<td>1.5</td>
<td>2-4</td>
<td>7</td>
<td>3-5</td>
</tr>
</tbody>
</table>

IPA= Inhibition of Platelet Aggregation

*With loading doses
Prasugrel (Effient®)

- Third generation thienopyridine, irreversibly binds to P2Y12 ADP receptor

- FDA approved indications
  - ACS
    - NSTE MI/UA who are to be managed with primary PCI
    - STEMI when managed with primary or delayed PCI
Black Box Warnings

- Can cause significant, sometimes fatal, bleeding

- Contraindications
  - Active pathological bleeding
  - Prior transient ischemic attack or stroke

  TRITON-TIMI 38 Results
  - Pts with history of TIA or stroke (> 3 months prior to enrollment)
    - Prasugrel group 6.5% stroke incidence; 4.2% were thrombotic and 2.3% were ICH versus clopidogrel 1.2% all thrombotic
  - Pts without a history of TIA or stroke
    - Prasugrel group 0.9%; 0.2% ICH and clopidogrel group 1%; 0.3% ICH
Black Box Warnings

Warnings and Precautions

- Not recommended for patients ≥75 yrs of age
- Not recommended for initiation in patients likely to undergo CABG
- Additional Risk factors for bleeding
  - Body weight < 60kg
  - Propensity to bleed
  - Concomitant use of medications that increase the risk of bleed
Dosing

- **Loading Dose**
  - 60mg orally once

- **Maintenance dose**
  - 10mg orally once daily
  - Used in combination with aspirin
  - Suggested 5mg for patient weight < 60kg
    - Never studied, lacks clinical evidence
Ticagrelor (Brilinta®)

- Cyclopentyltriazolopyrimidine, a direct acting, reversible antiplatelet agent

- FDA indication
  - ACS
    - Unstable angina
    - NSTEMI
    - STEMI
Black Box Warnings

- Can cause significant, sometimes fatal, bleeding

- Contraindications
  - Active pathological bleeding
  - History of intracranial hemorrhage

- Aspirin dose and effectiveness
  - A loading dose of 325mg of aspirin can be given
  - Maintenance doses of aspirin should not exceed 100mg
Dosing

- **Loading Dose**
  - 180mg orally once

- **Maintenance dose**
  - 90mg orally twice daily
  - Used in combination with aspirin
Aspirin dosing

- **PLATO Study**
  - Enrolled 18,624 patients admitted to the hospital with an ACS
  - Primary Endpoint
    - Time to death from vascular causes/MI/stroke
  - Those patients enrolled in North America
    - US adherence to randomized drug was 62.0% vs. 84.7% ROW
    - Aspirin dose:
      - Doses ≥ 300mg/day favored clopidogrel HR 1.45 (95%CI, 1.01 to 2.09)
      - Doses ≤ 100mg/day favored ticagrelor HR 0.77 (95%CI, 0.69 to 0.86)

Antiplatelets Role in Practice

2011 PCI guideline recommendations

- After PCI, use of aspirin should be continued indefinitely (LOE: A)
- After PCI, it is reasonable to use aspirin 81mg per day in preference to higher maintenance doses (LOE: B)

Levine et al. 2011 ACCF/AHA/SCAI PCI Guideline. JACC 2011: 58 (24); e44-122.
Antiplatelets Role in Practice

- **2011 PCI guideline recommendations**
  - A LD of a P2Y12 receptor inhibitor should be given to patients undergoing PCI with stenting
    - Options include:
      - Clopidogrel 600mg (ACS and non-ACS) (LOE: B)
      - Prasugrel 60mg (ACS) (LOE:B)
      - Ticagrelor 180mg (ACS) (LOE:B)
  - In patients receiving a stent (BMS or DES) during PCI for ACS, P2Y12 inhibitor therapy should be given for at least 12 months
    - Options include: clopidogrel 75mg daily, prasugrel 10mg daily, ticagrelor 90mg twice daily (all LOE:B)

Levine et al. 2011 ACCF/AHA/SCAI PCI Guideline. JACC 2011: 58 (24); e44-122.
Summary

Choice of antiplatelet is dependent on:

- FDA indications
- Contraindications
- Failure of therapy
- Compliance
- Cost