Reversal of Low-Molecular-Weight Heparin (Dalteparin, Fragmin), Enoxaparin (Lovenox), Hirudin, Tinzaparin (Innohep) and Fondaparinux (Arixtra)

Non-Urgent

<table>
<thead>
<tr>
<th>Agent*</th>
<th>Half-Life</th>
<th>Parenteral Sulfate Dosing for Reversal</th>
<th>Maximum Dose is 50 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heparin</td>
<td>1-2 hours</td>
<td>1-100 units/kg in previous 2-3 hours</td>
<td>e.g., 25-250 mg if 500-1500 units/hour heparin infusion</td>
</tr>
<tr>
<td>Dalteparin</td>
<td>3-4 hours</td>
<td>1 mg every 4 hours in previous 6-8 hours</td>
<td></td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>3.5 hours</td>
<td>1 mg every 12 hours in previous 6-8 hours</td>
<td></td>
</tr>
<tr>
<td>Tinzaparin</td>
<td>3.9 hours</td>
<td>1 mg every 12 hours in previous 4-8 hours</td>
<td></td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>4.5 hours</td>
<td>1 mg every 24 hours in previous 24 hours</td>
<td></td>
</tr>
</tbody>
</table>

*Half-life is longer with subcutaneous administration for all agents so may require monitoring. This is also true when accounting for renal function. Drug presence may be assessed by thrombin time. Non-urgent: Hold further doses of dabigatran, rivaroxaban, or apixaban and may be contributing to bleeding procedure.

Reversal of Dabigatran, Rivaroxaban or Apixaban

Non-Urgent

Dabigatran or Apixaban: Discontinue warfarin and start dabigatran or apixaban when INR < 2.0 and then discontinue dabigatran or apixaban 12 hours after last dose of dabigatran or 24 hours after last dose of apixaban.

Rivaroxaban or Apixaban: Discontinue LMWH or heparin and initiate rivaroxaban 24 hours after last scheduled LMWH/heparin dose.

Dabigatran or Apixaban: Discontinue rivaroxaban 24 hours after discontinuation of rivaroxaban.

Rivaroxaban or Apixaban: Discontinue LMWH or heparin 24 hours after discontinuation of rivaroxaban.

Apixaban: Discontinue Apixaban and start warfarin 24 hours later. If continuous anticoagulation desired, hold alternative anticoagulant while starting warfarin. Canada: Continue warfarin concurrently with warfarin until INR 2.2 and then discontinue warfarin.

C. Converting Between Anticoagulants

Converting anticoagulant to be converted is

<table>
<thead>
<tr>
<th>Agent*</th>
<th>Half-Life</th>
<th>Parenteral Sulfate Dosing for Reversal</th>
<th>Maximum Dose is 50 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin (INR 2-3)</td>
<td>1-2 days</td>
<td>Discontinue warfarin and start dabigatran or apixaban when INR &lt; 2.0</td>
<td></td>
</tr>
<tr>
<td>Warfarin (INR 2-3)</td>
<td>1-2 days</td>
<td>Discontinue warfarin and start rivaroxaban when INR &lt; 2.0</td>
<td></td>
</tr>
<tr>
<td>LMWH or Heparin</td>
<td>Dabigatran</td>
<td>Start dabigatran 0.2 hours before administration of last LMWH/Heparin dose, or at same time as discontinuation of therapeutic heparin.</td>
<td></td>
</tr>
<tr>
<td>LMWH or Heparin</td>
<td>Rivaroxaban or Apixaban</td>
<td>Discontinue LMWH or heparin and initiate rivaroxaban 24 hours after last scheduled LMWH/heparin dose.</td>
<td></td>
</tr>
<tr>
<td>LMWH or Heparin</td>
<td>Apixaban</td>
<td>Start apixaban 0.2 hours before administration of last LMWH/Heparin dose, or at same time as discontinuation of therapeutic heparin.</td>
<td></td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Warfarin (INR 2-3)</td>
<td>US: Discontinue warfarin and a parenteral anticoagulant 24 hours after discontinuation of warfarin. Canada: Continue warfarin concurrently with warfarin until INR 2.2 and then discontinue warfarin.</td>
<td></td>
</tr>
<tr>
<td>Apixaban</td>
<td>Warfarin (INR 2-3)</td>
<td>Initiate LMWH or Heparin 24 hours after discontinuation of Apixaban.</td>
<td></td>
</tr>
</tbody>
</table>

