2. Reversal of Low-Molecular-Weight Heparin (Dalteparin, Fragmin), Enoxaparin (Lovenox), Lovenox Imexpro, and Fondaparinux (Arixtra)

- Hold of procedure
- Close observation
- 15 dose day prior
- 5 dose day prior
- Hold evening dose day prior
- Wall 12-24 hours if possible
- Continue routine platelet count if dialyzer dose
- Half-life is longer with subcutaneous administration for all agents so may require monitoring

3. Protamine Dose for Reversal of Heparin and LMWH

<table>
<thead>
<tr>
<th>Agent*</th>
<th>Half-Life</th>
<th>Protamine Sulfate Dosing for Reversal</th>
<th>Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heparin</td>
<td>1-2 hours</td>
<td>1 mg per 100-1000 units heparin given in previous 2-3 hours</td>
<td>Discontinue warfarin and start dabigatran or apixaban when INR ≤2.0</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>4.5 hours</td>
<td>1 mg per 1 mg previously given in previous 4 hours</td>
<td>Discontinue warfarin and start intravenous heparin when aPTT &gt;1.5 x normal</td>
</tr>
<tr>
<td>Dalteparin</td>
<td>3.2 hours</td>
<td>1 mg per 100 units Dalteparin in previous 6 hours</td>
<td>Discontinue warfarin and start dabigatran 0.2 hours before administration of last LMWH/Heparin dose, or at the same time as discontinuation of intravenous heparin.</td>
</tr>
<tr>
<td>Tinzaparin</td>
<td>3.9 hours</td>
<td>1 mg per 1 mg Tinzaparin in previous 6 hours</td>
<td>Discontinue LMWH or heparin and initiate activated protein C complex (APC) inhibitors such as eslicaragon or fondaparinux.</td>
</tr>
</tbody>
</table>

Protamine has no specific antidote

Abbreviations: PC, protein C; PIVKA, prothrombin fragment 1+2; PCID, protein C inhibitor deficiency; PL, protein S level, RFT, Russell viper venom time; x PT, prothrombin time

3. Reversal of Heparin

- Hold further doses of dabigatran, rivaroxaban, or apixaban
- Hold evening dose day prior
- Wall 12-24 hours if possible
- Continue routine platelet count if dialyzer dose
- Half-life is longer with subcutaneous administration for all agents so may require monitoring

4. Reversal of Dalteparin, Rivaroxaban or Apixaban

- Hold further doses of dabigatran, rivaroxaban, or apixaban
- Hold evening dose day prior
- Wall 12-24 hours if possible
- Continue routine platelet count if dialyzer dose
- Half-life is longer with subcutaneous administration for all agents so may require monitoring

5. C. Converting Between Anticoagulants

Common anticoagulants to be converted to

- Warfarin (INR 2-3) Dabigatran or Apixaban
- Discontinue warfarin and start dabigatran or apixaban when INR ≤2.0

- Warfarin (INR 2-3) Rivaroxaban
- Discontinue warfarin and start intravenous heparin when aPTT >1.5 x normal

- LMWH or Heparin
- Dalteparin
- Start dabigatran 0.2 hours before administration of last LMWH/Heparin dose, or at the same time as discontinuation of intravenous heparin.

- LMWH or Heparin
- Rivaroxaban or Apixaban
- Discontinue LMWH or heparin and initiate activated protein C complex (APC) inhibitors such as eslicaragon or fondaparinux.

