Update on Anticoagulants & Antiplatelet Drugs

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Objectives

- Recall the basic principles of hemostasis
- Describe the basic and clinical pharmacology of the new oral Factor Xa inhibitors
- Discuss the basic and clinical pharmacology of the new oral direct thrombin inhibitor
- Compare new oral anticoagulant medications to warfarin
- State the differences between the irreversible platelet ADP receptor blockers and the new competitive inhibitor ticagrelor
Overview of Hemostasis

1. Blood Vessel Injury
2. Neural Mechanism
3. Platelet Activation
4. Contact/Tissue Factor
5. Blood Vessel Constriction
6. Platelet Aggregation
7. Coagulation Cascade
8. Reduced Blood flow
9. Stable Hemostatic Plug

The Platelet Aggregation Step

- Fibrinogen
- Thrombin
- Thromboxane A$_2$
- ADP
- Endothelium
- Glycoproteins IIb, IIIa
- VWF
The exciting, but really complicated biochemistry involving “factors”

Intrinsic Pathway
Contact Activation Pathway

Extrinsic Pathway

Final Common Pathway

Factor X
Factor III
Factor V
Factor Xa (PT activator)
Prothrombin (Factor II)
Thrombin Factor IIa
Fibrinogen
Fibrin
Fibrin Polymer

Pharmacology - Alan P. Agins, Ph.D.

2013
Comparing the Two Pathways

**Intrinsic Pathway**
- All clotting factors are present within the blood vessels
- Clotting slower
- Activated partial thromboplastin test (aPTT)

**Extrinsic Pathway**
- Initiating factor is outside the blood vessels - tissue factor
- Clotting - faster - in seconds
- Prothrombin time (PT)

Checks and Balances
Mechanisms to keep coagulation cascade and platelet activation in check

**Coagulation Cascade**
- Protein C
- Antithrombin
- Plasmin
- Tissue factor pathway inhibitor

**Platelets**
- Endothelial cell derived
  - Prostacyclin
  - Nitric oxide
  - ADPase

Abnormalities can lead to an increased tendency toward thrombosis.
Causes of Thrombosis

- Composition of the blood (hypercoagulability)
- Quality of the vessel wall (endothelial cell injury)
- Nature of the blood flow (hemostasis)

Virchow's triad

Arterial Thrombus

- Usually occur in association with pre-existing vascular disease
  - atherosclerotic plaque rupture most common.
- Clinical sequelae = tissue ischemia
  - Either local flow obstruction or embolism to distal microcirculation.
  - MI, occlusive stroke or other ischemic events.
Venous Thrombus

- Usually in the lower limbs
  - often asymptomatic

- Produce acute symptoms if:
  - Cause local inflammation of the vessel wall
  - Obstruct blood flow
  - Embolize into the pulmonary circulation.

Indications For Anticoagulant Therapy

**Arterial thromboembolic disease**
- Prosthetic heart valves
- Atrial fibrillation (AF)
- Mitral valve disease, especially with AF
- Congestive Heart Failure, especially with AF
- Mural cardiac thrombi
- Transient ischemic attacks
- Stroke in evolution

**Venous thromboembolic disease**
- Deep venous thrombosis (DVT)
- Pulmonary embolism (PE)
- Primary prophylaxis of DVT/PE
- Disseminated intravascular coagulation
- Maintenance of patency of vascular grafts, shunts, bypasses
## The standard (ie., “old”) anticoagulant / antiplatelet drugs

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Prototype</th>
<th>Action</th>
<th>Clinical Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticoagulant [Parenteral]</td>
<td>Heparin</td>
<td>Inactivation of clotting Factors</td>
<td>Prevent venous Thrombosis</td>
</tr>
<tr>
<td>Antiplatelet Drugs</td>
<td>Aspirin</td>
<td>↓ Platelet aggregation</td>
<td>Prevent arterial Thrombosis</td>
</tr>
</tbody>
</table>

## The ‘Ideal’ Anticoagulant

- Oral, preferably once daily
- Rapid onset and offset
- Predictable PK and PD
- Good tolerability
- Low propensity for food and drug interactions
- Fixed doses (one size fits all)
- Wide therapeutic window
- Easy to use with no need for monitoring
- Quick, effective and safe antidote
### Evolution of Anticoagulation

