THE NEW GENERATION OF ORAL ANTICOAGULANTS

Joseph Sweeney MD FACP FRCPA
Director, Transfusion Medicine and Coagulation
Lifespan Academic Medical Center
Professor of Pathology and Laboratory Medicine,
Warren Alpert School of Medicine at Brown University
OBJECTIVES

• Describe newer anticoagulants
• Describe tests which detect drug presence
• Describe the wash-out periods
• Outline reversal in urgent situations
OLDER GENERATION ANTICOAGULANTS

• Heparin:
  – Isolated from liver (hepar) as an anticoagulant (1926)
  – Use as an anticoagulant since the 1940s
  – Current sources are bovine lung and porcine mucosa
  – Antidote: protamine sulphate

• Warfarin
  – Sweet clover disease (1920s): vitamin K 1930s
  – Hydroxycoumarins synthesized in 1940s (Wisconsin Alumni Research Foundation)
  – Antidote: vitamin K

• Aspirin
  – Synthesized in 1897 (Acetyl- Spirea Ulea)
  – Anticoagulant function recognized in 1970s
  – Antidote: allogeneic platelet transfusion
MONITORING OF THE OLDER GENERATION ANTICOAGULANTS

• Heparin:
  – aPTT
  – Thrombin Time
  – Heparin assay

• Warfarin
  – PT/INR
  – Factor X

• Aspirin
  – Bleeding time
  – Aggregometry

• The older anticoagulants have been in use for 40-60 years

• The tests used to measure their effect have been in use for 60–100 years
HEPARIN

• Initially derived from liver (hence “hepar”)
• Mostly extracted form
  – Porcine gastro-intestinal mucosa
  – Bovine lung
• Partially purified
• Only about 1/3 has anticoagulant activity
• Dosed in USP units (US Pharmacopeia)
NORMAL PLASMA SPIKED WITH HEPARIN

\[ y = 273.37x + 11.691 \]
\[ R^2 = 0.9812 \]
HEPARIN ANTI-Xa SCATTERGRAM

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WHY NEWER ANTICOAGULANTS?

• Therapeutically, unfractionated heparin is optimally used as an IV infusion and needs dosage adjustment: SC administration requires BID or TID dosing. This is awkward.
  – HIT is becoming an unacceptable adverse event
• Warfarin has a poor therapeutic ratio and needs monitoring. Genetic polymorphisms and food and drug interactions create problems with dose prediction
• ASA provides weak prophylaxis for VTE and, in itself, not adequate for the prophylaxis of many arterial events
NEWER ANTICOAGULANTS

NOAC = Non Vitamin K antagonist Oral AntiCoagulants

• Synthesized chemicals with a more defined and predictable action
• Targeted to affect a specific enzyme, a specific receptor, or some aspect of intracellular signal-response transduction
• Monitoring unavailable/cumbersome at present
• Specific antidotes not available
NEWER ANTICOAGULANTS WHICH EFFECT CLOTTING
NEW ANTICOAGULANTS

- Drugs that inhibit thrombin formation or thrombin activity:
  - Anti-IIa
    - Intravenous direct thrombin inhibitors
    - Dabigatran etexilate (Pradaxa®)
  - Anti-Xa
    - Indirect
      - idraparinux
    - Direct
      - Rivaroxaban (Xarelto®)
      - Apixaban (Equilis®)
      - Edoxaban (Luxiana)
- Newer antiplatelet agents
  - Thienopyridines
    - Prasugrel (Effient®)
  - Non-thienopyridines
    - Ticagrelor (Brilinta®)
NEWER ANTICOAGULANTS

Direct Thrombin Inhibitors (DTI)
- Intravenous
- Oral
PARENTERAL DIRECT THROMBIN INHIBITORS: PRIMARILY USED IN HIT

lepirudin  argataban  •bivalirudin
NEWER ORAL ANTICOAGULANTS

Thrombotic Challenges

• NVAF: 6 million in the US increasing to 12 million by 2050
• Primary prophylaxis in THA/KA: 1 million increasing to 2 million by 2050
• Acute VTE: acute treatment and extended duration secondary prophylaxis: 330,000/year
• Mechanical valves: No role at present
• Other scenarios: No role at present