D. Converting Anticoagulants

Conversion between anticoagulants is based on 20 mg daily dose for non-valvular atrial fibrillation. **Pharmacokinetic and clinical data indicate that conversion to rivaroxaban is associated with a lower incidence of bleeding events compared to warfarin.**

A. Hemodialysis for dabigatran

For bleeding consider: Antithrombin (with normal renal function). Drug presence may be assessed by anti-Xa assay. Such events may be prolonged when dabigatran and rivaroxaban are used concomitantly, in which case monitoring of the anti-factor Xa activity is recommended. Warfarin, rivaroxaban and dabigatran are highly protein bound so dialysis is not effective.

B. Hemodialysis for rivaroxaban

For bleeding consider: Protamine sulfate. Drug presence may be assessed by thrombin time. Warfarin, rivaroxaban and dabigatran are highly protein bound so dialysis is not effective.

C. Hemodialysis for apixaban

For bleeding consider: Protamine sulfate. Drug presence may be assessed by anti-Xa assay. Warfarin, rivaroxaban and dabigatran are highly protein bound so dialysis is not effective.

D. Hemodialysis for dabigatran, rivaroxaban or apixaban

For bleeding consider: Protamine sulfate. Drug presence may be assessed by anti-Xa assay. Warfarin, rivaroxaban and dabigatran are highly protein bound so dialysis is not effective.

E. Hemodialysis for dabigatran, rivaroxaban or apixaban

For bleeding consider: Protamine sulfate. Drug presence may be assessed by anti-Xa assay. Warfarin, rivaroxaban and dabigatran are highly protein bound so dialysis is not effective.

F. Hemodialysis for dabigatran, rivaroxaban or apixaban

For bleeding consider: Protamine sulfate. Drug presence may be assessed by anti-Xa assay. Warfarin, rivaroxaban and dabigatran are highly protein bound so dialysis is not effective.

G. Hemodialysis for dabigatran, rivaroxaban or apixaban

For bleeding consider: Protamine sulfate. Drug presence may be assessed by anti-Xa assay. Warfarin, rivaroxaban and dabigatran are highly protein bound so dialysis is not effective.

H. Hemodialysis for dabigatran, rivaroxaban or apixaban

For bleeding consider: Protamine sulfate. Drug presence may be assessed by anti-Xa assay. Warfarin, rivaroxaban and dabigatran are highly protein bound so dialysis is not effective.

I. Hemodialysis for dabigatran, rivaroxaban or apixaban

For bleeding consider: Protamine sulfate. Drug presence may be assessed by anti-Xa assay. Warfarin, rivaroxaban and dabigatran are highly protein bound so dialysis is not effective.

J. Hemodialysis for dabigatran, rivaroxaban or apixaban

For bleeding consider: Protamine sulfate. Drug presence may be assessed by anti-Xa assay. Warfarin, rivaroxaban and dabigatran are highly protein bound so dialysis is not effective.

K. Hemodialysis for dabigatran, rivaroxaban or apixaban

For bleeding consider: Protamine sulfate. Drug presence may be assessed by anti-Xa assay. Warfarin, rivaroxaban and dabigatran are highly protein bound so dialysis is not effective.

L. Hemodialysis for dabigatran, rivaroxaban or apixaban

For bleeding consider: Protamine sulfate. Drug presence may be assessed by anti-Xa assay. Warfarin, rivaroxaban and dabigatran are highly protein bound so dialysis is not effective.

M. Hemodialysis for dabigatran, rivaroxaban or apixaban

For bleeding consider: Protamine sulfate. Drug presence may be assessed by anti-Xa assay. Warfarin, rivaroxaban and dabigatran are highly protein bound so dialysis is not effective.

N. Hemodialysis for dabigatran, rivaroxaban or apixaban

For bleeding consider: Protamine sulfate. Drug presence may be assessed by anti-Xa assay. Warfarin, rivaroxaban and dabigatran are highly protein bound so dialysis is not effective.