<table>
<thead>
<tr>
<th>1930s</th>
<th>1950s</th>
<th>1980s</th>
<th>1990s</th>
<th>2010</th>
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</thead>
<tbody>
<tr>
<td><strong>Heparin</strong></td>
<td><strong>Warfarin</strong></td>
<td><strong>LMWH</strong></td>
<td><strong>Xa Inhibitors</strong></td>
<td><strong>DTI / Xa</strong></td>
</tr>
<tr>
<td>Parenteral</td>
<td>Oral</td>
<td>Parenteral</td>
<td>Parenteral</td>
<td>Oral</td>
</tr>
<tr>
<td>Narrow TI</td>
<td>Narrow TI</td>
<td>HIT</td>
<td>Must transition to warfarin</td>
<td>Predictable</td>
</tr>
<tr>
<td>Unpredictable</td>
<td>Unpredictable</td>
<td>Req Monitoring</td>
<td>Direct Thrombin Inhibitors</td>
<td>Some drug interactions</td>
</tr>
<tr>
<td>HIT</td>
<td>Req Monitoring</td>
<td>Diet Interactions</td>
<td>parenteral</td>
<td>No monitoring</td>
</tr>
<tr>
<td>Bleeding risk</td>
<td>Lifestyle interactions</td>
<td>Antidote</td>
<td>Req Monitoring</td>
<td>No monitoring</td>
</tr>
<tr>
<td>Antidote (protamine)</td>
<td>Antidote (Vit K)</td>
<td></td>
<td>Limited use to HIT/CV</td>
<td>No antidote</td>
</tr>
</tbody>
</table>

### Heparin Mechanism

- Unfractionated Heparin
- AT III
- Thrombin
- Factor Xa
Heparin’s Limitations

- Parenteral only
- Extensive plasma protein binding
- Non-linear dose-response curve
- Variable bioavailability
- No effect on clot-bound thrombin and factor Xa
- Can activate platelets directly or indirectly via immune response = heparin-induced thrombocytopenia (HIT) and thrombosis (HITT)
- SE: Hemorrhage, osteoporosis

Low Molecular Weight Heparin

- LMWH: 4000 - 5000 (vs Heparin: 15,000 +)
  - Inactivates Xa but has less effect on thrombin
  - Ratio of anti-Xa to anti-thrombin activity of 3:1 / 4:1
  - Too short to inactivate thrombin (much like LMWH); need >18 saccharide units to inactivate thrombin
  - Less non-specific protein/cell binding than UFH
  - Better pharmacokinetics / less side effect potential
Heparin Limitations in general

- UFH and LMWHs are inconvenient for the outpatient setting (IV or SubQ only)

- UFH and LMWHs can cause HIT:
  - Risk 0.2% with LMWH vs. 2.6% with UFH
  - Pts with HIT still need to be anticoagulated

Warfarin

Serendipitous history
“WARF” = Wisconsin Alumni Research Foundation
    (the holder of original patent)
Taken by six – seven million patients in United States

THERAPEUTIC USES:
- Prophylaxis and treatment of venous thrombosis
- Treatment of atrial fibrillation with embolism
- Prophylaxis & treatment of pulmonary embolism
- Adjunctive therapy for coronary occlusion
- Prophylaxis in patients with prosthetic valves
Warfarin: Mechanism of Action

Vitamin K

Synthesis of Non-Functional Coagulation Factors

Warfarin

Contact system: HMWK, PK, F XII
FXa, Kallikrein

Cellular injury: Tissue Factor (TF)

Prothrombin (F II)

Fibrinogen

Fibrin monomer

Factor XIII

Crosslinked fibrin

Factor XIIa

Fibrin multimer

Protein S

Activated Protein C
**Warfarin’s Limitations**

- Narrow therapeutic index
- Genetic variability
  - Site of action (vit K epoxide hydrolase)
  - Clearance (CYP2C9)
- Interactions with drugs, food, lifestyle
- Bleeding risk
- Monitoring necessary
- Slow onset / slow offset

**Newer Anticoagulants**

- **Direct Thrombin Inhibitors:**
  - Dabigitran (Oral)
- **Factor Xa inhibitors:**
  - Rivaroxaban
  - Apixaban

Do they meet the IDEAL criteria?
Atrial Fibrillation and the need for effective anticoagulation

- Estimated 5.8 million Americans suffer from non-valvular atrial fibrillation.
- Lifetime risk of developing AF is estimated 25 percent for people > 40.
- In addition to the five times greater risk of stroke compared with people without the condition, strokes for those affected are twice as likely to be fatal or seriously disabling.

