Appendix

Antithrombotic: Reversal, Renal Dose Adjustments, and Surgery Considerations

Definition of Bleeding
Minor bleeding—any bleeding that is of concern
Major bleeding—any bleeding that requires transfusion, results in a significant hematocrit drop, hypotension, or in a critical area such as the brain or limb compartment.

Note on stopping agents for surgery—this applies only to procedures where it is thought that the risk of surgical related bleeding is greater than the risk of thrombosis.

PCC = Prothrombin Complex Concentrates

Antiplatelet Agents

Aspirin
Half-life: drug 15–30 min; antiplatelet effects up to 5 days
Renal Dosing: No change
Surgery: Hold 5 days before
Minor—Desmopressin 0.3 mcg/kg × 1
Major—Platelet transfusion—one pheresis unit or equivalent

Clopidogrel
Half-life: drug 8 h; antiplatelet effects up to 7 days
Renal Dosing: No change in dosing
Surgery: Hold 7 days before
Minor—Desmopressin 0.3 mcg/kg × 1
Major—Platelet transfusion—consider two pheresis units if life or brain threatening bleeding

Prasugrel
Half-life: drug 7 hr; antiplatelet effects up to 5 days
Renal Dosing: No change in dosing
Surgery: Hold 7 days before
Minor—Desmopressin 0.3 mcg/kg × 1
Major—Platelet transfusion—consider two pheresis units if life or brain threatening bleeding

Ticagrelor
Half-life: drug 9 h; antiplatelet effects up to 5 days
Renal Dosing: No change in dosing
Surgery: Hold 5 days
Minor—Desmopressin 0.3 mcg/kg × 1
Major—Platelet transfusion—consider two pheresis units if life or brain threatening bleeding

Sustained Release Aspirin/Dipyridamole
Half-life: 13 h (dipyridamole extended release formulation)
Renal Dosing: No change in dosing
Surgery: Hold 5 days
Minor—Desmopressin 0.3 mcg/kg × 1
Major—Platelet transfusion one pheresis unit

Abciximab
Half-life: 30 min
Renal Dosing: No change in dosing
Surgery: Hold 2 h
Major bleeding reversal—Platelet transfusion one pheresis unit

Eptifibatide
Half-life: 2–3 h
Renal Dosing: Decrease by 50 % if CrCl < 30 ml/min
Surgery: Hold 4–6 h
Minor—Desmopressin 0.3 mcg/kg × 1
Major bleeding reversal—Platelet transfusion—one pheresis unit plus infusion of 10 units of cryoprecipitate

Tirofiban
Half-life: 2 h
Renal Dosing: Decrease dose by 50 % if CrCl < 30 ml/min
Surgery: Hold 4–6 h
Minor—Desmopressin 0.3 mcg/kg × 1
Major—Platelet transfusion—one pheresis unit plus infusion of 10 units of cryoprecipitate

Vorapaxar
Half-life: 2–300 h
Renal Dosing: No change
Surgery: ?
Reversal: ?

Heparin and Heparin-Like Agents

Standard Heparin
Half-life: 30–150 min
Renal Dosing: No change in dosing—half-life may be 50 % longer
Surgery: Hold 4 h
Reversal for major bleeding: Protamine

<table>
<thead>
<tr>
<th>Time since last heparin dose (min)</th>
<th>Dose of protamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;30</td>
<td>1 unit/100 units of heparin</td>
</tr>
<tr>
<td>30–60</td>
<td>0.5–0.75 units/100 units of heparin</td>
</tr>
<tr>
<td>60–120</td>
<td>0.375–0.5 units/100 units of heparin</td>
</tr>
<tr>
<td>&gt;120</td>
<td>0.25–0.375 units/100 units of heparin</td>
</tr>
</tbody>
</table>

Infusion rate should not exceed 5 mg/min. Maximum dose is 50 mg per dose.

Low Molecular Weight Heparin
Half-life:
- Dalteparin: 3–4 h
- Enoxaparin: 4–5 h
- Nadroparin: 3–4 h
- Tinzaparin: 3–4 h
Renal Dosing: Decrease by 50 % if CrCl < 30 ml/min
Surgery: Hold 12 h
Reversal of major bleeding: Protamine:
4 h of dose: 1 mg of protamine for each 1 mg of enoxaparin or 100 units of other agents.
Repeat one-half dose of protamine in 4 h.
If 4–8 h after dose: give 0.5 mg for each 1 mg of enoxaparin or 100 units of other agents.