Studies

• 2009-2013: Several Phase III studies involving 70,000 patients in SPAF
• 2008-2014: 30 Phase III involving 170,000 patients in total for both SPAF and VTE
• Six different indications
### NEWER ORAL ANTICOAGULANTS

**Stroke prevention in atrial fibrillation**

<table>
<thead>
<tr>
<th>Stroke prevention in atrial fibrillation</th>
<th>Acute coronary syndromes</th>
<th>Primary VTE prevention (orthopaedic surgery)</th>
<th>Primary VTE prevention (medically ill)</th>
<th>Initial treatment of VTE</th>
<th>Extended treatment of VTE</th>
</tr>
</thead>
<tbody>
<tr>
<td>dabigatran RE-LY</td>
<td>dabigatran RE-MODEL RE-MOBILIZE RE-NOVATE RE-NOVATE II</td>
<td>dabigatran RE-COVER RE-COVER II</td>
<td>dabigatran RE-COVER RE-MEDY</td>
<td>dabigatran RE-COVER II</td>
<td>dabigatran RE-COVER II</td>
</tr>
<tr>
<td>rivaroxaban ROCKET AF</td>
<td>rivaroxaban RECORD I RECORD II RECORD III RECORD IV</td>
<td>rivaroxaban MAGELLAN</td>
<td>rivaroxaban EINSTEIN-DVT EINSTEIN-PE</td>
<td>rivaroxaban EINSTEIN-Extension</td>
<td>rivaroxaban EINSTEIN-Extension</td>
</tr>
<tr>
<td>apixaban AVERROES ARISTOTLE</td>
<td>apixaban APPRAISE-2</td>
<td>apixaban ADVANCE I ADVANCE I ADVANCE III</td>
<td>apixaban ADOPT</td>
<td>apixaban AMPLIFY</td>
<td>apixaban AMPLIFY-Extension</td>
</tr>
<tr>
<td>edoxaban TIMI 48-ENGAGE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

VTE, venous thromboembolism. *Studies with the oral thrombin inhibitor ximelagatran are not included since the drug was withdrawn from market in 2006.

Schulman S: Thromb Haemostas 2014. 111: 575-582
Dabigatran etexilate (Pradaxa®)

- March 18th 2008: EMA granted marketing approval for dabigatran for VTE thromboprophylaxis for hip or knee replacement and VTE thromboprophylaxis in NV AF
- June 10th 2008: Health Canada granted a Notice of Compliance for use of dabigatran as VTE thromboprophylaxis for hip or knee replacement
  - October 2010: NOC for VTE thromboprophylaxis in NVAF
- October 19th 2010: FDA approved dabigatran for VTE thromboprophylaxis in NV AF
Dabigatran etexilate (Pradaxa®)

- Two doses 110 mg and 150mg but only the 150mg tablet available in the US
  - Recently 75 mg introduced
- Requires low pH for absorption: peaks about 3 hours after oral intake
  - T1/2 is about 12-17 hours
- Excretion is renal: dose adjust to 75mg BID when CCR 15-30 mls /min

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RE-LY STUDY- VTE PROPHYLAXIS FOR NONVALULAR ATRIAL FIBRILLATION

![Graph showing study results](image)

**Patients at risk**

<table>
<thead>
<tr>
<th>Group</th>
<th>PRAD 110</th>
<th>PRAD 150</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRAD 110</td>
<td>6015</td>
<td>6076</td>
<td>6022</td>
</tr>
<tr>
<td>PRAD 150</td>
<td>5927</td>
<td>5940</td>
<td>5937</td>
</tr>
<tr>
<td>Warfarin</td>
<td>5862</td>
<td>5861</td>
<td>5862</td>
</tr>
</tbody>
</table>

**Time from randomization [months]**

- Warfarin
- PRADAXA 110mg bid
- PRADAXA 150mg bid

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Advantages

• Oral administration without laboratory test monitoring
• Fixed dosing - one size fits all
• Provides better VTE prophylaxis with the same number of bleeding events at the 150mg BID dose

Disadvantages

• Absence of an antidote
• Dyspepsia – 12 % vs 4% with warfarin
• Requires dose adjustment with renal failure
• Problem with major GI bleeding and all GI bleeding
• P-gp inhibitors increase levels – ketoconazole, quinidine, verapamil
• Concern regarding more AMI in patients taking dabigatran
• Overall expense ???
Dabigatran versus aPTT

Therapeutic Range
REVERSAL OF DIBIGATRAN

- Prothrombin exits in plasma at a concentration of about 1.4 µM
- Dabigatran in plasma has therapeutic levels of about 1.0 µM
  - The Kd of dabigatran for α-thrombin is 4.5 nM
- This means that nearly all α-thrombin active sites will be occupied by dabigatran.