The delicate balancing act with using anticoagulants for treating Atrial Fibrillation
**dabigatran (Pradaxa)**

- Oral Direct Thrombin Inhibitor
- Reversible
- Prodrug, converted to dabigatran
  - Binds clot-bound and free thrombin with high affinity and specificity
- Indication
  - Prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (AF)
  - Off-label - DVT prophylaxis after knee or hip surgery, Prevention of recurrent VTE

**dabigatran pharmacokinetic considerations**

**Absorption**
- Requires acidic pH for optimal absorption
- Capsules contain a tartaric acid core
- Possible explanation for increased dyspepsia and gastrointestinal bleeding

Half-life: 12–17 hours - BID dosing

**Hepatic impairment**
- No adjustment required

**Renal impairment**
- Clcr 15-30 mL/min: 75 mg twice daily
- Clcr <15 mL/min: no recommendation
**dabigatran**

**Summary of Clinical Studies (RE-LY):**

**Efficacy**
- 150 mg bid prevents more strokes (ischemic) than warfarin
  - ~ 5 more strokes per 1000 patients per year
  - (INR maintained in therapeutic range 64% of the time)

**Safety**
- Similar overall risk of bleeding for both drugs
  - Lower rate of major bleeding (life-threatening nature) than with warfarin
  - More major GI bleeding with 150 dabigatran
- Small, but real increase in MIs
  - Appears to be Direct Thrombin Inhibitor class effect

**dabigatran Drug interactions —**

- No cytochrome P450 issues
- Substrate for P-glycoprotein efflux transporter
  - P-gp inducers or inhibitors may alter dabigatran bioavailability
    - Inducers: rifampin
    - Inhibitors: quinidine, ketoconazole, verapamil, amiodarone clarithromycin
- PPIs may decrease bioavailability
Is dabigatran
The ‘Ideal’ Anticoagulant

- Oral (although b.i.d)
- Rapid onset and offset
- Predictable PK and PD
- Easy to use with no need for monitoring
- Low propensity for drug (etc) interactions
- Fixed doses (one size fits all)

Good tolerability ???
Wide therapeutic window ??
Effective & safe antidote ?? (short t<sub>1/2</sub> potential benefit)
Renal status for dosing critical
*Storage Issues – temp, moisture, light sensitive
Direct Factor Xa inhibitors

First oral direct factor Xa inhibitor

Rivaroxaban
Apixaban

rivaroxaban (Xarelto)

- First oral direct factor Xa inhibitor
- Once daily dosing - dose not affected by age, gender or weight
- More predictable pharmacology than warfarin
- No requirement for monitoring
- Cleared through CYP3A4
- No specific antidote if hemorrhage occurs
- Greater risk of stroke upon DC rivaroxaban in AF patients (black boxed warning)
rivaroxaban (Xarelto)

Currently indicated for

- Prevention of stroke & systemic embolism in pts with nonvalvular atrial fibrillation (ROCKET AF)
  - Non-inferior to warfarin
  - Major and nonmajor clinically relevant bleeding = warfarin
  - Intracranial hemorrhage < warfarin
  - Fatal bleeding < warfarin
- DVT prophylaxis after knee or hip surgery (RECORD)
  - reduced composite of symptomatic VTE and all-cause mortality compared to enoxaparin
  - major bleeding events = LMWH

rivaroxaban (Xarelto)

Currently indicated for

Deep vein thrombosis / pulmonary embolism (EINSTEIN-DVT / EINSTEIN-PE)

