4. Reversal of Dabigatran

Non-Urgent: Hold further doses of dabigatran
- **CCr > 50 ml/min**: Hold 1-2 days
- **CCr < 50 ml/min**: Hold 3-5 days
  Consider longer times for major surgery, placement of spinal or epidural catheter or port

Urgent:
- Hold dabigatran and check aPTT
- **Normal aPTT**: Likely dabigatran is not contributing to bleeding
- **Prolonged aPTT**: Dabigatran present and may be contributing to bleeding
- **HASHTI**: Reassess patient
- Repeat abnormal coagulation tests*

III. Antiplatelet Agent Reversal

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

General Considerations
1. Half-lives
   - **Clopidogrel, ticlopidine, dipyridamole, prasugrel, ticagrelor**: 7-10 hours
   - **Low-dose aspirin (150 mg daily)**: 2-4.5 hours
   - **Overdose aspirin (>4000 mg)**: 15-30 hours
2. Reversibility of anti-platelet effect
   - Aspirin, clopidogrel, ticlopidine, and prasugrel inhibit platelet function for lifetime of platelet. Inhibition takes 7-10 days to resolve as new platelets are generated.
   - 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
   - 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.
   - 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><strong>Discontinue agent 5-10 days prior to procedure</strong></td>
<td><strong>Consider platelet transfusion prior to high risk bleeding procedures</strong></td>
<td><strong>HASHTI</strong></td>
</tr>
</tbody>
</table>

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://chesonjournal.chestpubs.org/content/133/6_suppl/110S.abstract](http://chesonjournal.chestpubs.org/content/133/6_suppl/110S.abstract)
- ASH website: [www.hematology.org/practiceguidelines](http://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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Images courtesy of Kenneth Mann, PhD, and Matthew Whelihan, MS.

**Abbreviations:** CCl = creatinine clearance; INR = international normalized ratio; LMWH = low-molecular-weight heparin

*Pradaxa® product monograph, 2010

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

Mary Cushman, MD, MSc 1
Wendy Lim, MD, MSc, FRCP 2
Neil A Zakai, MD, MSc 1
1 University of Vermont
2 McMaster University

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.
5. If heparin exposed in >6 months, CBC in day 3.

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 3-5 days until INR therapeutic.

6. Recommend first INR check on day 3-4.

C. Chronic Warfarin Dosing 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 3.0-3.9 confirm no bleeding.
2. Consider noncompliance, illness, drug interaction, or dietary change as reason for out-of-range INR.

D. Dabigatran Dosing to Prevent Stroke and Embolism in Nonvalvular Atrial Fibrillation

C/O:CII>300 mg/m2: 150 mg orally, twice daily
C/O:CII 75-300 mg/m2: 110 mg orally, twice daily
C/O:CII 50-75 mg/m2: 75 mg orally, twice daily

* U.S. labeling, no recommendation for C/O:CII estimation or on dialysis

II. ANTICOAGULANT REVERSAL

A. General Principles of Management of Anticoagulant-Associated Bleeding

HASHTI

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

Definitions Used for Reversal Situations

Non-urgent: Reversal is elective (procedures in 7 days away)
Urgent (without bleeding): Reversal may be needed within 1-2 days
Urgent (with bleeding): Emergency reversal

B. Anticoagulant Reversal Agents

Agent | Comments
--- | ---
Protamine | Full reversal of unfractionated heparin
Vitamin K | Injection reactions rare; administer over 20-30 min
Protamine sulfate | * Half-life is longer with subcutaneous administration for all agents so may require monitoring with PTT
Recombinant factor VIIa (rFVIIa) | • Full reversal of unfractionated heparin
• 1 mg per 90-100 units heparin given in previous 8 hours
• Rapid INR correction in warfarin patients
Recombinant factor VIIa (rFVIIa) | • Full reversal of unfractionated heparin
• 1 mg per 90-100 units heparin given in previous 8 hours
• Large doses can cause warfarin resistance on reactivation
Prothrombin complex concentrate (PCC) | • Small volume infusion over 30-60 minutes
• Risk of thrombosis 1-4%
• Consider fibrinogen levels
Recombinant factor VIIa (rFVIIa) | • Small volume infusion over 30-60 minutes

