New(er) Anticoagulants:
Mechanism, Indication,
Pharmacokinetics, Monitoring
and Antidotes

Julie Golembiewski PharmD

OBJECTIVES

• Discuss the mechanism, indication and pharmacokinetics of newer anticoagulants
• Discuss the monitoring and antidotes of newer anticoagulants

ANTICOAGULANTS

- Keep existing clots from enlarging
- Prevent clot formation, thereby preventing or treating deep vein thrombosis, pulmonary embolism, myocardial infarction and stroke
- Agents
  - Heparin
  - Low molecular weight heparin (enoxaparin, dalaparin)
  - Fondaparinux
  - Warfarin
  - Daltaparin
  - Rivaroxaban
  - Apixaban

ANTIPLATELETS

- Prevent platelet aggregation and inhibit thrombus formation
- Used for primary and secondary prevention of thrombotic cerebrovascular or cardiovascular disease
- Agents
  - Aspirin
  - Clopidogrel
  - Prasugrel
  - Dipyridamole ER + aspirin

Injury → vessel spasm, contraction, formation of platelet plug

Clot retraction, then dissolution (fibrinolysis)

ANTICOAGULANTS –
THE “OLDIES”

Warfarin
(Factors II, VII, IX, Xa)

Fondaparinux
Rivaroxaban
Apixaban

Argatroban
Bivalirudin
Dabigatran
**HEPARIN & LMWH**

**“GENERAL” ANTICOAGULANTS**

- **Heparin**
  - Has anti-factor Xa and anti-thrombin activity
  - Long chain bridges AT & thrombin

- **LMWH**
  - Has greater anti-Xa activity than anti-thrombin activity
  - Shorter chain doesn’t bridge AT & thrombin as well

**Heparin**

- Binds to antithrombin (AT); Heparin-AT complex inactivates thrombin & Factor Xa

**LMWH**

- More predictable anticoagulation response
- Better SC bioavailability
- Longer duration
- Lower incidence of thrombocytopenia
- Less need for lab monitoring

**Heparin-induced thrombocytopenia (HIT)**

- Significantly lower incidence of HIT than heparin

**Reversed with protamine**

**WARFARIN**

**“GENERAL” ANTICOAGULANT**

- Inhibits vitamin K-dependent clotting factors (II, VII, IX, X)
- Anticoagulant effect in 2 - 7 days

**INTERPATIENT VARIABILITY**

- CYP2C9 and VKORC1 polymorphisms account for up to 35% of variance in warfarin dose requirement
- Pharmacogenetics algorithm superior to traditional clinical algorithm/5mg per day
  - 54% lower rate of serious adverse events
- FDA label change in 2010 to add recommendations for initial dosing ranges for patients with different combinations of CYP2C9 and VKORC1 genotypes

**FONDOPARINUX (ARIXTRA)**

**FACTOR Xa INHIBITOR**

- FDA-approved for prevention of DVT following hip fracture, hip replacement, knee replacement or abdominal surgery
- Treatment of DVT or acute PE in conjunction with warfarin
- SC (once daily), beginning 6 to 8 hrs following surgery
- No routine monitoring; measure anti-Xa activity if necessary
- No antidote but factor VII may be effective

**ARGATROBAN, BIVALIRUDIN**

**DIRECT THROMBIN INHIBITORS**

- Argatroban
  - IV
  - Used for anticoagulation in patients with HIT
  - Eliminated by the liver
  - 30 – 50 min half-life
  - Monitor aPTT and/or ACT

- Bivalirudin
  - IV
  - Used for anticoagulation during PCI
  - Percutaneous coronary intervention, especially in patients at risk for HIT
  - Cardiac surgery for patients with HIT
  - Enzymatic and renal elimination
  - 25 min half-life
  - Monitor ACT
### PERIOPERATIVE IMPLICATIONS

