Reversal of Antiplatelet and Anticoagulant Therapy: What You Need To Know

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Community Blood Services
Indications For Antithrombotic Therapy

• Venous thromboembolic disease
  — Deep venous thrombosis (DVT)
  — Pulmonary embolism (PE)
  — Primary prophylaxis of DVT or PE
• Arterial thromboembolic disease
  • Prosthetic heart valves
  • Mitral valve disease, especially with atrial fibrillation
  • Congestive cardiomyopathies, especially with atrial fibrillation
  • Atrial fibrillation
  • Mural cardiac thrombi
  • Transient ischemic attacks
  • Stroke in evolution
• Disseminated intravascular coagulation
• Maintenance of patency of vascular grafts, shunts, bypasses
Rationale for Antithrombotic Therapy

Thrombogenesis

Vascular injury
Platelet adherence and activation
Thrombin generation and fibrin formation
Plasmin generation and fibrinolysis

Therapy

Reduce risk factors
Platelet inhibitors
Anticoagulants
Fibrinolytics

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HEMOSTATIC PROCESS

• Initiation and formation of the platelet plug

• Platelets become activated and recruit additional platelets and trigger the coagulation system

• Generation of fibrin that overlays the platelet plug

• Termination of clotting by antithrombotic control mechanisms as well as the fibrinolytic system
The functional response of activated platelet:

1. Adhesion

2. Activation and secretion

3. Aggregation

4. Procoagulant activity
The platelet and its interactions

Schematic drawing of the platelet (top figure), showing its alpha and dense granules and canalicular system. The bottom figure illustrates the platelet's major functions, including secretion of stored products, as well as its attachment, via specific surface glycoproteins (GP), to denuded epithelium (bottom) and other platelets (left).

VWF: von Willebrand factor; TSP: thrombospondin; PF4: platelet factor 4; PDGF: platelet derived growth factor; β-TG: beta thromboglobulin; ADP: adenosine diphosphate; ATP: adenosine triphosphate.

Courtesy of Steven Coutre, MD.
Antiplatelet drugs

- ADP antagonists (Thienopyridines)
  - Ticlopidine
  - Clopidogrel
  - Prasugrel

- COX inhibitors
  - Aspirin

- Phosphodiesterase inhibitors
  - Dipyridamole
  - Tirofiban
  - Eptifibatide
  - Abciximab

http://pharmacologycorner.com/antiplatelet-agents/
### COX-1 inhibitors (aspirin and nonsteroidal anti-inflammatory drugs; Table 1)

Table 1. Oral APAs

<table>
<thead>
<tr>
<th>Features</th>
<th>ASA</th>
<th>Clopidogrel</th>
<th>Prasugrel</th>
<th>Ticlopidine</th>
<th>Dipyridamole</th>
</tr>
</thead>
<tbody>
<tr>
<td>MOA</td>
<td>COX-1 ↓</td>
<td>P2Y12 ↓</td>
<td>P2Y12 ↓</td>
<td>P2Y12 ↓</td>
<td>PD ↓</td>
</tr>
<tr>
<td>Onset of action</td>
<td>Minutes</td>
<td>&lt;24 hr</td>
<td>&lt;24 hr</td>
<td>4-7 days</td>
<td>Slow</td>
</tr>
<tr>
<td>Steady state of inhibition</td>
<td>Hours</td>
<td>3-7 days</td>
<td>3-5 days</td>
<td>8-11 days</td>
<td>Hours</td>
</tr>
<tr>
<td>Half-life (hr)</td>
<td>0.5</td>
<td>7-8</td>
<td>7</td>
<td>12.5</td>
<td>13.5</td>
</tr>
<tr>
<td>Reversible (days)</td>
<td>3-5</td>
<td>5</td>
<td>5-9</td>
<td>7</td>
<td>?</td>
</tr>
<tr>
<td>Bleeding risk</td>
<td>+</td>
<td>+++</td>
<td>++++</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>PLT transfusion for urgent surgery</td>
<td>No</td>
<td>1 dose</td>
<td>1 dose</td>
<td>1 dose</td>
<td>No</td>
</tr>
<tr>
<td>Neurosurgery, eye surgery, or ICH</td>
<td>One dose</td>
<td>Two doses</td>
<td>Two doses</td>
<td>Two doses</td>
<td>One dose</td>
</tr>
<tr>
<td>Elective surgery</td>
<td>No wait</td>
<td>5 days</td>
<td>5 days</td>
<td>7 days</td>
<td>No wait</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>No</td>
<td>Rare—TMA</td>
<td>Unknown</td>
<td>Yes—TTP</td>
<td>No</td>
</tr>
</tbody>
</table>

MOA = mechanism of action; P2Y12 = adenosine diphosphate receptor; PD = phosphodiesterase; TMA = thrombotic microangiopathy.