1. Warfarin is no longer used with substitution administration for all agents so may require monitoring with PTT
2. Heparin or LMWH every 3 hours will reverse protamine (50 IU/kg) and indicate amount of LMWH or heparin bleeding continues

1. Reversal of Warfarin (Coumadin®, Jantoven®)

Non-Urgent | Urgent (Not Bleeding) | Urgent (Bleeding)
--- | --- | ---
• Stop 5 days prior to: 6-7 days, vitamin K 5-10 mg PO/IV, rFVIIa as indicated
• Check INR 1-2 days prior to: vitamin K 5-10 mg PO, rFVIIa as indicated
• INR >1.5: vitamin K 5-10 mg PO, rFVIIa as indicated
• INR >4.0: vitamin K 5-10 mg PO, rFVIIa as indicated

2. Reversal of Low-Molecular-Weight Heparins (Enoxaparin/Loxen®/Dalteparin/Fragmin®, Tinzaparin/Innohep®) and Fondaparinux® (Arixtra®)

Non-Urgent | Urgent (Not Bleeding) | Urgent (Bleeding)
--- | --- | ---
• Hold day of procedure if possible
• Onset 24 hours prior to procedure
• * Half-dose prior day
• * Once-daily regimens
• Hold evening dose day

3. Protonate Dose for Reversal of Heparin and LMWH

Agent* | Half-Life | Protonate Sulfate Dosing for Reversal
--- | --- | ---
Heparin | 2-3 hours | Maximum dose is 50 mg
Enoxaparin | 3-4 hours | 1 mg per 100-200 units heparin given in previous 3-2 hours
Dalteparin | 4-5 hours | * e.g. 25-50 mg if 1000-1500 units/hour heparin infusion
Tinzaparin | 3-4 hours | 1 mg per 1 mg Enoxaparin in previous 8 hours
Fondaparinux | 3-4 hours | 1 mg per 100 units Fondaparinux in previous 8 hours

REFERENCES

**Abbreviations:** ADD = average daily dose
**a** = mg for frailty, liver disease, malnutrition, drugs that enhance warfarin activity, or Asian ethnicity; **b** = mg/kg for young healthy patients
**c** = Check INR 3-4 times a day if possible
**d** = 25 mg for frailty, liver disease, malnutrition, drugs that enhance warfarin activity, or Asian ethnicity; 0-75 mg for young healthy patients
**e** = 25% for frailty, liver disease, malnutrition, drugs that enhance warfarin activity, or Asian ethnicity; 0-75 mg for young healthy patients
### 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.
5. If heparin exposed >6 months, CBC day 3.
6. LMWH not recommended if creatinine clearance (C-Cr) <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, factor Xa daily dosing

**Dalteparin**: 200 IU/kg daily

In cancer patients for long-term treatment: 200 IU/kg for 4 weeks (up at 18,000 IU, then: a. ≤55 kg: 350 IU/kg daily b. >68-87 kg: 200IU/kg daily c. >88.6 kg: 18,000 IU daily)

**Tinzaparin**: 175 IU/kg

**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. Obtain baseline PT/INR.
4. Consider monitoring anti-Xa heparin levels for weight >120 kg or <60 kg.
5. Local or surgical Hemostatic measures: topical agents (aminocaproic acid, tranexamic acid) or surgical or surgical
6. Provide patient education on safety, monitoring, drug and food interactions.