- If we could raise the concentration of prothrombin to about 2.8 µM (100% increase)
- More than 50% of the α-thrombin active suites will be free to act on fibrinogen
- This would require about 3 liters of plasma or a PCC at a dose of about 100 U/kG
PROTHROMBIN COMPLEX CONCENTRATES (PCCs)

- Derived from large pools (> 10,000) of donors
- Primarily used historically to treat Hemophilia B (Factor IX deficiency) and interestingly Hemophilia A with inhibitors
- Contain variable amounts of FVII, FX and factor II
- Can be prothrombotic
- Traditional dosage is 25-50 units per kilogram
PROFILNINE AND KCENTRA

Vial Size:
- 500 IU
- 1000 IU
- 1500 IU

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PROTHROMBIN COMPLEX CONCENTRATES

<table>
<thead>
<tr>
<th>Proprietary Name</th>
<th>Manufacturer</th>
<th>FII</th>
<th>FVII</th>
<th>FIX</th>
<th>FX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Profilnine HT (500 U/vial)</td>
<td>Grifols</td>
<td>148</td>
<td>11</td>
<td>100</td>
<td>64</td>
</tr>
<tr>
<td>Kcentra (500 U/vial )</td>
<td>CSLBehring</td>
<td>111</td>
<td>57</td>
<td>100</td>
<td>150</td>
</tr>
</tbody>
</table>

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REVERSAL OF DIBIGATRAN


• Six healthy volunteers received dabigatran 150mg BID for 2.5 days
  – Prolonged the aPTT about two-fold (33.6 ± 3 to 59.4 ± 16 seconds)

• Received a bolus of saline versus PCCs at a dose of 50 U/Kg
  – Remeasured the aPTT

• After a washout period, repeated the same dose and received the alternative (PCCs or saline) with aPTT measurements

• The aPTT after PCC administration was 70 ± 15 seconds versus saline 60 ± 10
REVERSAL OF DIBIGATRAN

REVERSAL OF DIBIGATRAN

Zhou W et al: Stroke 2011; 42: December

- Mice were treated with dabigatran at 4.5 – 9 mg/Kg
- Experimental intracranial hematoma induced by collagenase injection
- 30 minutes later, mice received saline, mouse FFP, PCCs (100U/Kg) or rFVIIa
- Measured ICH volume
- Significantly reduced by PCCs consistently only at 100 U/Kg
  - Not by lower doses of PCCs or rFVIIa and minimally by plasma
REVERSAL OF DIBIGATRAN

Zhou W et al: Stroke 2011; 42: December

A

<table>
<thead>
<tr>
<th>TVBT (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
</tr>
<tr>
<td>Dabigatran</td>
</tr>
<tr>
<td>+ 25 U/kg PCC</td>
</tr>
<tr>
<td>+ 50 U/kg PCC</td>
</tr>
<tr>
<td>+ 100 U/kg PCC</td>
</tr>
</tbody>
</table>

B

<table>
<thead>
<tr>
<th>Hematoma volume (mm^3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
</tr>
<tr>
<td>Dabigatran</td>
</tr>
<tr>
<td>+ 25 U/kg PCC</td>
</tr>
<tr>
<td>+ 50 U/kg PCC</td>
</tr>
<tr>
<td>+ 100 U/kg PCC</td>
</tr>
</tbody>
</table>

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RECOMBINANT hFVIIa (NovoSeven)

Vial Sizes:
1000 mcg (1 mg)
2000 mcg (2 mg)
5000 mcg (5 mg)
ACTION OF rhFVIIa

rhFVIIa (NovoSeven) is a recombinant activated form of FVIIa. Dosing varies from 15 µG/Kg to 270 µG/Kg. Approved only for the treatment of Hemophilia A with inhibitors (90 µG/Kg) but most use is off-label. Suggested dose about 50 µG/Kg or about 5 mg as a rapid IV bolus.