Abbreviations: INR, international normalized ratio; LMWH, low molecular weight heparin; Warfarin, vitamin K antagonist; aPTT, activated partial thromboplastin time; INR, international normalized ratio; PT, prothrombin time

III. ANTIPATELET AGENT REVERSAL

Aspirin, Clopidogrel/Dipyridamole (Aggrenox), Cilostazol (Plavix), Prasugrel (Effient), Ticagrelor (Brilinta)

General Considerations

1. Plateau half-life
- a. Clopidogrel, dipyridamole, prasugrel, ticagrelor: 7-10 hours
- b. Low-dose aspirin (350 mg daily): 2-4 hours
- c. Overdose aspirin (4000 mg): 15-20 hours

2. Reversibility of antiplatelet effect
- a. Aspirin, clopidogrel/prasugrel inhibit platelet function for lifetime of the platelets. 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. Hold a minimum of 5 days to resolve effect. Unclear if platelet function will be effective in reversing effect given within 5-7 days of last dose.

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. Consider antithrombotic or current guideline recommendations if uncertain.

Reversal of Antipatelet Agents

- Discontinue agent ≥5 days prior to procedure
- Consider platelet transfusion prior to high risk bleeding procedures
- HASHTI
- Consider platelet transfusion

This document summarizes selected recommendations from the American College of Chest Physicians Evidence-Based Clinical Practice Guidelines on Antithrombotic and Thrombolytic Therapy (9th 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.

For further information, please see the complete guidelines on the Chest Website at http://www.chestjournal.org for the American College of Chest Physicians Evidence-Based Clinical Practice Guidelines on Antithrombotic and Thrombolytic Therapy (9th Edition).

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Images courtesy of Kenneth Mann, PhD, and Matthew Whelihan, MS.
III. ANTIPLATELET AGENT REVERSAL

A. Aspirin

- **Dosing and Management of Antithrombotic Drug-Associated Bleeding Complications in Adults**

**American Society of Hematology**

2021 L Street NW, Suite 900
Washington, DC 20036

**Look for this pocket guide as a downloadable app by searching “ASH Guides” in the iTunes store or Android market.**
Reversal of Low-Molecular-Weight Heparins (Dalteparin, Fragmin), Enoxaparin (Lovenox), Tinzaparin (Innohep) and Fondaparinux (Arixtra)  

- Half-life is longer with subcutaneous administration for all agents so may require monitoring.

### Urgent:

1. **Protamine Dose for Reversal of Heparin and LMWH**

2. Reversal of Low-Molecular-Weight Heparins

   - Dalteparin
     - 4.5 hours
     - 1 mg per 100 units Dalteparin in previous 8 hours

   - Enoxaparin
     - 3.9 hours
     - 1 mg per 100 units Enoxaparin in previous 8 hours

   - Tinzaparin
     - 3.2 hours
     - 1 mg per 100 units Tinzaparin in previous 8 hours

   - Fondaparinux
     - 2.1 hours
     - 1 mg per 100 units Fondaparinux in previous 8 hours

   - Hirudin
     - 1.7 hours
     - 1 mg per 100 units Hirudin in previous 8 hours

   - Argatroban
     - 1.5 hours
     - 1 mg per 100 units Argatroban in previous 8 hours

- Antiplatelet agents are inactivated in the urine, therefore maintain adequate diuresis. Rivaroxaban and apixaban are highly protein bound so dosing is not effective.

### C. Converting Between Anticoagulants

<table>
<thead>
<tr>
<th>Agent</th>
<th>Half-Life</th>
<th>Protamine Sulfate Dosing for Reversal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin (INR 2-3)</td>
<td>Dalteparin or Apixaban: Discontinue warfarin and start dalteparin or apixaban when INR ≤2.0</td>
<td></td>
</tr>
<tr>
<td>LMWH or Heparin</td>
<td>Dalteparin: Start dalteparin 0.2 hours before administration of low molecular weight heparin/Heparin dose, or same time as discontinuation of intravenous heparin.</td>
<td></td>
</tr>
<tr>
<td>LMWH or Heparin</td>
<td>Apixaban: Start apixaban 1 hour before low-dose warfarin dose or start apixaban 24 hours after last dose of dalteparin.</td>
<td></td>
</tr>
<tr>
<td>Dabigatran</td>
<td>Rivaroxaban (Warfarin Discontinue Dabigatran and start warfarin 24 hours after last dose of dabigatran.</td>
<td></td>
</tr>
</tbody>
</table>