**GPIIb/IIIa inhibitors (fibrinogen receptor antagonists; Table 2)**

**Table 2. Intravenous APAs: GPIIb/IIIa inhibitors**

<table>
<thead>
<tr>
<th>Features</th>
<th>Abciximab</th>
<th>Eptifibatide</th>
<th>Tirofiban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset of action</td>
<td>Immediate</td>
<td>Immediate</td>
<td>Immediate</td>
</tr>
<tr>
<td>Steady state of inhibition</td>
<td>Minutes</td>
<td>Minutes</td>
<td>Minutes</td>
</tr>
<tr>
<td>Half-life</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma</td>
<td>20-30 min</td>
<td>2.5 hr</td>
<td>1.4-1.8 hr</td>
</tr>
<tr>
<td>Receptor</td>
<td>days</td>
<td>2-4 hours</td>
<td>2-4 hours</td>
</tr>
<tr>
<td>Reversible</td>
<td>12-18 hours</td>
<td>&lt;4 hours</td>
<td>&lt;6 hours</td>
</tr>
<tr>
<td>Bleeding risk</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>PLT transfusion for bleeding</td>
<td>One dose</td>
<td>One dose</td>
<td>One dose</td>
</tr>
<tr>
<td>PLT transfusion for urgent surgery</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Neurosurgery or ICH</td>
<td>One dose</td>
<td>One dose</td>
<td>One dose</td>
</tr>
<tr>
<td>Elective surgery</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>Pseudo and true</td>
<td>True</td>
<td>True</td>
</tr>
</tbody>
</table>

MOA = mechanism of action.

Alternatives to plt transfusion
- DDAVP
- Recombinant Factor VIIa
# Anticoagulants

## OLD
- Warfarin
- Heparin
- LMWHs
- Fondaparinux
- Argatroban
- Bivalirudin

## NEW
- Dabigatran
- Rivaroxaban
- Apixaban
Warfarin

- PO
- Narrow therapeutic window
- Multiple food and drug interactions
- Unpredictable pharmacokinetic and pharmacodynamics
- Relatively slow onset and offset of action
- Requires regular coagulation monitoring and dose adjustment
Warfarin- Mechanism of Action

Warfarin blocks the conversion of vitamin K-dependent factors to their active forms, leading to the inhibition of blood clotting factors II, VII, IX, and X, as well as proteins C, S, and Z.

Warfarin Reversal

• The optimal method for correcting excess anticoagulation after the use of warfarin depends upon the degree of elevation of the INR and whether clinically significant bleeding is present
Warfarin Reversal

Vitamin K

• Promotes liver synthesis of functional clotting factors II, VII, IX and X

• Fat soluble, so effects can linger

• Extremely small risk of anaphylaxis with IV formulation
Warfarin Reversal- FFP

Advantages

• Widely available

• Contains all coagulation factors, along with fibrinogen

Disadvantages

• Compatibility testing

• Possible delay related to thawing

• Variable content of factors

• Risk of volume overload

• TRALI, allergic rxns, and infectious disease
Warfarin Reversal- PCCs

Advantages
• Rapid correction of INR
• Small infusion volume
• No blood type matching or thawing

Disadvantages
• Possible thrombogenic effects or DIC
• ? Availability among different institutions
Not All PCCs Are The Same

- 3 Factor PCCs
  Bebulin VH
  Profilnine SD

- 4 Factor PCCs
  KCentra
Reversal of Warfarin

Urgent (Not Bleeding)

- If procedure can be delayed 6-24 hrs, vit K 5-10 mg PO/IV; otherwise FFP or PCC prior to procedure and repeat INR.