NovoSeven has no clinically proven value in this context.
REVERSAL OF DIBIGATRAN

• For elective procedures
  – Minor- stop for 2 doses -24 hours
  – Major- stop for 4 doses -48 hours

• For urgent procedures
  – Check when last dose administered and perform a stat aPTT
    • aPTT is normal or near normal- absence of a drug effect
    • aPTT prolonged
      – Wait for several hours and repeat
      – Consider PCCs at 100 U/Kg
      – rFVIIa (NovoSeven) at 50 µg/Kg
NEWER ANTICOAGULANTS

Anti- Xa Inhibitors
Rivaroxaban (Xarelto®)

- September 2008: rivaroxaban approved for use as thromboprophylaxis in hip/knee replacement in both Canada and EU
- July 1st 2011: FDA approves for above indications
- November 4th 2011: approved VTE thromboprophylaxis for NV atrial fibrillation
- Effective T1/2 is about 17 hours but effect persists for 24 hours – once daily dosing
  - Prophylaxis 10 mg daily
  - Therapeutic 15 -20 mg daily
Rivaroxaban (Xarelto®)

Advantages

• RECORDS studies (hip/knee prophylaxis) have shown rivaroxaban to be superior to enoxaparin 40 mg daily
• ROCKET-AF study showed efficacy in Atrial fibrillation

Disadvantages

• Non fatal bleeding is increased in some reports with rivaroxaban at doses which show superior efficacy
• No clear antidote
• Monitoring is not recommended but the PT/INR is prolonged and can be used to detect a drug effect or anti-Xa assay
Rivaroxaban: Pharmacokinetics

- 20 mg od (CL_{CR} >50 mL/min)
- 20 mg od: 5th and 95th percentiles
- 15 mg od (CL_{CR} \leq 50 mL/min)
- 15 mg od: 5th and 95th percentiles
Rivaroxaban versus INR

Initial [rivaroxaban] (ng/mL)
Rivaroxaban versus Anti-Xa level

Typical drug concentrations from $C_{\text{trough}}$ to $C_{\text{max}}$
REVERSAL OF RIVAROXABAN


• Six healthy volunteers received rivaroxaban 20 mg daily for 2.5 days
  – Prolonged the PT (15.8 ± 1.3 v baseline 12.3 ± 0.7 seconds)
• Received a bolus of saline versus PCCs at a dose of 50 U/Kg
  – Remeasured the PT
• After a washout period, repeated the same dose and received the alternative (PCCs or saline) with PT
• The PT after PCC administration was normalized at 12.8 ± 1.0
REVERSAL OF RIVAROXABAN


Graph A:
- Rivaroxaban 20mg BID for two and a half days
- PCC or placebo infusion
- PT
- Time
- Baseline, 15 min, 30 min, 1h, 2h, 4h, 6h, 24h
- Placebo
- PCC

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REVERSAL OF RIVAROXABAN

• R-Antidote reported ( PRT064445)
  – Modified form of FXa ( truncated) which is devoid of enzymatic activity but has a binding site for the anti-Xa drugs
  – Competes with the active site of FXa for the anti-Xa drug

• Antibodies or F(ab)2 fragments with high affinity for the anti-Xa drug
REVERSAL OF RIVAROXABAN

• Discontinue the use for at least one, probably two, days
  – Measure for drug effect with the anti-Xa assay or the PT/INR, if the anti-Xa not available

• Urgent situations
  – PCCs at 50 U/Kg reverse the effect of rivaroxaban:
    • Prothrombin is present in plasma at about 1.4 µM but FX is present at about 0.17 µM
Apixaban (Eliquis®)

- DVT prophylaxis studies show apixaban to be of equivalent efficacy or superior with similar bleeding
- ARISTOTLE study (2011) showed superior efficacy to warfarin for VTE prophylaxis in NV AF with less bleeding
- Received FDA approval for SPAF on 12/28/2012
  - Dosing at 5mg twice daily
- Approved for primary VTE thromboprophylaxis in surgery – 3/14/2014
Apixaban (Eliquis®)

Approved by FDA for NVAF on 12/28/2012
Apixaban: Pharmacokinetics
Apixaban:INR
Apixaban: Anti-Xa

Typical drug concentrations from $C_{trough}$ to $C_{max}$
ARISTOTLE STUDY:
WARFARIN v APIXABAN