- Acute, systematic, proximal DVT w/o pulmonary embolism (PE)
  - Rivaroxaban (daily or b.i.d.) had similar efficacy and safety to standard therapy
- Acute symptomatic PE with or without DVT:
  - Non-inferiority to LMWH/VKA for efficacy
  - Similar findings for principal safety outcome
  - Superiority for major bleeding
- Reduction in the risk of recurrent DVT/PE (in select patients)
Drug interactions - rivaroxaban

- CYP3A4 substrate
  - **Inhibitors: Increase risk of bleeds**
    - Emycin, clarithromycin, azole antifungals, verapamil, amiodarone, protease inhibitors, grapefruit juice
  - **Inducers: Decrease efficacy (↑ clot risk)**
    - Rifampin, phenytoin, carbamazepine, pioglitazone, St John’s wort

Is rivaroxaban
The ‘Ideal’ Anticoagulant

- Oral, preferably once daily
- Rapid onset and offset
- Predictable PK and PD
- Good tolerability
- Fixed doses (one size fits all)
- Easy to use with no need for monitoring
- Low propensity for drug (etc) interactions
- Wide therapeutic window
- Effective & safe antidote (short t½ potential benefit)
apixaban (Eliquis)

- Second approved oral direct factor Xa inhibitor
- Twice daily dosing
- More predictable pharmacology than warfarin
- No requirement for monitoring
- Cleared through CYP3A4
- Less renal adjustment issues compared to dabigatran & rivaroxaban
- No specific antidote if hemorrhage occurs
- Greater risk of stroke upon DC rivaroxaban in AF patients (black boxed warning)

apixaban (Eliquis)

Currently indicated for

Prevention of stroke or systemic embolism in patients with atrial fibrillation (ARISTOTLE)
- Apixaban superior to warfarin in preventing stroke or systemic embolism
- Associated with less bleeding than warfarin
- Associated with lower all cause mortality than warfarin
Drug interactions - apixaban

- CYP3A4 substrate
  - **Inhibitors: Increase risk of bleeds**
    - Emycin, clarithromycin, azole antifungals, verapamil, amiodarone, protease inhibitors, grapefruit juice
  - **Inducers: Decrease efficacy (↑ clot risk)**
    - Rifampin, phenytoin, carbamazepine, pioglitazone, St John’s wort

Is apixaban
The ‘Ideal’ Anticoagulant

- Oral (although b.i.d)
- Rapid onset and offset
- Predictable PK and PD
- Good tolerability
- Fixed doses (one size fits all)
- Easy to use with no need for monitoring
- Low propensity for food and drug interactions
- Wide therapeutic window
- Effective & safe antidote (short t_{1/2} potential benefit)
The New Kids Compared to Warfarin in AF Stroke Prevention

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran (RE-LY)</th>
<th>Rivaroxaban (ROCKET-AF)</th>
<th>Apixaban (ARISTOTLE)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy</strong></td>
<td>Superior ↓ 5 strokes/1000 per year</td>
<td>Non-inferior</td>
<td>Superior ↓ 3 strokes/1000 per year</td>
</tr>
<tr>
<td><strong>Hemorrhagic Stroke</strong></td>
<td>74% reduction</td>
<td>40% reduction</td>
<td>50% reduction</td>
</tr>
<tr>
<td><strong>Major Bleeding</strong></td>
<td>Similar to warfarin</td>
<td>Similar to Warfarin</td>
<td>30% reduction</td>
</tr>
<tr>
<td><strong>Ischemic Strokes</strong></td>
<td>Reduction</td>
<td>Similar to warfarin</td>
<td>Similar to warfarin</td>
</tr>
<tr>
<td><strong>All cause Mortality</strong></td>
<td>No difference</td>
<td>No difference</td>
<td>11% Reduction</td>
</tr>
</tbody>
</table>