<table>
<thead>
<tr>
<th>Anticoagulant</th>
<th>Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Heparin</strong></td>
<td>Stop 4 – 6 hours before surgery. Spinal/epidural hematoma risk – must consider heparin dose and timing.</td>
</tr>
<tr>
<td><strong>LMWH</strong></td>
<td>Last dose 24 hours before surgery. Spinal/epidural hematoma risk – must consider LMWH dose and timing.</td>
</tr>
<tr>
<td><strong>Warfarin</strong></td>
<td>Discontinue 5 days before major surgery. May or may not discontinue 2 – 3 days before minor surgery. Spinal/epidural hematoma risk; remove epidural catheter when INR &lt; 1.5.</td>
</tr>
<tr>
<td><strong>Fondaparinux</strong></td>
<td>Not used pre-op for bridging therapy. Spinal/epidural hematoma risk; remove epidural 36 hours after dose.</td>
</tr>
<tr>
<td><strong>Argatroban</strong></td>
<td>Generally stopped before major surgery. Avoid spinal/epidural.</td>
</tr>
<tr>
<td><strong>Bivalirudin</strong></td>
<td>Alternative anticoagulant during cardiopulmonary bypass in patients with HIT; avoid spinal/epidural.</td>
</tr>
</tbody>
</table>

### ANTICOAGULANTS – THE “NEWBIES”

#### DABIGATRAN (PRADAXA®)
**ORAL DIRECT THROMBIN INHIBITOR** *(APPROVED OCTOBER 2010)*
- **Indication**
  - Prevention of stroke and systemic embolism in nonvalvular A-fib
  - Not for patients with mechanical prosthetic heart valves → increased incidence of stroke, MI and bleeding vs. warfarin
- **Oral**
  - Pellets of dabigatran etexilate (prodrug) coated on acid core
  - Once absorbed, rapidly converted to dabigatran via ester enzymes
  - 150 mg twice daily; reduce dose in renal impairment
- **Regular monitoring is not required**
  - PT, aPTT or INR do not accurately predict degree of anticoagulation
  - A normal thrombin clotting time or aPTT suggest little anticoagulant activity; these tests, however, are not sensitive in drug overdose/excess anticoagulation

#### RIVAROXABAN (XARELTO®)
**ORAL FACTOR Xa INHIBITOR** *(APPROVED JULY 2011)*
- **Indications**
  - DVT prophylaxis in knee or hip replacement surgery
  - Prevention of stroke and systemic embolism in nonvalvular A-fib
- **Oral**
  - 10 mg daily following knee or hip replacement surgery
  - 20 mg daily for stroke prevention in A-fib
  - 15 mg daily CrCl 15-50 ml/min
  - Drug interactions with CYP3A4 inducers or inhibitors
- **Regular monitoring is not required**
  - PT, aPTT, INR do not accurately predict degree of anticoagulation
  - Measure anti-Xa activity, if assay is calibrated for rivaroxaban

#### APIXABAN (ELIQUIs®)
**ORAL FACTOR Xa INHIBITOR** *(APPROVED DECEMBER 2012)*
- **Indication**
  - Prevention of stroke and systemic embolism in nonvalvular A-fib
- **Oral**
  - 5 mg twice daily; reduce dose in renal impairment, ≥ 80 y/o, ≤ 60kg
  - Drug interactions with CYP3A4 inducers or inhibitors, P-glycoprotein inhibitors
- **Regular monitoring is not required**
  - PT, aPTT, INR do not accurately predict degree of anticoagulation
  - Measure anti-Xa activity if assay is calibrated for apixaban

### UNIQUE ISSUES
**DABIGATRAN, RIVAROXABAN, APIXABAN vs. WARFARIN**
- **Gaps in antithrombotic coverage due to:**
  - Missed doses
  - Transitioning to warfarin
- **Lack of reversal agent / antidote for major bleeding**
  - Management of major bleeding is empiric
  - Prothrombin complex concentrate ??? Recombinant Factor VIII ???
  - Rivaroxaban & apixaban are not dialyzable
  - Dabigatran is dialyzable
- Dabigatran cannot be repackaged from original manufacturers package, crushed or administered through feeding tube
- Potential for breakdown from moisture, loss of potency, dyspepsia
Effective in animal models, but thrombosis and disseminated intravascular coagulation have occurred following administration of PCC or rFVIIa. Factor IXa inhibitor antidote is in development.