### III. Antifibrinolytic Agent Reversal

- Aspirin, Clopidogrel

### General Considerations

1. **Phase 1:**
   - Aspirin, clopidogrel, prasugrel, ticagrelor: 3-10 hours
   - Low-dose aspirin (150 mg daily): 2-4 hours
   - Clopidogrel (600 mg): 15-90 hours

2. **Reversibility of antiplatelet effect**
   - Aspirin, clopidogrel, prasugrel inhibit platelet function for lifetime of the platelets. Inhibition takes 7-10 days to resolve as new platelets are generated.
   - Ticagrelor is a reversible inhibitor so platelet function normalizes after drug clearance. Hold a minimum of 5 days to reverse effect. Unclear if platelet transfusion will be effective in reversing effect given well 5-7 days of last dose.

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.

5. Consult apheresis or current guideline recommendations if uncertain.

### Reversal of Anticoagulant Agents

- **Non-Urgent**
  - Hold further (refer to table for recommended duration). Consider longer times for major surgery, placement of spinal or epidural catheter or port.

- **Urgent**
  - Hold at least 24 hours.
  - Hold for normal renal function (Drug) procedures. Drug persistence can be assessed by anti-Xa.
  - Hold at least 24 hours.

- **Normal aPTT**
  - Unlikely to produce a measurable effect.

- **PT**
  - Unlikely to produce a measurable effect.

- **INR**
  - Unlikely to produce a measurable effect.

Reversal of Anticoagulant-Associated Bleeding Complications in Adults

- **Non-Urgent**
  - Hold further (refer to table for recommended duration). Consider longer times for major surgery, placement of spinal or epidural catheter or port.

- **Urgent**
  - Hold at least 24 hours.
  - Hold for normal renal function (Drug) procedures. Drug persistence can be assessed by anti-Xa.
  - Hold at least 24 hours.

### No antidote available

For additional information, please see the complete guidelines on the Chest Website at http://journals.chestpubs.org.

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American Society of Hematology 2021 L Street NW, Suite 900 Washington, DC 20036

Clinical Practice Guide on Antithrombotic Drug Dosing and Management of Antithrombotic-Associated Bleeding Complications in Adults

This pocket guide is a revision of the 2011 Clinical Practice Guide on Antithrombotic Drug Dosing and Management of Antithrombotic-Associated Bleeding Complications in Adults.
Non-Urgent Urgent (Not Bleeding) Urgent (Bleeding)

III. ANTIPLATELET AGENT REVERSAL

Aspirin, Apixaban/Dabigatran, Edoxaban, Rivaroxaban

General Considerations

1. Risk of coronary stent exclusion (which can be lethal) within 3 months of bare metal stent implantation; period of risk is likely longer for drug-eluting stents.

C. Converting Between Anticoagulants

Warfarin

INR 2-3

• Discontinue warfarin and start dabigatran or apixaban when INR 2-3

Reversal of Low-Molecular-Weight Heparin (Dalteparin, Fragmin, Enoxaparin, Tinzaparin, Castrol Forte, and others)

1. Urgent

2. Reversal of Low-Molecular-Weight Heparins (Dalteparin (Fragmin), Enoxaparin (Lexem), and others)

*Half-life is longer with subcutaneous administration for all agents so may require monitoring

Half-life:

LMWH

Heparin

LMWH or Heparin

Dabigatran

Rivaroxaban

Apixaban

Warfarin (INR 2-3)

Discontinue warfarin and start dabigatran or apixaban when INR 2-3

Dabigatran

Discontinue dabigatran 0-2 hours before administration of iatrogenic LMWH/epoprostenol dose or up to time as discontinuation of intrahepatic dose.

Dabigatran

Discontinue LMWH or heparin and initiate recombinant factor VIIa (rFVIIa) within 1 hour of most recent scheduled LMWH/heparin dose.