**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

**II. ANTICOAGULANT REVERSAL**

**A. General Principles of Management of Anticoagulant-Associated Bleeding**

**HASHTI**
1. Hold further doses of anticoagulant
2. Consider Anticoagulants
3. Supportive treatment: volume resuscitation, intropes 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

**B. Anticoagulant Reversal Agents**

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<td>1-10 mg IV (PO), not SQ or IM</td>
<td>Full reversal of unfractionated heparin; no reversal of LMWH</td>
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<td><strong>Protamine</strong></td>
<td>1Fondaparinux has no specific antidote</td>
<td>Reversal needed within hours</td>
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</table>

**Protamine sulfate** 125-500 mg IV

- Full reversal of unfractionated heparin
- **No reversal of fondaparinux**

**Platelets**

- **No reversal of fondaparinux**

**Frozen plasma** 10-30 mL/kg

- Rapid INR correction of warfarin patients

**Prothrombin complex concentrate** (PCC) 20-50 units/kg

- Rapid reversal of warfarin patients

**Heparin 1-2 hours**

- Reversal needed within hours

### II. ANTICOAGULANT REVERSAL

**A. General Principles of Management of Anticoagulant-Associated Bleeding**

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**Protamine sulfate** 125-500 mg IV

- Full reversal of unfractionated heparin
- **No reversal of fondaparinux**

**Platelets**

- **No reversal of fondaparinux**

**Frozen plasma** 10-30 mL/kg (1 unit = ~250 ml)

- Replacement of all coagulation factors, but cannot fully correct
- **Past episodic usage usually requires factor replacement**
- **Factor X may only reach 20%**
- **May need repeat dose after 8 hours**
- **Large volume, take hours to thrive**

**Prothrombin complex concentrate** (PCC) 20-50 units/kg

- **Rapid reversal of warfarin patients**
- Small volume infusion over 10-30 minutes
- Risk of thrombosis 1-2%
- **Consider adding FFP if 3-factor PCC used**

**Heparin 1-2 hours**

- **Reversal needed within hours**
- **May need repeat dose after 8 hours**
- **Large volume, take hours to thrive**

**Prothrombin complex concentrate** (PCC) 20-50 units/kg

- **Rapid reversal of warfarin patients**
- Small volume infusion over 10-30 minutes
- **Risk of thrombosis 1-2%**
- **Consider adding FFP if 3-factor PCC used**

**Recombinant factor VIIa (FVIIa)**

- **Rapid infusion of small volume**
- **Rapid reversal of warfarin, but may not correct bleeding because only restores FVIIa**
- **Risk of thrombosis 5-10%**
- **May need repeat dose after 2 hours**

### 1. Reversal of Warfarin (Coumadin®, Jantoven®)

**Non-Urgent**
- **Urgent (Not Bleeding)**
  - **Urgent**
  - **Non-urgent**
  - **Urgent**

**Non-Urgent**
- **Urgent (Not Bleeding)**
  - **Urgent**
  - **Non-urgent**

**2. Reversal of Low-Molecular-Weight Heparins (Enoxaparin, Cinrinova®, Dalteparin/Fragmin®, Tinzaparin/Innohep®) and Fondaparinux®**

**Non-Urgent**
- **Urgent (Not Bleeding)**
  - **Urgent**
  - **Non-urgent**

**3. Prothrombin Dose for Reversal of Heparin and LMWH**

**Agent** | Half-Life | Prothrombin Sulfate Dose for Reversal | **Maximum dose is 50 mg**
<table>
<thead>
<tr>
<th></th>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Heparin</td>
<td>1-2 hours</td>
<td>1 mg per 500 units heparin given in previous 2-3 hours</td>
<td></td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>3.9 hours</td>
<td>1 mg per 100 units Fondaparinux in previous 8 hours</td>
<td></td>
</tr>
</tbody>
</table>

**Adapted:** average daily dose

- **0.25 mg for frail, low dose, minimal risk drug that enhance warfarin activity or Asian ethnicity, 0.5-7.5 mg for young healthy patients