A Primary Outcome: Stroke or Systemic Embolism

No. at Risk
Apixaban      9120  8726  8440  6051  3464  1754
Warfarin      9081  8620  8301  5972  3405  1768

B Major Bleeding

No. at Risk
Apixaban      9088  8103  7564  5365  3048  1515
Warfarin      9052  7910  7335  5196  2956  1491

Hazard ratio, 0.79 (95% CI, 0.66–0.95)
P=0.01

Hazard ratio, 0.69 (95% CI, 0.60–0.80)
P<0.001

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**ARISTOTLE STUDY**

<table>
<thead>
<tr>
<th>End point</th>
<th>Apixaban (%/year)</th>
<th>Warfarin (%/year)</th>
<th>HR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcome</strong>*</td>
<td>1.27</td>
<td>1.60</td>
<td>0.79 (0.66-0.95)</td>
<td>0.01</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>2.13</td>
<td>3.09</td>
<td>0.69 (0.60-0.80)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>3.52</td>
<td>3.94</td>
<td>0.89 (0.80-0.99)</td>
<td>0.047</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>0.24</td>
<td>0.47</td>
<td>0.51 (0.35-0.75)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ischemic/uncertain stroke</td>
<td>0.97</td>
<td>1.05</td>
<td>0.92 (0.74-1.13)</td>
<td>0.42</td>
</tr>
</tbody>
</table>

*Primary outcome: Ischemic or hemorrhagic stroke or systemic embolization*
REVERSAL OF APIXABAN

• Discontinue use for probably two days
  – Measure for drug effect with the anti-Xa assay
• Urgent situations
  – ? PCCs at 50 U/Kg
Edoxaban (Lixiana)

- Approved in Japan for primary Thromboprophylaxis in Orthopedic surgery in July 2011
  - Once daily dosage: 60mg or 30mg
  - Two trials on SPAV and VTE Rx published in 2013 in N Eng J Med
  - ? Approval in 2015
Edoxaban (Lixiana)

**SPAF STUDY**
Edoxaban at 30mg (low dose) or 60mg (high dose) once daily

**VTE STUDY**
Edoxaban at 60mg once daily or 30mg if CC 30-50ml/min or low body weight (62Kg)

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New Anti-Xa drugs

- rivaroxaban
- apixaban
- edoxaban
## DRUG COMPARISON

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug/prodrug</td>
<td>Prodrug (dabigatran etexilate)</td>
<td>Drug</td>
<td>Drug</td>
<td>Drug</td>
</tr>
<tr>
<td>Bioavailability</td>
<td>6%</td>
<td>Almost 100% for 10 mg, less for higher doses</td>
<td>50%</td>
<td>62%</td>
</tr>
<tr>
<td>Time to maximum effect ($t_{max}$)</td>
<td>1.5–2 h</td>
<td>2 h</td>
<td>3–4 h</td>
<td>1–2 h</td>
</tr>
<tr>
<td>Half-life ($t\frac{1}{2}$)</td>
<td>12–17 h</td>
<td>5–9 h*</td>
<td>8–15 h</td>
<td>9–10 h</td>
</tr>
<tr>
<td>Plasma protein binding</td>
<td>35%</td>
<td>92–95%</td>
<td>87%</td>
<td>40–59%</td>
</tr>
<tr>
<td>Renal elimination of active drug</td>
<td>80%</td>
<td>33%</td>
<td>25%</td>
<td>35–39%</td>
</tr>
<tr>
<td>Interactions mediated by</td>
<td>P-gp</td>
<td>P-gp, CYP3A4</td>
<td>P-gp, CYP3A4</td>
<td>P-gp, (CYP3A4)</td>
</tr>
<tr>
<td>Food effect</td>
<td>Absorption delayed, not reduced</td>
<td>Required for absorption of doses &gt;10 mg</td>
<td>Not reported</td>
<td>No</td>
</tr>
</tbody>
</table>

P-gp, P-glycoprotein or permeability glycoprotein; CYP, cytochrome P450. *In elderly, the candidate population, the $t\frac{1}{2}$ is 11–13 h.