Rivaroxaban

Discontinue LMWH or heparin 24 hours after discontinuation of Rivaroxaban.

Apixaban

Discontinue Apixaban and start warfarin 24 hours later if continuous anticoagulation desired; start alternative anticoagulant while starting warfarin.

Canada: Continue apixaban concomitantly with warfarin until INR 2.2 and then discontinue rivaroxaban.

Dosages

Warfarin

INR 2-3

• Discontinue warfarin and start apixaban 24 hours later if continuous anticoagulation desired; start alternative anticoagulant while starting warfarin.

Canada: Continue apixaban concomitantly with warfarin until INR 2.2 and then discontinue rivaroxaban.

 Abrasions:CCI, creatinine clearance, INR, international normalized ratio, LMWH, low-molecular-weight heparin

Converting between anticoagulants based on 20 mg daily dose for non-valvular atrial fibrillation.


• Dabigatran affects INR; so INR measurements made during coadministration with warfarin may not be useful for determining the appropriate dose of warfarin. If coadministered with warfarin, measure INR at nadir. If continuous anticoagulation desired, stop dabigatran and initiate alternative anticoagulant while starting warfarin. Xarelto® product monograph 2011

• Apixaban affects INR; so INR measurements made during coadministration with warfarin may not be useful for determining appropriate dose of warfarin. To minimize this phenomenon, measure INR at apixaban trough.

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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

• Consider platelet transfusion

Clinical Practice Guide on Antithrombotic Drug Dosing and Management of Antithrombotic-Associated Bleeding Complications in Adults

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Images courtesy of Kenneth Mann, PhD, and Matthew Whellan, MS.
A. Subcutaneous Heparin Dosing for Treatment of Acute Venous Thromboembolism

**General Considerations**
1. Round weight-based dose to nearest predefined syringe size for LMWH.
2. No dose cap for critically ill despite low platelet count in cancer patients.
3. Consider measuring anti-Xa heparin levels after 3rd dose for weight >120 kg or ≥50 kg.
4. Repeat CBC day 4 and consider heparin-induced thrombocytopenia if platelets declining.

**Subcutaneous Dosing**
- **Enoxaparin**: 1 mg/kg every 12 hours or 1.5 mg/kg daily
- **Dekaparinux**: <50 kg: 5 mg daily. 50-100 kg: 7.5 mg daily. >100 kg: 10 mg daily
- **Low-molecular-weight heparin (LMWH)**: Use LMWH with caution if at all, and monitor anti-Xa levels if creatinine clearance (CrCl) <30 ml/min.

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

**General Considerations**
1. Obtain baseline PT/INR and investigate if abnormal.
2. Determine use of potential warfarin interacting medications.
3. Consider measuring anti-Xa heparin levels after 3rd dose for weight >120 kg or CrCl <30 ml/min.

**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. Provide patient education on safety, monitoring, drug and food interactions.

**Day 1**
- INR DAILY DOSE
  - **INR <1.5**: 1 mg
  - **1.5 ≤ INR <2.5**: 1 mg
  - **2.5 ≤ INR <3.5**: 1.5 mg
  - **3.5 ≤ INR <4.0**: 2 mg
  - **INR >4.0**: 2.5 mg

**Day 2**
- INR DAILY DOSE
  - **INR <1.5**: 1 mg
  - **1.5 ≤ INR <2.5**: 1 mg
  - **2.5 ≤ INR <3.5**: 1.25 mg
  - **3.5 ≤ INR <4.0**: 1.75 mg
  - **INR >4.0**: 2.5 mg

**Day 3**
- INR DAILY DOSE
  - **INR <1.5**: 1 mg
  - **1.5 ≤ INR <2.5**: 1 mg
  - **2.5 ≤ INR <3.5**: 1.25 mg
  - **3.5 ≤ INR <4.0**: 1.75 mg
  - **INR >4.0**: 2.5 mg