**1 Check INR twice daily frequency**
C. Chronic Warfarin Dosing Adjustment in Non-Bleeding Patients

<table>
<thead>
<tr>
<th>Day</th>
<th>INR DAILY DOSE</th>
<th>Day</th>
<th>INR DAILY DOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-2</td>
<td>0-1.0 1.0 mg</td>
<td>3 or 4</td>
<td>1.0-1.2 1.2 mg</td>
</tr>
<tr>
<td>3 or 4</td>
<td>1.0-1.3 1.3 mg</td>
<td>3 or 4</td>
<td>1.3-1.5 1.5 mg</td>
</tr>
<tr>
<td>4-6</td>
<td>1.5-1.8 1.8 mg</td>
<td>3 or 4</td>
<td>1.8-2.0 2.0 mg</td>
</tr>
<tr>
<td>7 &amp; 10</td>
<td>2.0-3.0 3.0 mg</td>
<td>3 or 4</td>
<td>2.0-3.0 3.0 mg</td>
</tr>
</tbody>
</table>

*Consider 15% increase in INR if INR < 1.5 without explanation

D. Dabigatran Dosing to Prevent Stroke and Embolism in Nonvalvular Atrial Fibrillation

<table>
<thead>
<tr>
<th>INR &gt;300 mg/L</th>
<th>150 mg orally, twice daily</th>
<th>Consider noncompliance, illness, drug interaction, or dietary change as reason for subtherapeutic INR</th>
</tr>
</thead>
<tbody>
<tr>
<td>INR 150-299 mg/L</td>
<td>75 mg orally, twice daily</td>
<td></td>
</tr>
</tbody>
</table>

* U.S. labeling; no recommendation for CrCl <15 ml/min or on dialysis

Abbreviations: ADD = average daily dose; mg = milligram; kg = kilogram; Heparin: INR >9.0

II. ANTICOAGULANT REVERSAL

A. General Principles of Management of Anticoagulant-Associated Bleeding

<table>
<thead>
<tr>
<th>Agent</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Vitamin K</td>
<td>1:1-1 mg IV/PO, not IV or IM</td>
</tr>
<tr>
<td>Protamine sulfate</td>
<td>Full reversal of unfractionated heparin</td>
</tr>
<tr>
<td>Platelet complex</td>
<td>5-8 whole blood units</td>
</tr>
<tr>
<td>Vitamin K</td>
<td>2.5-5 mg IV, 0.5 mg oral, twice daily</td>
</tr>
<tr>
<td>Protamine Dose for Reversal of Heparin and LMWH</td>
<td>(heparin) or anti-Xa level (LMWH) every 3 hours with repeat protamine (0.5 mg per indicated amount of heparin or LMWH) if bleeding continues</td>
</tr>
</tbody>
</table>

1. Reversal of Warfarin (Coumadin®, Jantoven®)

Non-Urgent | Urgent (Not Bleeding) | Urgent (Bleeding) |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Hashti</td>
<td>• Stop 5 days prior to</td>
<td>• Procedure can be delayed</td>
</tr>
<tr>
<td>Protamine sulfate</td>
<td>6-24 hours, vitamin K 5-10 mg PO</td>
<td>• Vitamin K 5-10 mg PO per day</td>
</tr>
<tr>
<td>Protamine sulfate</td>
<td>• Repeat every 12 hours as needed</td>
<td></td>
</tr>
<tr>
<td>Protamine sulfate</td>
<td>• Vitamin K 5-10 mg PO IV</td>
<td>• Protamine sulfate, 2.0 mg/kg IV over 10-30 minutes</td>
</tr>
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2. Reversal of Low-Molecular-Weight Heparins (Enoxaparin/Loxenova®/Dalteparin/Fragmin®/INNAPridge®/Tinzaparin/innohep®) and Fondaparinux® (Arixtra®)

Non-Urgent | Urgent (Not Bleeding) | Urgent (Bleeding) |
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</thead>
<tbody>
<tr>
<td>Hashti</td>
<td>• Hold day of procedure</td>
<td>• Vitamin K 5-10 mg PO or IV in high bleeding risk patients</td>
</tr>
<tr>
<td>Protamine sulfate</td>
<td>• Consider protamine sulfate if delay not possible for high bleeding risk procedure</td>
<td></td>
</tr>
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</tr>
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</tr>
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3. Protonate Dose of Reversal for Heparin and LMWH

