2011 Clinical Practice Guide on Anticoagulant Dosing and Management of Anticoagulant-Associated Bleeding Complications in Adults

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Presented by the American Society of Hematology, adapted in part from the: American College of Chest Physicians Evidence-Based Clinical Practice Guideline on Antithrombotic and Thrombolytic Therapy (8th Edition).
I. ANTICOAGULANT DOSING

A. Subcutaneous Heparin Dosing for Treatment of Acute Venous Thromboembolism

General Considerations
1. Round weight-based dose to nearest prefilled syringe size.
2. No dose cap for obesity except dalteparin in cancer patients.
3. Consider monitoring anti-Xa heparin levels for weight >120 kg or <60 kg.
4. Repeat CBC day 7 to assess for heparin-induced thrombocytopenia.
   a. If heparin exposed in prior 6 months, CBC on day 3.
5. LMWH not recommended if creatinine clearance (CrCl) <30 ml/min.

Dosing
Enoxaparin: 1 mg/kg every 12 hours or 1.5 mg/kg daily
For cancer patients and those at high bleeding or thrombosis risk, favor twice-daily dosing
Dalteparin: 200 IU/kg daily
In cancer patients for long-term treatment: 200 IU/kg daily for 4 weeks (cap at 18,000 IU), then:
   a. ≤56 kg: 7,500 IU daily
d. >98 kg: 18,000 IU daily
c. 57-68 kg: 10,000 IU daily
e. 69-82 kg: 12,500 IU daily
Tinzaparin: 175 IU/kg daily
Fondaparinux: Daily dose: <50 kg: 5 mg.
   50-100 kg: 7.5 mg.
   >100 kg: 10 mg.
Unfractionated heparin: 333 IU/kg x 1, then 250 IU/kg every 12 hours

B. Initial Warfarin Dosing for Venous Thromboembolism or Atrial Fibrillation in Ambulatory Outpatients, Target INR 2.0-3.0

General Considerations
1. Obtain baseline PT/INR and investigate if abnormal.
2. Determine use of potential warfarin interacting medications.
3. Document target INR and prescribed warfarin tablet strength.
4. Provide patient education on safety, monitoring, drug and food interactions.
5. For acute thrombosis, overlap with heparin/LMWH/fondaparinux for 5+ days until INR therapeutic.
6. Recommend first INR check on day 3-4.

<table>
<thead>
<tr>
<th>Day</th>
<th>INR</th>
<th>DAILY DOSE</th>
<th>Day</th>
<th>INR</th>
<th>DAILY DOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-3</td>
<td>≤ 1.5</td>
<td>Increase by 15% of ADD</td>
<td>7 &amp; 10</td>
<td>≤ 1.5</td>
<td>Increase by 15% of ADD</td>
</tr>
<tr>
<td>1.6-1.9</td>
<td>Increase by 10% of ADD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.0-3.0</td>
<td>No Change</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.1-3.5</td>
<td>Decrease by 10% of ADD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.6-4.0</td>
<td>Decrease by 15% of ADD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 4.1</td>
<td>Hold 1 day, decrease by 15% (or more)†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 6.0</td>
<td>Consider Vitamin K†</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Abbreviations: ADD = average daily dose
* 2.0 mg for frailty, liver disease, malnutrition, drugs that enhance warfarin activity, or Asian ethnicity; 5-7.5 mg for young healthy patients
† Check INR more frequently

C. Chronic Warfarin Dose Adjustment in Non-Bleeding Patients

This nomogram is suggested for non-bleeding patients with target INR 2.0-3.0 who are out of range and who are not at high risk of bleeding.
1. If INR >3.0 confirm no bleeding.
2. Consider noncompliance, illness, drug interaction, or dietary change as reason for out-of-range INR.
3. Refer to nomogram.

II. ANTICOAGULANT REVERSAL

A. General Principles of Management of Anticoagulant-Associated Bleeding

HASHTI
1. Hold further doses of anticoagulant
2. Consider Antidote
3. Supportive treatment: volume resuscitation, inotropes as needed
4. Local or surgical Hemostatic measures: topical agents (aminocaproic acid, tranexamic acid)
5. Transfusion (red cells, platelets, FFP as indicated)
6. Investigate for bleeding source

Definitions Used for Reversal Situations
Non-urgent: Reversal is elective (procedures >7 days away)
Urgent (without bleeding): Reversal needed within hours
Urgent (with bleeding): Emergency reversal

B. Anticoagulant Reversal Agents

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose</th>
<th>Comments</th>
</tr>
</thead>
</table>
| Vitamin K        | 1-10 mg IV/PO, not SQ or IM | Infusion reactions rare; administer over 20-30 min
|                  |        | Takes 6 (IV) to 24 (PO) hours to reverse warfarin
|                  |        | Large doses can cause warfarin resistance on resumption |
| Protamine sulfate| 125-50 mg IV | Full reversal of unfractionated heparin
|                  |        | 60%-80% reversal of LMWH
|                  |        | No reversal of fondaparinux

*Consider 15% increase if INR ≤1.5 without explanation
## 1. Reversal of Warfarin (Coumadin®, Jantoven®)

### Non-Urgent
- Stop 5 days prior to procedure
- Check INR 1-2 days prior
  - If INR >1.5 administer vitamin K 1-2 mg PO