**Day 4**
- INR DAILY DOSE
  - **INR <1.5**: 1 mg
  - **1.5 ≤ INR <2.5**: 1 mg
  - **2.5 ≤ INR <3.5**: 1.25 mg
  - **3.5 ≤ INR <4.0**: 1.75 mg
  - **INR >4.0**: 2.5 mg

**Day 5 and beyond**
- INR DAILY DOSE
  - **INR <1.5**: 1 mg
  - **1.5 ≤ INR <2.5**: 1 mg
  - **2.5 ≤ INR <3.5**: 1.25 mg
  - **3.5 ≤ INR <4.0**: 1.75 mg
  - **INR >4.0**: 2.5 mg

**B. Agents to Stop Bleeding**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin K</td>
<td>110-120 mg IV/PO</td>
<td>Full reversal of unfractionated heparin</td>
</tr>
<tr>
<td>Prothrombin complex concentrate (PCC)</td>
<td>2.5-10 units (FFP)</td>
<td>Full reversal of factor Xa inhibitors</td>
</tr>
<tr>
<td>Platelets</td>
<td>~200 x10^9/L</td>
<td>* Use for other indications currently off label</td>
</tr>
<tr>
<td>Fibrin sealant</td>
<td>~250 ml</td>
<td>Follow local Institutional policy</td>
</tr>
<tr>
<td>Recombinant factor VIIa</td>
<td>15-50 microgram/kg (lower doses studied)</td>
<td>Rapid, complete INR correction in warfarin-treated patients</td>
</tr>
<tr>
<td>Aminocaproic acid</td>
<td>4-5 g orally every 1 hour; 1 g/hr if IV</td>
<td>May increase risk of thrombosis</td>
</tr>
<tr>
<td>Tranexamic acid</td>
<td>1500 mg PO q6h</td>
<td>May accumulate in patients with renal impairment, reduce loading dose of oral dose</td>
</tr>
<tr>
<td>Hemostatic agents</td>
<td></td>
<td>Use for other indications currently off label</td>
</tr>
</tbody>
</table>

**C. Chronic Warfarin Dose Adjustment in Non-Bleeding Patients**

Thisnomogram 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 <2.0 confirm no bleeding.
2. No dose cap for frailty, liver disease, malnutrition, drugs that enhance warfarin activity, or Asian ethnicity.
3. Use enoxaparin 1 mg/kg every 12 hours or 1.5 mg/kg daily

**Subcutaneous Dosing**
- **Enoxaparin**: 1 mg/kg every 12 hours or 1.5 mg/kg daily
- **Fondaparinux**: <50 kg: 5 mg daily. 50-100 kg: 7.5 mg daily. >100 kg: 10 mg daily

**E. Rivaroxaban Dosing to Prevent Stroke and Systemic Embolism in Nonvalvular Atrial Fibrillation and to Treat Venous Thromboembolism**

- **Intravenous bolus**: 1 mg/kg IV over 4-5 minutes
- **Handout**: 10 mg IV over 60 minutes

**F. Apixaban Dosing to Prevent Stroke and Systemic Embolism in Nonvalvular Atrial Fibrillation**

- **Dose**: 5 mg twice daily
- **Dose adjustment**: Dose 2.5 mg twice daily if:
  - Age >75 years or propensity for GI bleeding
  - Rebleeding within 1 week