Comparing them all

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran Pradaxa® [b.i.d.]</th>
<th>Rivaroxaban Xarelto® [Once daily]</th>
<th>Apixaban Eliquis® [b.i.d.]</th>
<th>Warfarin [Once daily]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bioavailability (%)</strong></td>
<td>~7%</td>
<td>~90%</td>
<td>~66%</td>
<td>~100%</td>
</tr>
<tr>
<td><strong>Onset of action</strong></td>
<td>0.5 - 2 hrs</td>
<td>2 - 4 hours</td>
<td>1 - 3 hours</td>
<td>24 - 72 hours Peak Effect: 5 - 7 days</td>
</tr>
<tr>
<td><strong>T_{1/2} (hrs)</strong></td>
<td>12-14</td>
<td>9-13</td>
<td>8-15</td>
<td>20-60; Mean: 40</td>
</tr>
<tr>
<td><strong>Renal excretion</strong></td>
<td>90-95%</td>
<td>70%</td>
<td>30%</td>
<td>92% (inactive metabolites)</td>
</tr>
<tr>
<td><strong>Drug interactions</strong></td>
<td>PPIs decrease absorption P-glycoprotein substrate</td>
<td>Potent 3A4 inhibitors P-glycoprotein inhibitors</td>
<td>Potent 3A4 inhibitors</td>
<td>Inhibitors of CYP3A4, 1A2, 2C9/19</td>
</tr>
<tr>
<td><strong>Monitoring</strong></td>
<td>aPTT, ECT, TT - qualitative only</td>
<td>Anti Xa – qualitative only</td>
<td>Anti Xa – qualitative only</td>
<td>PT/INR quantitative</td>
</tr>
<tr>
<td><strong>Monthly cost</strong></td>
<td>$300</td>
<td>$300</td>
<td>$200 - 300</td>
<td>$20 – 30 generic $40 – 80 Coumadin</td>
</tr>
</tbody>
</table>
Antidotes

No standard antidote

- Factor VIIa (theoretical)
  - Cost: ~$10,000 for single 90 µg/kg dose in 80 kg pt
- Prothrombin complex concentrate (PCC) (theoretical)
  - Usefulness in clinical settings not yet established
- Fresh frozen plasma
  - Short-term reversal, short half-life of 3-5 hours
- Activated charcoal ????

- Investigational agent PRT064445: designed to reverse the actions factor Xa inhibitors.
- Dabigatran - Maintain adequate diuresis; 60% is dialyzable

Antidote(s)

“The drug industry has spent years developing a drug that we could take orally that you don’t have to measure, and all we want to do is measure it. We would like to know just how much anticoagulant effect is present, and if our reversal strategies are working”

Mark Cipolle, MD
Medical Director trauma and neurocritical care,
Christiana Care Health System
Wilmington, DE
Apples-to-Oranges
Problems with comparing new drugs

- Differences between the trial designs
  - RE-LY open label / ROCKET & ARISTOTLE blinded

- Patient Populations
  - Dabigatran - Mean age 82, mean CHADS$_2$ score 2.1
    - (31% having a score of 0 or 1)
  - Rivaroxaban Mean age 73, mean CHADS$_2$ score 3.5
  - Apixaban Median age 70, mean CHADS$_2$ score 2.1

- Warfarin comparators – Time in therapeutic range (INR)
  - RE-LY (dabigatran) 64%, ROCKET (rivaroxaban) 57.8%, ARISTOTLE (apixaban) 62%

- End points
  - Rivaroxaban – many events occurred post ROCKET when pts crossed back to warfarin

Summary: Limitations of New Agents

- No monitoring
  - Unable to titrate dose
  - Treatment failure vs. poor compliance ???

- Short $t_{1/2}$
  - Poor compliance may affect efficacy more than VKA

- No antidote

- Renal / hepatic dose adjustments likely required

- High Cost

- Lack “real life” data & post-marketing surveillance
  - No long term (greater than 2yr) follow up
  - Providers lack experience with their use
Remember

- Patients already taking warfarin with excellent INR control (and good tolerability) may have little to gain in switching to a newer agent.
- A bad (poorly compliant) warfarin patient makes for a very bad dabigatran or apixaban patient. Twice daily dosing – short half-life is not forgiving of missed doses and . . . . a bad (poorly compliant) warfarin patient may make for a bad rivaroxaban patient. Once daily dosing may improve adherence over other agents but shorter half-life (than warfarin) is not forgiving of missed doses.