O. Hemodialysis for dabigatran, rivaroxaban or apixaban

For bleeding consider: Protamine sulfate. Drug presence may be assessed by anti-Xa assay. Warfarin, rivaroxaban and dabigatran are highly protein bound so dialysis is not effective.

P. Hemodialysis for dabigatran, rivaroxaban or apixaban

For bleeding consider: Protamine sulfate. Drug presence may be assessed by anti-Xa assay. Warfarin, rivaroxaban and dabigatran are highly protein bound so dialysis is not effective.

Q. Hemodialysis for dabigatran, rivaroxaban or apixaban

For bleeding consider: Protamine sulfate. Drug presence may be assessed by anti-Xa assay. Warfarin, rivaroxaban and dabigatran are highly protein bound so dialysis is not effective.

R. Hemodialysis for dabigatran, rivaroxaban or apixaban

For bleeding consider: Protamine sulfate. Drug presence may be assessed by anti-Xa assay. Warfarin, rivaroxaban and dabigatran are highly protein bound so dialysis is not effective.

S. Hemodialysis for dabigatran, rivaroxaban or apixaban

For bleeding consider: Protamine sulfate. Drug presence may be assessed by anti-Xa assay. Warfarin, rivaroxaban and dabigatran are highly protein bound so dialysis is not effective.

T. Hemodialysis for dabigatran, rivaroxaban or apixaban

For bleeding consider: Protamine sulfate. Drug presence may be assessed by anti-Xa assay. Warfarin, rivaroxaban and dabigatran are highly protein bound so dialysis is not effective.

U. Hemodialysis for dabigatran, rivaroxaban or apixaban

For bleeding consider: Protamine sulfate. Drug presence may be assessed by anti-Xa assay. Warfarin, rivaroxaban and dabigatran are highly protein bound so dialysis is not effective.

V. Hemodialysis for dabigatran, rivaroxaban or apixaban

For bleeding consider: Protamine sulfate. Drug presence may be assessed by anti-Xa assay. Warfarin, rivaroxaban and dabigatran are highly protein bound so dialysis is not effective.

W. Hemodialysis for dabigatran, rivaroxaban or apixaban

For bleeding consider: Protamine sulfate. Drug presence may be assessed by anti-Xa assay. Warfarin, rivaroxaban and dabigatran are highly protein bound so dialysis is not effective.

X. Hemodialysis for dabigatran, rivaroxaban or apixaban

For bleeding consider: Protamine sulfate. Drug presence may be assessed by anti-Xa assay. Warfarin, rivaroxaban and dabigatran are highly protein bound so dialysis is not effective.

Y. Hemodialysis for dabigatran, rivaroxaban or apixaban

For bleeding consider: Protamine sulfate. Drug presence may be assessed by anti-Xa assay. Warfarin, rivaroxaban and dabigatran are highly protein bound so dialysis is not effective.

Z. Hemodialysis for dabigatran, rivaroxaban or apixaban

For bleeding consider: Protamine sulfate. Drug presence may be assessed by anti-Xa assay. Warfarin, rivaroxaban and dabigatran are highly protein bound so dialysis is not effective.
III. ANTICOAGULANT AGENT REVERSAL

A. Dabigatran, Rivaroxaban or Apixaban

1. Chronic anticoagulant

2. Transient anticoagulant to be converted to

3. Prevention

4. Reversal of Dabigatran, Rivaroxaban or Apixaban

   a. Fondaparinux has no specific antidote

   b. **Dabigatran, rivaroxaban and apixaban are excreted in the urine, therefore maintain adequate diuresis. Rivaroxaban and apixaban are highly protein bound so dabigatran is not effective.**

   c. Commonly available tests to assess for presence of dabigatran are the aPTT and for warfarin the PT. These tests may be prolonged when dabigatran and rivaroxaban are used at recommended doses but they do not reliably reflect anticoagulant activity. Therapeutic levels of apixaban may not elevate the PT. To measure anticoagulant activity, the scan clotting time (ECT) or dilute thrombin time for dabigatran and chromogenic anti-Factor Xa assays using validated calibrators and controls may be used for rivaroxaban and apixaban.