Agent* | Half-Life | Protonate Sulfate Dosing for Reversal |
<table>
<thead>
<tr>
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<td>Heparin</td>
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<td>• 1 mg per 100 units heparin given in 12-24 hours</td>
</tr>
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<td>Enoxaparin</td>
<td>4.5 hours</td>
<td>• e.g., 25-35 mg if 1000-1250 units/hour heparin infusion</td>
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<td>3.0 hours</td>
<td>• 1 mg per 100 units Fondaparinux in high bleeding risk patients</td>
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* A prothrombin time (PT) >20 seconds or activated partial thromboplastin time (aPTT) >1.5 times normal indicates need for reversal of anticoagulant

1. Stop 5 days prior to procedure; can be delayed up to 1 week if procedure can be delayed

2. Reversal of Warfarin (Coumadin®, Jantoven®)

Non-Urgent | Urgent (Not Bleeding) | Urgent (Bleeding) |
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2. Reversal of Low-Molecular-Weight Heparins (Enoxaparin/Loxenova®/Dalteparin/Fragmin®/INNAPridge®/Tinzaparin/innohep®) and Fondaparinux® (Arixtra®)

Non-Urgent | Urgent (Not Bleeding) | Urgent (Bleeding) |
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</table>

1. Stop 5 days prior to procedure; can be delayed up to 1 week if procedure can be delayed

2. Reversal of Warfarin (Coumadin®, Jantoven®)

Non-Urgent | Urgent (Not Bleeding) | Urgent (Bleeding) |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Hashti</td>
<td>• Stop 5 days prior to</td>
<td>• Procedure can be delayed</td>
</tr>
<tr>
<td>Protamine sulfate</td>
<td>6-24 hours, vitamin K 5-10 mg PO</td>
<td>• Vitamin K 5-10 mg PO per day</td>
</tr>
<tr>
<td>Protamine sulfate</td>
<td>• Repeat every 12 hours as needed</td>
<td></td>
</tr>
<tr>
<td>Protamine sulfate</td>
<td>• Vitamin K 5-10 mg PO IV</td>
<td>• Protamine sulfate, 2.0 mg/kg IV over 10-30 minutes</td>
</tr>
<tr>
<td>Protamine sulfate</td>
<td>• Protamine sulfate, 2.0 mg/kg IV over 10-30 minutes</td>
<td>• Protamine sulfate, 2.0 mg/kg IV over 10-30 minutes</td>
</tr>
</tbody>
</table>

2. Reversal of Low-Molecular-Weight Heparins (Enoxaparin/Loxenova®/Dalteparin/Fragmin®/INNAPridge®/Tinzaparin/innohep®) and Fondaparinux® (Arixtra®)

Non-Urgent | Urgent (Not Bleeding) | Urgent (Bleeding) |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Hashti</td>
<td>• Hold day of procedure</td>
<td>• Vitamin K 5-10 mg PO or IV in high bleeding risk patients</td>
</tr>
<tr>
<td>Protamine sulfate</td>
<td>• Consider protamine sulfate if delay not possible for high bleeding risk procedure</td>
<td></td>
</tr>
<tr>
<td>Protamine sulfate</td>
<td>• Consider protamine sulfate</td>
<td></td>
</tr>
<tr>
<td>Protamine sulfate</td>
<td>• Protamine sulfate</td>
<td></td>
</tr>
</tbody>
</table>