**Agent** | **Dose** | **Comments** |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin K</td>
<td>110-120 mg IV/PO</td>
<td>Full reversal of unfractionated heparin</td>
</tr>
<tr>
<td>Prothrombin complex concentrate (PCC)</td>
<td>2.5-10 units (FFP)</td>
<td>Full reversal of factor Xa inhibitors</td>
</tr>
<tr>
<td>Platelets</td>
<td>~200 x10^9/L</td>
<td>* Use for other indications currently off label</td>
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<tr>
<td>Fibrin sealant</td>
<td>~250 ml</td>
<td>Follow local Institutional policy</td>
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<td>Recombinant factor VIIa</td>
<td>15-50 microgram/kg</td>
<td>Rapid, complete INR correction in warfarin-treated patients</td>
</tr>
<tr>
<td>Aminocaproic acid</td>
<td>4-5 g orally every 1 hour; 1 g/hr if IV</td>
<td>May increase risk of thrombosis</td>
</tr>
<tr>
<td>Tranexamic acid</td>
<td>1500 mg PO q6h</td>
<td>May accumulate in patients with renal impairment, reduce loading dose of oral dose</td>
</tr>
<tr>
<td>Hemostatic agents</td>
<td></td>
<td>Use for other indications currently off label</td>
</tr>
</tbody>
</table>

**References**

1. Check INR more frequently
2. Do not administer apixaban in patients with both #1 and #2.
3. **Use of strong dual inhibitors of CYP3A4 and P-glycoprotein (e.g., ketoconazole, itraconazole, ritonavir).**
4. **Avoid use in patients taking strong dual inducers of CYP3A4 and P-glycoprotein (e.g., rifampin, phenytoin, carbamazepine, phenobarbital, St. John’s Wort); this may lead to reduced rivaroxaban plasma concentrations.**
5. **Reversal of Warfarin (Coumadin)**
   - **INR >4.0**: 2.5 mg IV
   - **INR >5.0**: 5 mg IV
   - **INR >6.0**: 7.5 mg IV

**For INR >5.0 add approx. 1.25 mg of vitamin K per 1 unit of INR higher than 5.0.**

**For INR >6.0 add approx. 1.875 mg of vitamin K per 1 unit of INR higher than 6.0.**
**I. ANTICOAGULANT DOING**

### A. Subcutaneous Heparin Dosing for Treatment of Acute Venous Thromboembolism

**General Considerations**

1. Round weight-based dose to closest premixed syringe size for LMWH.
2. No dose cap for elderly or debilitated patients in cancer patients.
3. Consider measuring anti-Xa heparin levels after 3rd dose for weight >120 kg or >50 kg.
4. Repeat CBC daily and consider heparin-induced thrombocytopenia if platelets declining.

**Subcutaneous 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 doses.

Dabigatran: 200 mg twice daily or 100 mg every 12 hours

Dalteparin: 200 IU/kg daily

Tinzaparin: 175 IU/kg daily

- For cancer patients and those at high bleeding or thrombosis risk

**5. For acute thrombosis, overlap with heparin/LMWH/fondaparinux for 5 days.**

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

**7. Clinical judgment should supersede this nomogram.**

- If heparin exposure in previous 3 months, CBC on day 3 rather than day 7.

**8. Repeat CBC day 7 and consider heparin-induced thrombocytopenia if platelets <75,000 and day 12.**

**9. INR therapeutic.**

**10. Consider noncompliance, illness, drug interaction, or dietary change as reason for out-of-range INR.**

**C. Chronic Warfarin Dose Adjustment in Non-Bleeding Patients**

**Definitions Used for Reversal Situations**

- **HASHTI**
  - **H**emostasis usually requires coagulation factor levels ~30%
  - **A**nticoagulation may persist for 6-8 hours after INR normalizes
  - **S**evere or symptomatic anemia
  - **T**ransfusion
  - **H**old further doses of anticoagulant
  - **I**nvestigate for bleeding source

- **R**apid infusion of small volume (e.g., 10 mg/kg over 15-30 min)

**Recombinant factor VIIa (FVIIa)**

- **1.90 micrograms/kg (lower doses studied).**

**E. Rivaroxaban Dosing to Prevent Stroke and Systemic Embolism in Nonvalvular Atrial Fibrillation and to Treat Venous Thromboembolism**

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

**Definition of Urgency**

- **Non-urgent** (electrolyte or procedural): >5 days away

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

**General Considerations**

1. Obtain baseline PT/INR and investigate if abnormal.
2. Determine use of potential warfarin interacting medications.
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 therapy.