**PERIOPERATIVE IMPLICATIONS**

**DABIGATRAN, RIVAROXABAN, APIXABAN**

- Timing of discontinuation before surgery depends on:
  - Half-life of drug
  - Renal function
  - Surgical risk of bleeding

<table>
<thead>
<tr>
<th>Drug</th>
<th>Low Bleeding Risk Procedure</th>
<th>Moderate to High Bleeding Risk Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CrCl &gt; 50 ml/min</td>
<td>1 day</td>
</tr>
<tr>
<td></td>
<td>CrCl 30 - 50 ml/min</td>
<td>2 - 4 days</td>
</tr>
<tr>
<td></td>
<td>CrCl &lt;30 ml/min</td>
<td>2 - 5 days</td>
</tr>
<tr>
<td>Dabigatran</td>
<td></td>
<td>&gt; 5 days</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>CrCl &gt; 50 ml/min</td>
<td>1 day</td>
</tr>
<tr>
<td></td>
<td>CrCl 15 - 50 ml/min</td>
<td>2 - 3 days</td>
</tr>
<tr>
<td>Apixaban</td>
<td>CrCl &gt; 50 ml/min</td>
<td>1 day</td>
</tr>
<tr>
<td></td>
<td>CrCl 15 - 50 ml/min</td>
<td>2 - 3 days</td>
</tr>
<tr>
<td></td>
<td>CrCl &lt;30 ml/min</td>
<td>2 - 5 days</td>
</tr>
</tbody>
</table>

**ASPIRIN**

- Antiplatelet therapy for prevention of:
  - New coronary or PV thrombosis (primary prophylaxis)
  - Further events (fx of MI, stroke, PVD, DM, HTN, coronary stents) (secondary prophylaxis)

- Platelet inhibition is irreversible.

**ANTIPLATELET AGENTS**

- ADP inhibitors
  - Ticlopidine
  - Clopidogrel
  - Prasugrel

- GPIIb/IIIa inhibitors
  - Abciximab
  - Eptifibatide
  - Tirofiban

- Phosphodiesterase Inhibitors
  - Cilostazol
  - Dipyridamole

- Thromboxane inhibitors
  - Aspirin

**Timeline**

- Time for Hemostasis: At least two half-lives
- Time for Hemostasis: Anticoag dose
- End of Surgery: Epidural catheter removal
- Anticoag dose: Time for Hemostasis

- Adapted from Curr Opin Anaesthesiol 2009;22:661
- ASA Newsletter Spring-Summer 2012 pg. 14
SURGICAL CONSIDERATIONS

• General teaching: Stop aspirin 7 – 10 days before surgery

• **However**, cardiovascular risk from acute aspirin withdrawal often outweighs risk of complications from excessive surgical bleeding.

• Stopping aspirin in *secondary prophylaxis* patients should be discussed with cardiologist; most recommendations are to continue aspirin in these patients

(Script 2012/14/12(Suppl15S)

MGH Guidelines for Perioperative Aspirin Administration

ADP INHIBITORS - THIENOPYRIDINES

• Agents
  - Ticlopidine (Ticlid®)
  - Clopidogrel (Plavix®)
  - Prasugrel (Effient®)

• Mechanism of action: Irreversibly block ADP activation of P2Y12 receptor on platelets thereby inhibiting platelet activation and aggregation

• Ticlopidine was the first FDA-approved ADP inhibitor but rarely used today due to risk of neutropenia (clopidogrel is safer)