Conversions from Warfarin

- **Dabigatran and Apixaban**
  - Discontinue warfarin - initiate when INR <2.0
- **Rivaroxaban** –
  - Discontinue warfarin – initiate when INR falls to <3.0
Antiplatelet Drugs

<table>
<thead>
<tr>
<th>Antiplatelet Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
</tr>
<tr>
<td>ADP receptor</td>
</tr>
<tr>
<td>ReoPro</td>
</tr>
<tr>
<td>Aggrestat Integralin</td>
</tr>
<tr>
<td>Integralin</td>
</tr>
<tr>
<td>Ticagrelor</td>
</tr>
<tr>
<td>Dipyramide</td>
</tr>
<tr>
<td>Ca++</td>
</tr>
<tr>
<td>Ticlopidine</td>
</tr>
<tr>
<td>Clopidogrel</td>
</tr>
<tr>
<td>AA</td>
</tr>
<tr>
<td>cyclooxygenase</td>
</tr>
<tr>
<td>TxA2</td>
</tr>
<tr>
<td>Collagen</td>
</tr>
<tr>
<td>VWF</td>
</tr>
</tbody>
</table>
Endothelium

**Why Low Dose ASA?**

TxA₂ (Thromboxane)
- Increases calcium flux
  - Adhesion
  - Aggregation
  - Vasoconstriction

PGI₂ (Prostacyclin)
- Increases cAMP
  - Prevents Adhesion
  - Prevents Aggregation
  - Vasodilation

---

Endothelium

**No nucleus**

No new protein synthesis (ie., cyclooxygenase) for life of platelet

Nucleated Cells
- Produce mRNA
- Synthesize new cyclooxygenase
- Continue to make beneficial PGI₂
Aspirin

- Antiaggregation occurs within 1hr
- Side Effects: allergy, GI discomfort, GI bleed
- OTC, easy to crush, inexpensive, small tablet, enteric coated available to decrease stomach upset
- Remember: effect on cyclooxygenase is irreversible. It will take at least 7 - 8 days after stopping therapy to completely restore platelet function
- Potential issues: Bleeds, aspirin “resistance”

Aspirin Dosing

- 81 mg dose usually works as well as higher doses (ie., 325 mg)
  - even after an acute coronary syndrome, stent, or ischemic stroke.
- Higher doses can double the risk of GI bleeding
- Newer guidelines endorsing the lower aspirin doses *(75 – 100 mg)*
- Continue use of 162 to 325 mg for the FIRST DOSE for an acute MI or ischemic stroke.
“aspirin resistance”

- On average 15% to 25% of individuals will be aspirin-resistant (ie, lack of the anticipated antiplatelet response when taking aspirin).
  - Largest meta-analysis included 42 studies and reported a 27% rate of aspirin resistance.
  - Attributed primarily to increased platelet turnover with reappearance of new platelets with intact COX-1

- Reduced bioavailability of aspirin
  - poor compliance
  - Reduced absorption / increased metabolism

- Altered binding to COX-1
  - Concurrent use of other non-steroidal anti-inflammatory drugs possibly preventing the access of aspirin to COX-1 binding site

- Other sources of thromboxane production
  - Biosynthesis of thromboxane by pathways that are not blocked by aspirin (ie., COX-2 in monocytes, macrophages, vascular endothelial cells)
“aspirin resistance”

- **Alternative pathways of platelet activation**
  - Platelet activation by pathways that are not blocked by aspirin (eg. collagen, ADP, epi, thrombin)
  - Increased platelet sensitivity to collagen and ADP

- **Increased turnover of platelets**
  - Increased production of platelets by bone marrow in response to stress (ie., post surgery like CABG) or increased peripheral consumption by injured blood vessels (ie., DM, CAD, tobacco use)

- **Non-atherothrombotic vascular events**
  - Embolism from heart or DVT, tumors, prostheses

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**Thienopyridine ADP receptor inhibitors**

- **clopidogrel**
  - 2 steps
  - CYP 2C19
  - CYP 3A4

- **prasugrel**
  - Forms disulfie bound

- **Platelet**
  - ADP P2Y_{12} receptor

- **Genetics**
  - PPIs
Clopidogrel

- Once daily – generic available (finally)
- Onset: 4-6 hours (after loading dose with 8 x maintenance dose)
- Offset: 5-7 days
- Variable response: 25-30% of patients achieve less than 25% inhibition of platelet activity
- Must undergo 2 step metabolism (CYP3A4 mediated) to active agent
- Binds irreversibly to P2Y<sub>12</sub> receptor
- Postulated but unproven interaction with PPIs.