**Recommended for INR check on day 3-4.**

**Clinical judgment should supersede this nomogram.**

**Target INR**

- INR < 2.0 – 3.5
- INR > 3.5

**Dose**

- Dabigatran 150 mg twice daily

**Dosage Adjustments**

- INR < 1.9 (1.7-1.9):
  - Reduce by 10-15% for each 0.1 units up to 2.5 units of INR

- INR > 4:
  - Increase by 10-15% for each 0.1 units up to 2.5 units of INR

**Side Effects**

- **Gastrointestinal**
  - Nausea, vomiting, diarrhea

- **Hematologic**
  - Thrombocytopenia

**References**


C. Vitamin K Antagonist 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 <2.0, confirm no bleeding.
2. Consider adjusting INR for antecedent illness, drugs, diet, or dietary change as reason for out-of-range INR. Consider-clinical judgment.
3. Clinical judgment should supersede this nomogram.

**General Considerations**

1. Obtain baseline PT/INR and investigate if abnormal.
2. Determine use of potential warfarin interacting medications.
3. Consider monitoring INR, aPTT, and anti-Xa levels if creatinine clearance (CrCl) <60 kg.
4. For acute thrombosis, overlap with heparin/LMWH/fondaparinux for 5 days.
5. For cancer patients and those at high bleeding or thrombosis risk, use LMWH for 7 days.
6. Recommend first INR check on day 3-4.
7. Clinical judgment should supersede this nomogram.

**TARGET INR**

<table>
<thead>
<tr>
<th>INR</th>
<th>Daily Dose</th>
</tr>
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<tbody>
<tr>
<td>&gt;2.0</td>
<td>2.0 – 3.0</td>
</tr>
<tr>
<td>1.6-1.9</td>
<td>Increase by 15% of ADD</td>
</tr>
<tr>
<td>1.4-1.5</td>
<td>5 mg</td>
</tr>
<tr>
<td>1.2-1.3</td>
<td>10 mg</td>
</tr>
<tr>
<td>&lt;1.2</td>
<td>15 mg</td>
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**Day 1 Dose**

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**Day 2 Dose**

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**Day 3 Dose**

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<tr>
<th>INR</th>
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**Day 4 Dose**

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<thead>
<tr>
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**Day 5 Dose**

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**Anticoagulant Reversal**

1. General Principles of Management of Anticoagulant-Associated Bleeding

**Hashti**

1. Hold further doses of anticoagulant
2. Consider Antidote
3. Supportive treatment

**Aminocaproic Acid**

• May increase risk of thrombosis
• May accumulate in patients with renal impairment
• Reduce bleeding dose of smallest effective
• Caution on use in hematology due to possible urinary tract slit

**Tranexamic Acid**

• Labelled indication for menorrhagia
• Use for other indications currently off label

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<tr>
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A. Subcutaneous Heparin Dosing for Treatment of Acute Venous Thromboembolism

General Considerations
1. Round weight-based dose to nearest predefined syringe size for LMWH.
2. No dose cap for rapidly escalating heparin in cancer patients.
3. Consider measuring anti-Xa heparin levels after 3rd dose for weight >120 kg or >80 years.
4. Repeat CBC day 7 and consider heparin-induced thrombocytopenia if platelets declining.
   • If heparin exposure in previous 3 months, CBC on day 3 rather than 7.
5. Use anti-Xa levels or monitoring anti-Xa levels if creatinine clearance (<50 mL/min).

Subcutaneous Dosing
Enoxaparin: 1 mg/kg every 12 hours or 1.5 mg/kg daily
Subcutaneous Dosing
Unfractionated Fondaparinux: <50 kg: 5 mg daily. 50-100 kg: 7.5 mg daily. >100 kg: 10 mg
Tinzaparin: 175 IU/kg daily

3. Document target INR and prescribed warfarin tablet strength.
2. Determine use of potential warfarin interacting medications.
1. Obtain baseline PT/INR and investigate if abnormal.