Cleveland Clinic Journal of Medicine 2009;76(supp 4):S37; Anesth Analg 2011;112(2):292

CLOPIDOGREL (PLAVIX®)

• Two step activation, including CYP2C19, to active metabolite

• Poor metabolizers → less active metabolite → stent thrombosis

• Consider CYP2C19 genetic testing in patients having CV events while on clopidogrel therapy or high-risk PCI patients

• Alternative antiplatelet therapy (prasugrel) for poor metabolizers and possibly, intermediate metabolizers

(Please refer to CYP2C19 Polygenic Testing in Patients with Stable Ischemic Syndrome and for Routine Use Before PCI for further details.)

Clopidogrel in Patients with Stable Ischemic Syndrome and for Routine Use Before PCI

PRASUGREL (EFFIENT®)

• More potent inhibitor of platelet function than clopidogrel

• Converted to its active metabolite in a single step (primarily by CYP3A4)

• Compared with clopidogrel, prasugrel has:
  - Less genetic variability
  - Fewer drug interactions
  - Higher incidence of bleeding
  - Do not use in cerebrovascular disease
  - Similar surgical considerations
  - Stop 5 days before surgery
  - Consider risk vs. benefit in high-risk patients

Cleveland Clinic Journal of Medicine 2009;76(supp 4):S37; Anesth Analg 2011;112(2):292

DIPYRIDAMOLE ER + ASPIRIN (AGGRENOX®)

• Indication: Stroke prevention in patients who’ve had a TIA or stroke

• Mechanism of action
  - Increased plasma levels of adenosine → vasodilation and inhibition of platelet aggregation
  - Inhibits platelet phosphodiesterase 5 → increased cAMP → inhibition of platelet aggregation and vasodilation

• **However**, little clinical evidence that dipyridamole alone exerts an antithrombotic effect

• Must be combined with aspirin; combination is effective


Dipiridamol + Aspirina (Aggrenox®)
**CILOSTAZOL (PLETAL®)**

- Indication: moderate to severe intermittent claudication
- Mechanism of action:
  - Inhibits platelet phosphodiesterase 3
  - Increased cAMP
  - Inhibition of platelet aggregation and vasodilation
- High rate of discontinuation due to adverse effects (headache, GI upset)

---

**CONCLUSION – ANTICOAGULANTS**

<table>
<thead>
<tr>
<th>Anticoagulant</th>
<th>Significant Interpatient Variability</th>
<th>Routine Monitoring</th>
<th>Antidote</th>
<th>Stop before surgery; concern with epidural catheter removal &amp; first/next dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heparin</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Warfarin</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>LMWH (enoxaparin, dalteparin)</td>
<td>?</td>
<td>?</td>
<td>✓</td>
<td>?</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>?</td>
<td>?</td>
<td>✓</td>
<td>?</td>
</tr>
<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>

---

**CONCLUSION – ANTIPLATELET AGENTS**

- Aspirin:
  - Risk of CV events vs. risk of bleeding
  - Most continue aspirin in secondary prophylaxis
- Clopidogrel (Plavix®):
  - Genetic predisposition
  - Poor and intermediate metabolizers
  - Risk of CV events vs. risk of bleeding
- Prasugrel (Effient®):
  - More potent than clopidogrel & less genetic variability
- Dipyridamole ER + Aspirin (Aggrenox®):
  - Stroke prevention; effective only when combined with aspirin
- Cilostazol (Pletal®):
  - Intermittent claudication only

---

**CONCLUSION – LAST THOUGHTS**

- Risk of bleeding increases with combination of agents
  - Aspirin or NSAID alone may be OK, but risk of bleeding / spinal hematoma increases when combined with another agent that affects clotting
- ASRA guidelines are derived from surgical patients and may not always apply to parturients or a peripheral nerve block performed in a compressible area
- Consider the pharmacokinetics (half life, renal function) of the new oral anticoagulant, as well as the risk for bleeding

---

**QUESTIONS?**