3. Protonate Dose of Reversal for Heparin and LMWH

Agent* | Half-Life | Protonate Sulfate Dosing for Reversal |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Heparin</td>
<td>1-2 hours</td>
<td>• 1 mg per 100 units heparin given in 12-24 hours</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>4.5 hours</td>
<td>• e.g., 25-35 mg if 1000-1250 units/hour heparin infusion</td>
</tr>
<tr>
<td>Dalteparin</td>
<td>4.5 hours</td>
<td>• 1 mg per 1 mg Enoxaparin in high bleeding risk patients</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>2.0 hours</td>
<td>• 1 mg per 100 units Dalteparin in high bleeding risk patients</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>3.0 hours</td>
<td>• 1 mg per 100 units Fondaparinux in high bleeding risk patients</td>
</tr>
</tbody>
</table>
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.
5. IF heparin exposure >6 months, CBC in day 3.
6. LMMH 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, twice-daily dosing Dalteparin: 200 IU/kg/day In cancer patients for long-term treatment: 200 IU/kg/day for 4 weeks (up to 100U/kg/hour), then:
- <54 kg: 7500 IU daily
- 54-98 kg: 15,000 IU daily
- 99-122 kg: 10,000 IU daily
- >122 kg: 10,000 IU daily
Tinzaparin: 175 IU/kg Fondaparinux: Daily dose: <50 kg: 5 mg, 50-100 kg: 7.5 mg, >100 kg: 10 mg Unfractionated heparin: 333 IU/kg x day, 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-interactive 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 if heparin exposure >1 week.
6. Consider risk factors for GI bleeding

C. Chronic Warfarin Dosing Adjustments 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.

D. Dabigatran Dosing to Prevent Stroke and Embolism in Nonvalvular Atrial Fibrillation

<table>
<thead>
<tr>
<th>Day</th>
<th>INR DAILY DOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-2</td>
<td>1.0-1.3 mg/150 kg</td>
</tr>
<tr>
<td>3 or 4</td>
<td>1.4-1.5 mg/150 kg</td>
</tr>
<tr>
<td>7-10</td>
<td>1.6-1.8 mg/150 kg</td>
</tr>
</tbody>
</table>

* INR < 1.5: 1 mg/150 kg; INR 1.5-2.0: 1.5 mg/150 kg; INR 2.0-3.0: 2.0 mg/150 kg

1. U.S. labeling; no recommendation for CrCl <15 ml/min or on dialysis

II. ANTICOAGULANT REVERSAL

A. General Principles of Management of Anticoagulant-Associated Bleeding

HATHI
1. Hold further doses of anticoagulant.
2. Consider Anticoagulant
3. Supportive treatment: volume resuscitation, intropes 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 days
Urgent (with bleeding): Immediate reversal

B. Anticoagulant Reversal Agents

<table>
<thead>
<tr>
<th>Agent</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin K</td>
<td>1-10 mg IV/PO, not SD or IM</td>
</tr>
<tr>
<td>Protamine</td>
<td>12.5-50 mg IV</td>
</tr>
<tr>
<td>Heparin</td>
<td>1-2 hours</td>
</tr>
</tbody>
</table>

Agent* Half-Life Prothrombin Sulfate Dosing for Reversal

<table>
<thead>
<tr>
<th>All</th>
<th>Heparin</th>
<th>1-2 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 mg per 100 units heparin given in previous 2-3 hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td>e.g., 25-50 mg if 1000-1500 units/hour heparin infusion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enoxaprin</td>
<td>4.5 hours</td>
<td></td>
</tr>
<tr>
<td>Dalteparin 2.0 hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 mg per 100 units Dalteparin in previous 8 hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fondaparinux 3.0 hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 mg per 100 units Fondaparinux in previous 8 hours</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1 U.S. labeling; no recommendation for CrCl <15 ml/min or on dialysis

2. Reversal of Low-Molecular-Weight Heparins (Exoxparin/Loxovan®, Dalteparin/Fragmin®, Tinzaparin/Innohep®) and Fondaparinux (Daxil®)

Non-urgent: Reversal needed within days
Urgent: Reversal needed within hours

3. Prothrombin Dose for Reversal of Heparin and LMWH

Agent** Half-Life Prothrombin Sulfate Dosing for Reversal

* INR 3.1-3.5 Decrease by 10%* INR 3.6-4.0 Increase by 10% of ADD

1. Reversal of Warfarin (Coumadin®, Jantoven®)

30-90 units/kg (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

1. If patient is longer than subcutaneous administration; for all agents so may require monitoring with PTT therapy vs.
2. APTT therapy or anticoagulant level LMMH 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.