Schulman S: Thromb Haemostas 2014. 111: 575-582
<table>
<thead>
<tr>
<th>Drug Interaction Category</th>
<th>Dabigatran</th>
<th>Rivaroxaban, edoxaban, apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>P-glycoprotein inhibitors</strong> (amiodarone, phenothiazin, carboxylic acid, azole antifungals, verapamil, antimalarial, cyclosporine, thioxanthenes)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>P-glycoprotein inducers</strong> (dexamethasone, rifampicin, St. John’s Wort)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>CYP3A4 inhibitors</strong> (phenothiazin, carboxylic acid, azole antifungals, verapamil, erythromycin, telithromycin, nefazodone, antimalarial, cyclosporine, thioxanthenes)</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>CYP3A4 inducers</strong> (carbamazepine, efavirenz, nevirapine, phenytoin, phenobarbitone, rifabutin, rifapentine, rifampicin, St. John’s Wort, alcohol, eucalyptol)</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>NSAIDS</strong> (aspirin, naproxen, diclofenac)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Antiplatelet agents</strong> (clopidogrel)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

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WARFARIN OR NOAC?

• Predicted dose of WARFARIN

\[
\ln(\text{Dose}) = 1.35 - 0.008 \text{ Age (years)} - 0.116 \text{ (Gender)} + 0.004 \text{ (Weight, lbs)} - 0.376 \text{ (VKORC1 TT)} - 0.271 \text{ (VKORC1 TC)} - 0.307 \text{ (2C9*2)} - 0.318 \text{ (2C9*3)}
\]
WARFARIN OR NOAC?

• Warfarin Experienced:
  – Occurrence of ICH
  – Unstable INR *unrelated* to poor adherence
  – Geography or venous access
  – Frequent use of antibiotics

• Warfarin naïve:
  – Insurance dependent
  – Group O
  – Asian or Asian descent
  – Trial of warfarin with low time in therapeutic ratio
WHICH NOAC DRUG SHOULD I USE?

• Reduce risk of ischemic stroke in AF:
  – Dabigatran 150 mg BID (Caution in elderly)

• Minimize risk of bleeding (esp ICH):
  – Apixaban 5 mg BID or dabigatran 110 mg BID

• Concern for ACS:
  – Apixaban or rivaroxaban

• History of dyspepsia:
  • Apixaban or rivaroxaban

• Dislike of twice daily regimen
  – Rivaroxaban or edoxaban
NEWER ANTICOAGULANTS

Anti-Platelet Drugs
MEMBRANE RECEPTORS

- \( \alpha_6 \beta_1 \) (Laminin)
- \( \alpha_1 \beta_1 \) (Collagen)
- \( \alpha_{IIb} \beta_3 \) (VWF & Fibrinogen)
- \( \alpha_v \beta_3 \) (Vitronectin)
- \( \alpha_{IIb} \beta_3 \) (GPIb-IX-V)
- \( \alpha_2 \beta_1 \) (Collagen)

- \( \alpha_2 \) adrenergic (Epinephrin)
- PAR1 (Thrombin)
- PAR4 (Thrombin)
- \( \alpha_5 \beta_1 \) (Fibronectin)

Low shear rates:
- (Thromboxan \( \Delta_2 \))
- GPIb-IX-V (vWF)

High shear rates:
- \( \alpha_{IIb} \beta_3 \)

ADP receptors:
- P2x1
- P2Y1
- P2T(AC)
MECHANISM OF ACTION OF COMMON ANTIPLATELET AGENTS

**Thienopyridines**
- clopidogrel (Plavix)
- ticlopidine (Ticlid)
- prasugrel (Effient)

**NonThienopyridines**
- ticagrelor (Brilinta)

ADP

- COX
- TxA₂
- P₂Y₁₂

Arachidonic Acid

Aspirin

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ADP RECEPTOR ANTAGONISTS

Normal

Plavix
VERIFYNOW DEVICE

• Measures Plavix effect:
  – PRU (purine responsive units) N > 195 PRU
  – % inhibition: Normal < 20%

• Measures ASA effect: Expressed in ARU (aspirin resistance units)
  – Normal > 550 ARU; ASA effect < 550 ARU
• Channels contain no platelet agonist (baseline), ADP to assess the presence or absence of an inhibitor effect and thrombin/TRAP to fully (maximally) aggregate the platelets.
Available 24/7: order as CPEFF
One blue top tube
RIH- 45560: TMH 34215