Urgent (Bleeding)

- Vitamin K 5-10 mg IV; repeat every 12 hours as needed
- PCC or FFP
Reversal of Warfarin- FFP Dosing

- 10-20 ml/kg

- May need to repeat dose after 6 hours
# Reversal of Warfarin- PCC Dosing

<table>
<thead>
<tr>
<th>Pre-treatment INR</th>
<th>2 to &lt;4</th>
<th>4-6</th>
<th>&gt;6</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV Dose of Kcentra units/kg body weight</td>
<td>25</td>
<td>35</td>
<td>50</td>
</tr>
<tr>
<td>Maximum dose</td>
<td>2500</td>
<td>3500</td>
<td>5000</td>
</tr>
</tbody>
</table>
Reversal of Warfarin (cont)

• rFVIIa is NOT recommended as a solo agent to reverse warfarin

• FEIBA contains activated factors and is more likely to produce unwanted thrombosis than other agents
rFVIIa (Novoseven)

• FDA approved for congenital VII deficiency, pts with acquired inhibitors and hemophiliac with inhibitors

• MOA- direct activation of factor X on surface of platelets; provides thrombin necessary fibrin mesh formation
rFVIIa (Novoseven)

- Widely varied dosing 20-120 mcg/kg
- Short duration of action (half-life 2-3 hours)
- 1, 2 and 5 mg vials
- IV bolus 3-5 minutes
- Use within 3 hrs of reconstitution
- Thrombogenic potential (use with caution in CAD, DIC, recent cardiac surgery, h/o thrombosis, CVA, ECMO or VAD use)
Heparin

- Binds and activates ATIII
- Complex inactivates Xa and thrombin
- Half life 30-150 minutes (rate dependent)
- Monitor via PTT
LMWHs

• Binds to ATIII

• Complex inactivates Xa

• No effect on thrombin

• Half life 3-4 hour

• Monitor via Xa levels
Schematic representation of the actions of unfractionated heparin, low molecular weight (LMW) heparin, and the heparin pentasaccharide analog fondaparinux. Unfractionated heparin binds to antithrombin (AT) at the site of the native pentasaccharide sequence (shown as "S"), changing its conformation and converting it from a slow to a rapid inactivator of several coagulation factors, particularly factor Xa (yellow circle, left upper panel). However, in order to inactivate thrombin (Th, factor IIa, red circle), heparin must bind to thrombin and AT simultaneously, an effect that occurs only when the molecule exceeds 18 monosaccharide units (greater than 6000 daltons) (lower left panel). LMW heparins have a similar mechanism of action and retain the ability to inactivate factor Xa (right upper panel). However, they have a lesser effect on thrombin because most of the molecules are not long enough to simultaneously bind to thrombin and AT (right lower panel). Fondaparinux, which contains only a more highly modified (sulfated) pentasaccharide unit with higher antithrombin affinity than the native pentasaccharide, inactivates factor Xa, but cannot inactivate thrombin because of its extremely short length.

Protamine Dose for Reversal of Heparin and LMWH

- Maximum dose is 50 mg

- Heparin: 1 mg per 90-100 units heparin given in previous 2-3 hours

- LMWHs: 1 mg per 1 mg LMWH given in previous 8 hours
### “Older” Direct Thrombin Inhibitors

<table>
<thead>
<tr>
<th></th>
<th>Argatroban</th>
<th>Bivalirudin (Angiomax)</th>
<th>Desirudin (Iprivask)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Half Life</strong></td>
<td>45 mins</td>
<td>25 mins</td>
<td>60 min (IV)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>120 min (SC)</td>
</tr>
<tr>
<td><strong>Metabolism</strong></td>
<td>Liver</td>
<td>Liver</td>
<td>Kidneys</td>
</tr>
<tr>
<td><strong>Indications</strong></td>
<td>HIT; Prophylaxis and tx including pts undergoing PCI</td>
<td>- PCTA w/ unstable angina</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- PCI w/ GPIIb/IIIa inhibitor</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- HIT</td>
<td>- DVT prophylaxis prophylaxis for elective hip replacement</td>
</tr>
</tbody>
</table>
Reversal of “Older” Direct Thrombin Inhibitors

• No specific antidote exists

• Currently, discontinuation of drug plus application of locally directed hemostasis serve as the primary counter agent
Newer Anticoagulants

• Dabigatran (Pradaxa)

• Rivaroxaban (Xarelto)

• Apixaban (Eliquis)
The coagulation cascade and how the new oral anticoagulants block it.
Dabigatran (Pradaxa)