C. Converting Anticoagulants to and from Dabigatran

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://chessjournal.chestpubs.org/content/133/6_suppl/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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Images courtesy of Kenneth Mann, PhD, and Matthew Whelihan, MS.
III. Antifibrinolytic Agent Reversal

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

**General Considerations**

1. **Half-lives**
   - Aspirin, clopidogrel, ticlopidine, prasugrel: 7-10 days
   - Ticagrelor: Resolution takes 7-10 days to resolve as new platelets are generated.

2. **Circulating drug or active metabolites can inhibit transfused platelets.**

3. **Must consider indication for use in decision to reverse**
   - 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.
   - Consult cardiologist if uncertain.

**Reversal of Antifibrinolytic Agents**

<table>
<thead>
<tr>
<th>Non-Urgent</th>
<th>Urgent (Not Bleeding)</th>
<th>Urgent (Bleeding)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Discontinue agent 9-10 days prior to procedure</td>
<td>• Consider platelet transfusion prior to high risk bleeding procedures</td>
<td>• HASHTI*</td>
</tr>
<tr>
<td>• Platelet transfusion</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

**C. Converting Anticoagulants to and from Dabigatran**

<table>
<thead>
<tr>
<th>Current Anticoagulant</th>
<th>Anticoagulant to be Converted to</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin (INR 2-3)</td>
<td>Dabigatran</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>Warfarin (INR 2-3)</td>
</tr>
<tr>
<td>LMWH, heparin</td>
<td>Dabigatran</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>LMWH, heparin</td>
</tr>
</tbody>
</table>

**Dabigatran**

- **Non-Urgent**: Hold further doses of dabigatran
  - **CrCl > 50 ml/min**: Hold 1-2 days
  - **CrCl < 50 ml/min**: Hold 3-5 days
  - **Consider longer times for major surgery, placement of spinal or epidural catheter or port**

- **Urgent**: Hold dabigatran and check aPTT

<table>
<thead>
<tr>
<th>Clinical Considerations</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-urgent</strong></td>
<td><strong>Urgent</strong></td>
</tr>
<tr>
<td><strong>A.</strong></td>
<td><strong>B.</strong></td>
</tr>
<tr>
<td><strong>a.</strong></td>
<td><strong>a.</strong></td>
</tr>
<tr>
<td><strong>b.</strong></td>
<td><strong>b.</strong></td>
</tr>
<tr>
<td><strong>c.</strong></td>
<td><strong>c.</strong></td>
</tr>
<tr>
<td><strong>HASHTI</strong></td>
<td><strong>HASHTI</strong></td>
</tr>
</tbody>
</table>

**Abbreviations**: PCC = prothrombin complex concentrates; rFVIIa = recombinant factor VIIa

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Mary Cushman, MD, MSc; Wendy Lim, MD, MSc, FRCP; Neil A Zakai, MD, MSc

1 University of Vermont
2 McMaster University

Presented by the American Society of Hematology, adapted in part from the American College of Chest Physicians Evidence-Based Clinical Practice Guidelines on Antithrombotic and Thrombolytic Therapy (8th Edition).
4. Reversal of Dabigatran

Non-Urgent: Hold further doses of dabigatran
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Consider longer times for major surgery, placement of spinal or epidural catheter or port

Urgent:
- CrCl > 50 ml/min: Hold 1-2 days
- CrCl < 50 ml/min: Hold 3-5 days
Consider longer times for major surgery, placement of spinal or epidural catheter or port

Non-Urgent Urgent (Not Bleeding) Urgent (Bleeding)
- Discontinue agent 5-10 days prior to procedure
- Consider platelet transfusion prior to high risk bleeding procedures
- HASHTI

III. Antiplatelet Agent Reversal

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4. Must consider indication for use in decision to reverse
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   - Consult cardiologist if uncertain.

Reversal of Antiplatelet Agents

Non-Urgent Urgent (Not Bleeding) Urgent (Bleeding)
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- Consider platelet transfusion prior to high risk bleeding procedures
- HASHTI
- Platelet transfusion

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