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NORMALS VERSUS PATIENTS ON PLAVIX
PLATELET TRANSFUSION TO ANTAGONIZE ANTI-P2Y12 DRUGS

PATIENT GIVEN CLOPIDOGREL REQUIRING ABDOMINAL EXPLORATION

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**Graph Description**

- **Y-axis (PRU):**
  - Normal - No Inhibition: 200.0
  - Abnormal: 150.0

- **X-axis (Hours):**
  - 0.0 to 14.0

- **Events:**
  - Platelet Transfusions
  - Arrows indicating increases

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PLATELET TRANSFUSION TO ANTAGONIZE ANTI-P2Y12 DRUGS

PATIENT GIVEN CLOPIDOGREL REQUIRING ABDOMINAL EXPLORATION

% INHIBITION

HOURS

Platelet Transfusions

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ADP INHIBITOR DRUGS

TICLOPIDINE

CLOPIDOGREL

PRASUGREL

TICAGRELOR

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prasurgrel (Effient®)

- February, 2009: Approved for use in the EU
- July 10th, 2009: Approved for use in ACS managed with PCI
- Prodrug, like clopidogrel, requires activation in the liver.
- TRITON-TIMI 38 study:
  - Prasugrel v clopidogrel
    - Efficacy better than clopidogrel (12.1% v 9.9%)
    - BUT bleeding a problem: (1.4% v 0.9% - all bleeds; 0.4% v 0.1% - fatal bleeds)
- Loading dose of 60mg
  - Maintenance dose of 10 mg/day

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NEWER THIENOPYRIDINES

- Prasugrel 60 mg
- Clopidogrel 300 mg

Brandt et al. ACC 2005.
REVERSAL OF PRASUGREL

• Requires a longer fall off period
  – 5 days for clopidogrel
  – 7 days for prasugrel

• DDAVP 0.4 µG/Kg in 50-100 mls saline over 20-30 minutes

• Platelet transfusion
PLATELET TRANSFUSION TO ANTAGONIZE ANTI-\(P_2Y_{12}\) DRUGS

PATIENT ON PRASUGREL WITH INTRACRANIAL BLEED

Platelet Transfusion

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PATIENT ON CLOPIDOGREL REQUIRING ABDOMINAL EXPLORATION
Ticagrelor (Brilinta®)

- December 3rd, 2010: Approved for use in EU
- July 20th, 2011: US FDA Approval for use in ACS or AMI with ST elevation
- Loading dose 180mg: maintenance 90mg daily
  - Taken with Aspirin in low dose – 81mg NOT 325mg
- PLATO study: clopidogrel v ticagrelor
  - Less mortality with ticagrelor (9.8% v 11.7%) but more bleeding (16.1% v 14.6%)
Ticagrelor binds to a contiguous site close to the P2Y12 receptor and is therefore a reversible non-competitive inhibitor of the receptor. This was hoped to cause a more rapid fall off in anti-platelet activity but this has not been fully realized.
Ticagrelor versus clopidogrel

IPA (%) Induced by 20uM ADP

- Ticagrelor 180 mg
- Clopidogrel 600 mg
- Placebo

Time (hour)

IPA (%) Induced by 20uM ADP

- Ticagrelor
- Clopidogrel
- Placebo

Time (day)
Ticagrelor Reversal

Patient on ticagrelor with active GI bleeding requiring 14 units of red cells
CONCLUSIONS

• Parenteral direct thrombin inhibitors:
  – Detect effect with aPTT
  – No antidote but have a short T1/2 so effect should be gone in a few hours

• Oral DTI (Pradaxa)
  – Detect effect with the aPTT
  – No antidote - need to wait at least 24, maybe 48 hours
  – Possibly reversed by PCCs at high dose – 100 U/Kg or rFVIIa (at least 50ug/kg)

• Oral anti-Xa (Xarelto, Equilis)
  – Detect effect with the anti-Xa assay
  • No antidote - need to wait at least 24, maybe 48 hours
  • PCCs at 50 U/Kg for urgent reversal

– P2Y12 inhibitors:
  • Detect effect using the VerifyNow test
  • Allow for fall-off (7 days for prasugrel; 5 days for ticagrelor)
  • DDAVP or platelet transfusion, or both, for urgent reversal

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Thank You

Email: jsweeney@lifespan.org

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