Fondaparinux
Half-life: 17–21 h
Renal Dosing: Not advised when CrCl < 50 ml/min
Surgery: Hold 24 h
Major bleeding reversal—Protamine ineffective—rVIIa (90 mcg/kg) may be of use

Argatroban
Half-life: 45 min
Renal Dosing: No change
Surgery: Hold 4 h
Major bleeding reversal: 4-factor PCC 50 units/kg

Bivalirudin
Half-life: 25 min
Renal Dosing: No change in bolus but change infusion:
- 30–59 ml/min CrCl: 1.75 mg/kg/h
- <30 ml/min CrCl: 1 mg/kg/h
On dialysis: 0.25 mg/kg/h
Surgery: Hold 2–4 h
Major bleeding reversal: 4-factor PCC 50 units/kg

Dabigatran
Half-life: 12–17 h
Renal Dosing: Dose reduce to 75 mg bid if CrCl < 30 ml/min and contraindicated if CrCl < 15 ml/min
Surgery:
- Normal renal function: Hold 24 h (48 h for surgery at high risk of bleeding)
- Impaired renal function—CrCl < 50 ml/min: Hold 48 h (72 h for surgery at high risk of bleeding)
Major bleeding reversal—4 factor PCC 50 units/kg, neutralizing antibody in development

Apixaban
Half-life: 12 h
Renal Dosing:
- Venous thrombosis—contraindicated it CrCl < 25
- Stroke prevention—50 % dose reduction if two out of the three: age over 80, creatine >1.5, weight less than 60 kg
Surgery: Hold 24 h for surgeries with low risk of bleeding and 48 h for surgeries with high risk
Major bleeding reversal l: 4-factor PCC 50 units/kg, antidote in development

Edoxaban
Half-life: 9–12 h
Renal Dosing:
- CrCl 30–60 ml/min 50 % dose reduction
- CrCl 15–30 ml/min 75 % reduction
Surgery: Hold 24 h for surgeries with low risk of bleeding and 48 h for surgeries with high risk
Major bleeding reversal: 4-factor PCC 50 units/kg, antidote in development

Rivaroxaban
Half-life: 5–9 h
Renal Dosing:
- Venous thrombosis: contraindicated CrCl < 30 ml/min
- Stroke prevention dose reduce to 15 mg/day CrCl 15–50 ml/min
Surgery:
- Normal renal function: Hold 24 h
Impaired renal function—CrCl < 50 ml/min: Hold 48 h
(72 h for surgery at high risk of bleeding)
Major bleeding reversal: 4 factor PCC—50 units/kg

Thrombolytic Therapy

Half-Life: All less than 30 min, tenecteplase is 22 min
Renal Dosing: No change
Surgery: Given short half-life would reverse coagulation defects
Major bleeding reversal: one platelet pheresis product, 2 units of plasma, and 10 units of cryoprecipitate. No value in infusing anti-fibrinolytic agents

Warfarin

Half-Life: 36 h
Renal Dosing: No change—consider lower starting dose
Surgery: Hold 5 days—see Chap. 25 about bridging considerations

Reversal:

**Not Bleeding: Goal is INR in 2–3 range**

<table>
<thead>
<tr>
<th>INR</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>3–4.5</td>
<td>Hold dose until INR decreased</td>
</tr>
<tr>
<td>4.5–10</td>
<td>1.25 mg Vitamin K PO</td>
</tr>
<tr>
<td>&gt;10</td>
<td>2.5–5 mg Vitamin K PO</td>
</tr>
</tbody>
</table>

Should see INR back in therapeutic range in 24–48 h

**Bleeding: Goal is INR under 2**

<table>
<thead>
<tr>
<th>INR</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>2–4.5</td>
<td>2.5 mg Vitamin K ± FFP (15 ml/kg)</td>
</tr>
<tr>
<td>4.5–10</td>
<td>5 mg Vitamin K ± FFP (15 ml/kg)</td>
</tr>
<tr>
<td>&gt;10</td>
<td>5–10 mg Vitamin K ± FFP (15 ml/kg)</td>
</tr>
</tbody>
</table>

*FFP Fresh Frozen Plasma*

Warfarin Life or Brain Threatening Bleeding:

4-factor PCC:
If INR 2–4: 25 units/kg (not to exceed 2500 units)
If INR 4–6: 35 units/kg (not to exceed 3500 units)
If INR > 6: 50 units/kg (not to exceed 5000 units)
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