3. Consider measuring anti-Xa heparin levels after 3rd dose for weight >120 kg or
A. Subcutaneous Heparin Dosing for Treatment of Acute Venous Thromboembolism

I. ANTICOAGULANT DOSING

7. Clinical judgment should supersede this nomogram.

3. INR therapeutic.
2. INR >3.0 confirm no bleeding.
1. If INR >3.0 administer vitamin K.†

1. 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. INR >1.5: decrease dose by 15%. ≤1.5: increase dose by 15%.
3. Clinical judgment should supersede this nomogram.

E. Rivaroxaban Dosing to Prevent Stroke and Systemic Embolism in Nonvalvular Atrial Fibrillation and to Treat Venous Thromboembolism

• Avoid use in patients taking strong dual inhibitors of CYP3A4 and P-glycoprotein (e.g., ketoconazole, clarithromycin, ritonavir).
• Avoid use in patients taking strong dual inhibitors of P-glycoprotein and CYP3A4 (e.g., amiodarone, telmisartan, azolamycins).
• Use with caution in patients taking strong dual inhibitors of CYP3A4 and CYP2C19 (e.g., rifampicin, saquinavir, clarithromycin).

Rivaroxaban: 20 mg orally, twice daily.

A. Subcutaneous Heparin Dosing for Treatment of Acute Venous Thromboembolism

I. ANTICOAGULANT DOSING

7. Clinical judgment should supersede this nomogram.

3. Dabigatran Dosing to Prevent Stroke and Systemic Embolism in Nonvalvular Atrial Fibrillation and to Treat Venous Thromboembolism

Dose: 2.5 mg/day
• INR >1.5: increase dose by 15%.
• Use in patients who are not taking strong dual inhibitors of CYP3A4 and P-glycoprotein (e.g., rifampicin, carbamazepine, phenytoin, St. John’s Wort).

Dose adjustments:
• INR 2.5-2.9: decrease by 10-15%.
• INR 2.0-2.4: decrease by 20-25%.
• INR <2.0: decrease by 25-30%.

B. Agents to Stop Bleeding

Vitamin K
• 1-10 mg IV/PO
• Transient effects are usually observed within 20-26 hours.
• Reversal is not always consistent.

Prothrombin
• Vitamin K 5-10 mg IV
• Full reversal of heparin by 1-1.5 hours.
• No reversal of fondaparinux.

Platelets
• 1-2 units of platelets
• Washed platelet count 30-100 x 10^9/L
• Platelet count >100 x 10^9/L (400 x 10^9/L if independent).

Recombinant FVIII
• 1-2 units/kg in 2-3 doses
• Repeat in 12 hours if no reversal.

Factor VIIa
• 10-20 mcg/kg
• Reversal is elective (procedures >5 days away).

Factor XIII
• 50 mcg/kg
• Reversal is not usually considered.

Hemostatic measures
• Esmalterform, recombinant factor VIIa, Factor IXa
• Factor IXa may only reach 20%.
• Risk of thrombosis 1.4%; contraindicated with history of HIT.
• Consider concurrent FFP or Factor VIII co-factor used.

• Use for other indications currently off label.

Aminocaproic acid
• 4.0 gm orally
• 1 g/hr for 6 hrs
• 1.5 gm/hr for up to 18 hrs
• 12 gm over 24 hrs
• No reversal of fondaparinux.

HepaReX®
• 10-20 mL/kg
• Short half-life, may need repeat dosing after 6 hours.

Heparin flush
• 1-2 units/kg
• Reversal is not usually considered.

Warfarin
• Check INR more frequently

1. Reversal of Warfarin (Coumadin®, Jantoven)

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