• Oral direct thrombin inhibitor which was approved by FDA in 2010

• Reducing the risk of stroke and systemic embolism in pts w/ non-valvular A-fib

• RE-LY study found that Pradaxa at dose 150 mg, as compared to warfarin, was associated with lower rates of stroke
Dabigatran (Pradaxa)

- More predictable pharmacokinetics
- No cytochrome p450 enzyme
- Same dosing for pts
- No monitoring
Rivaroxaban and Apixaban

• Work on Factor Xa

• Approved for A-fib and DVT prevention

• No need to monitor
<table>
<thead>
<tr>
<th>Feature</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prodrug</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Mode of action</td>
<td>Thrombin inhibition</td>
<td>Factor Xa inhibition</td>
<td>Factor Xa inhibition</td>
</tr>
<tr>
<td>Bioavailability</td>
<td>6%–8%</td>
<td>80%</td>
<td>50%</td>
</tr>
<tr>
<td>Time to peak</td>
<td>1.5–2 hours</td>
<td>2–3 hours</td>
<td>3 hours</td>
</tr>
<tr>
<td>Half-life</td>
<td>14–17 hours</td>
<td>7–11 hours</td>
<td>8–14 hours</td>
</tr>
<tr>
<td>Excretion</td>
<td>Renal (unchanged) &gt; 80%</td>
<td>Renal (half inactive) 66%</td>
<td>Renal 25%–30%</td>
</tr>
<tr>
<td></td>
<td>Bile 5%–10%</td>
<td>Feces 33%</td>
<td>Feces 56%</td>
</tr>
<tr>
<td>Plasma protein binding</td>
<td>35%</td>
<td>95%</td>
<td>87%</td>
</tr>
</tbody>
</table>

Data from references 13, 16, and 18.
**TABLE 2**

How long to delay elective surgery or procedures after last anticoagulant dose

<table>
<thead>
<tr>
<th>Anticoagulant drug</th>
<th>Creatinine clearance (mL/min)</th>
<th>Low-risk surgery</th>
<th>High-risk surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dabigatran</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 50</td>
<td>24 hours</td>
<td>2 days</td>
<td>2 days</td>
</tr>
<tr>
<td>31–50</td>
<td>4 days</td>
<td>4 days</td>
<td>4 days</td>
</tr>
<tr>
<td>≤ 30</td>
<td>6 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Rivaroxaban</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 30</td>
<td>24 hours</td>
<td>2 days</td>
<td>2 days</td>
</tr>
<tr>
<td>≤ 30</td>
<td>4 days</td>
<td></td>
<td>4 days</td>
</tr>
<tr>
<td><strong>Apixaban</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 30</td>
<td>24 hours</td>
<td>2 days</td>
<td>2 days</td>
</tr>
<tr>
<td>≤ 30</td>
<td>4 days</td>
<td></td>
<td>4 days</td>
</tr>
</tbody>
</table>

| *Examples include cardiac catheterization, diagnostic endoscopy, breast biopsy, and minor orthopedic procedures* |
| *Examples include cardiac surgery, vascular surgery, spinal or neurosurgery, and abdominal surgery* |
Coagulation Tests for Monitoring

• Normal thrombin time and normal aPTT implies no hemostatic dysfunction due to dabigatran

• Normal PT or undetectable anti-factor Xa activity would exclude hemostatic dysfunction due to rivaroxaban or apixaban
Bleeding Due to New Oral Anticoagulants

- General measures
  - D/C anticoagulant

- Volume resuscitation

- Monitor body temp, pH and electrolytes

- Periodically assess blood counts and coags

- Gastric lavage and activated charcoal if within 3 hours of dose
If bleeding is severe or life-threatening

• Consider multidisciplinary team care in ICU setting

• Mechanical compression of accessible sites

• Surgical interventions as appropriate

• Hemodialysis (only dabigatran)

• Off label use of nonspecific hemostatic agents
New Oral Anticoagulants

• No specific antidote/reversal strategy

• Unapproved and untested strategies may be required in patients with life-threatening bleeding

• Recommend that individual institutions review available data and implement guidelines for management
Nonspecific Reversal Agents

- FFP
- Recombinant factor VIIa
- 3 or 4 factor PCC
- Activated prothrombin complex concentrate (FEIBA NF)
Future Therapies

• Neutralizing, dabigatran-specific monoclonal antibody

• rFXa which would form complexes with and neutralize Xa inhibitor drugs
References