### Urgent (Not Bleeding)
- Hold further doses of dabigatran

### Urgent (Bleeding)
- Hold dabigatran and check aPTT
- HASHTI
  - Vitamin K 5-10 mg IV; repeat every 12 hours as needed
- Protamine sulfate
  - Consider adding FFP if 3-factor PCC used
- FFP or PCC; repeat every 12 hours as needed

### Abbreviations:
- PCC = prothrombin complex concentrates
- rFVIIa = recombinant factor VIIa
- HASHTI = Hemostasis Usually requires factor levels ~30% — Factor IX may only reach 20%
- **Non-Urgent:** Hold further doses of dabigatran
- **Urgent:** Hold dabigatran and check aPTT

### C. Converting Anticoagulants to and from Dabigatran

<table>
<thead>
<tr>
<th>Current Anticoagulant</th>
<th>Anticoagulant to be Converted to</th>
<th>Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin (INR 2-3)</td>
<td>Dabigatran</td>
<td>Discontinue warfarin and start dabigatran when INR &lt;2.0</td>
</tr>
</tbody>
</table>
| Dabigatran            | Warfarin (INR 2-3)              | CrCl >50 ml/min: start warfarin 3 days before stopping dabigatran
|                       |                                 | CrCl 31-50 ml/min: start warfarin 2 days before stopping dabigatran |
|                       |                                 | CrCl 15-30 ml/min: start warfarin 1 day before stopping dabigatran
|                       |                                 | CrCl <15 ml/min: no recommendation |
| LMWH, heparin         | Dabigatran                      | Start dabigatran 0-2 hours before administration of last heparin/LMWH dose, or at same time as discontinuation of infusional heparin |
| Dabigatran            | LMWH, heparin                   | CrCl ≥ 30 ml/min: start 12 hours after last dose of dabigatran
|                       |                                 | CrCl < 30 ml/min: start 24 hours after last dose of dabigatran |

### Abbreviations:
- CrCl = creatinine clearance
- INR = international normalized ratio
- LMWH = low-molecular-weight heparin
- *Pradaxa® product monograph, 2010*

### Agent

<table>
<thead>
<tr>
<th>Anticoagulant</th>
<th>Half-Life</th>
<th>Protamine Sulfate Dosing for Reversal</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Maximum dose is 50 mg</td>
</tr>
<tr>
<td>Heparin 1-2 hours</td>
<td></td>
<td>1 mg per 90-100 units heparin given in previous 2-3 hours</td>
</tr>
<tr>
<td></td>
<td></td>
<td>e.g., 25-35 mg if 1000-1250 units/hour heparin infusion</td>
</tr>
<tr>
<td>Enoxaparin 4.5 hours</td>
<td></td>
<td>1 mg per 1 mg Enoxaparin in previous 8 hours</td>
</tr>
<tr>
<td>Dalteparin 2.2 hours</td>
<td></td>
<td>1 mg per 100 units Dalteparin in previous 8 hours</td>
</tr>
<tr>
<td>Tinzaparin 3.9 hours</td>
<td></td>
<td>1 mg per 100 units Tinzaparin in previous 8 hours</td>
</tr>
</tbody>
</table>

### Footnotes:
- *Half-life is longer with subcutaneous administration for all agents so may require monitoring with PTT (heparin) or anti-Xa level (LMWH) every 3 hours with repeat protamine (0.5 mg per indicated amount of LMWH or heparin) if bleeding continues
III. Antiplatelet Agent Reversal

Aspirin, Dipyridamole/Persantine®, Aggrenox®, Clopidogrel/Plavix®, Ticlopidine/Ticlid®, Prasugrel/Effient®, Ticagrelor/Brilinta®

General Considerations

1. Half-lives
   a. Clopidogrel, ticlopidine, dipyridamole, prasugrel, ticagrelor: 7-10 hours
   b. Low-dose aspirin (150 mg daily): 2-4.5 hours
   c. Overdose aspirin (>4000 mg): 15-30 hours

2. Reversibility of anti-platelet effect
   a. Aspirin, clopidogrel, ticlopidine, and prasugrel inhibit platelet function for lifetime of platelet. Inhibition takes 7-10 days to resolve as new platelets are generated.
   b. Ticagrelor is a reversible inhibitor, so platelet function normalizes after drug clearance.

3. Circulating drug or active metabolites can inhibit transfused platelets.

4. Must consider indication for use in decision to reverse
   a. Risk of coronary stent occlusion (which can be fatal) within 3 months of bare metal stent implantation; period of risk is likely longer for drug-eluting stents.
   b. Consult cardiologist if uncertain.

Reversal of Antiplatelet Agents

<table>
<thead>
<tr>
<th>Non-Urgent</th>
<th>Urgent (Not Bleeding)</th>
<th>Urgent (Bleeding)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Discontinue agent 5-10 days prior to procedure</td>
<td>• Consider platelet transfusion prior to high risk bleeding procedures</td>
<td>• HASHTI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Platelet transfusion</td>
</tr>
</tbody>
</table>

About this Clinical Quick Reference Guide

This document summarizes selected recommendations from the: American College of Chest Physicians Evidence-Based Clinical Practice Guideline on Antithrombotic and Thrombolytic Therapy (8th Edition).

This guide is intended to provide the practitioner with clear principles and strategies for quality patient care and does not establish a fixed set of rules that preempt physician judgment.

Complete guidelines are available at:
Chest website: http://chestjournal.chestpubs.org/content/133/6_supp/110S.abstract
ASH website: www.hematology.org/practiceguidelines

For further information, contact the ASH Department of Government Relations, Practice, and Scientific Affairs at 202-776-0544.

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