Pharmacogenetics and clopidogrel

- CYP2C19 defective genotypes, particularly CYPC19*2, are common with frequencies ranging from:
  - 20 to 30% in Caucasians
  - 30 to 45% in African-Americans
  - up to 50 to 65% in East Asians
- Genetic Testing?
  - Genotype does not always correlate with phenotype
  - Difficult to predict outcome
Clopidogrel and PPI: Summary

- Retrospective data suggest an interaction between clopidogrel and PPIs, with more than a 30% increase in the risk for poor cardiovascular outcomes.
- Prospective data suggest the opposite, that adding a PPI to clopidogrel may not increase the risk for cardiac events and also strengthens the evidence that adding a PPI to clopidogrel plus aspirin reduces GI events.
- If PPI is warranted, use of pantoprazole recommended, or H-2 antagonists.

Prasugrel

- Approved for the reduction of thrombotic cardiovascular events (including stent thrombosis) in pts with ACS who are managed with an artery-opening procedure known as percutaneous coronary intervention (PCI).
- In clinical trials (TRITON-TIMI 38) prasugrel was associated with:
  - Significantly reduced rates of ischemic events, including stent thrombosis.
  - An increased risk of major bleeding, including fatal bleeding.
- Overall mortality did not differ significantly between treatment groups.
Prasugrel vs Clopidogrel

- Differences exist in the efficacy of clopidogrel and prasugrel
- The higher efficacy of prasugrel is related to:
  - simpler metabolism
  - more rapid conversion to active metabolite
  - lack of influence of genetic variability
- Also may explain greater risk of bleeding with prasugrel
- HOWEVER – CYP3A4 may be involved and strong inhibitors may prevent conversion to active form!

TRILOGY ACS study, 2012

- Prasugrel 10 mg daily vs clopidogrel 75 mg daily
- In patients with acute coronary syndromes selected for a final treatment strategy of medical management without revascularization within 10 days after the index event
- Results: No better than clopidogrel
- Prasugrel is not currently recommended for ACS patients undergoing conservative, noninvasive (medical) management.
**Ticagrelor (Brillinta)**

- Reversible inhibitor of Platelet ADP receptor
  - Doesn’t require P450 activation
  - Less likelihood of interaction
  - Less likelihood of genetic variations in efficacy
  - Easier to titrate

Compared with clopidogrel, ticagrelor provided earlier onset and more consistent and more pronounced platelet aggregation (PLATO Trials)

**Ticagrelor Mechanism**

[Diagram showing the mechanism of action of ticagrelor]
**Ticagrelor (Brilinta)**

- Indicated for patients who have experienced an ACS requiring anticoagulation for prevention of thrombotic events
- Compared to clopidogrel, ticagrelor is associated with fewer thrombotic events, MI, and overall mortality (PLATO)
- However, ticagrelor is associated with increased risk of major bleeding and **dyspnea** (10 – 14 %)

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**Ticagrelor (Brilinta)**

- Dose is 90 mg bid (after 180 mg loading)
- Administered with aspirin within the range of 75 – 100 mg once daily
  - Aspirin > 100 mg: decreased ticagrelor effect
- CYP3A4 substrate
  - Avoid with concomitant inhibitors / inducers
Comparing the antiplatelet drugs

**Clopidogrel**
- Generic
- Once daily dosing
- With or without ASA
- Irreversible inhibition
- Prodrug
  - Requires CYP activation
  - caution with PPIs
- Genetic polymorphism

**Ticagrelor**
- Brand ($$)
- Bid dosing
- ASA required
- Reversible
- Active drug
  - No metabolism necessary
- Cleared by CYP3A4
  - Potential for drug interactions
- No genetic variability

Questions?
Thanks for listening.

Alan

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