   d. Warfarin (INR 2.0) and dabigatran may be used together in the same patient if anticoagulation is needed in the setting of cancer. Warfarin may be started after dabigatran, or dabigatran may be started after warfarin, or both agents may be maintained at steady state at the same time. Therapeutic levels of apixaban may not elevate the PT. To measure anticoagulant activity the ecarin clotting time (ECT) or dilute thrombin time for dabigatran and chromogenic anti-Factor Xa assays using validated calibrators and controls may be used for rivaroxaban and apixaban.

   e. Aspirin, clopidogrel and prasugrel inhibit platelet function for lifetime of the platelet. Inhibition takes 7-10 days to reach new platelet levels. Inhibition is fully reversible after discontinuation of therapy.

   f. Must consider indication for use in decision to reverse

   g. 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 manufacturer or current guideline recommendations if uncertain.

   h. For bleeding consider:

      1. Plasma half-life

      2. Reversal of Dabigatran, Rivaroxaban or Apixaban

         a. Dabigatran present

         b. Rivaroxaban present

         c. Apixaban present

         d. Discontinue LMWH or heparin

         e. Discontinue warfarin

         f. Discontinue dabigatran

   i. For further information, please see the complete guidelines on the Chest Website at http://www.chestjournal.org. 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.

   j. Look for this pocket guide as a part of the American College of Chest Physicians Evidence-Based Clinical Practice Guidelines 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.

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

   l. Physicians Evidence-Based Clinical Practice Guideline on Antithrombotic Dosing and Management of Antithrombotic Drug-Associated Bleeding Complications in Adults

   m. For bleeding consider:

      1. Dabigatran present

      2. Rivaroxaban present

      3. Apixaban present

         a. **Dabigatran**

         b. **Rivaroxaban**

         c. **Apixaban**

   n. ± Prasugrel present

   o. ± Aspirin present

   p. ± Clopidogrel present

   q. ± Antithrombotic drug

   r. ± BLEEDING

   s. ± BLEEDING

   t. ± BLEEDING

   u. ± BLEEDING

   v. ± BLEEDING

   w. ± BLEEDING

   x. ± BLEEDING

   y. ± BLEEDING

   z. ± BLEEDING

AA.** One low molecular weight heparin dose should be used for each pharmacological dose of LMWH given. Maximum intensity of anticoagulation is targeted by the LMWH dose (if patient has renal failure)
2. Reversal of Low-Molecular-Weight Heparin (Dalteparin, Fragmin), Enoxaparin (Lovenox), Enoxaparin (Lovenox)* and Fondaparinux (Arixtra)*

- Half-life is longer with subcutaneous administration for all agents so may require monitoring
- Urgent:
  1. Reversal of Low-Molecular-Weight Heparins (Dalteparin (Fragmin)
  2. Reversal of Fondaparinux

- Fondaparinux has no specific antidote
- Enoxaparin 4.5 hours • 1 mg per 1 mg Enoxaparin in previous 8 hours
- Dalteparin 2.2 hours • 1 mg per 100 units Dalteparin in previous 8 hours
- Enoxaparin 3.9 hours • 1 mg per 100 units Tinzaparin in previous 8 hours

3. Reversal of Dabigatran, Rivaroxaban or Apixaban

- Most appropriate tests to assess for presence of dabigatran are the aPTT and Prothrombin time (PT). These tests may be prolonged when dabigatran and rivaroxaban are used at recommended doses but they do not reliably measure the anticoagulant activity. Therapeutic levels of dabigatran may not elevate the PT. To measure anticoagulant activity, the exam Alf evolved clotting time (ECT) or dilute thrombin time for dabigatran and chromogenic anti-Factor Xa assay using validated calibrators and controls may be used for marcouer and apixaban.

4. Reversal of Dabigatran, Rivaroxaban or Apixaban

- Dabigatran, rivaroxaban and apixaban are isolated in the urine, therefore maintenance antidiuretic diuretics. Rivaroxaban and apixaban are highly protein bound so diafiltration is not effective.

- Common anticoagulant to be converted to

- Protamine sulfate

<table>
<thead>
<tr>
<th>Agent</th>
<th>50 ml/min</th>
<th>30 ml/min</th>
<th>20 ml/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>300 ml/min 12 hours</td>
<td>150 ml/min 24 hours</td>
<td>100 ml/min 36 hours</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>100 ml/min 12 hours</td>
<td>75 ml/min 24 hours</td>
<td>50 ml/min 36 hours</td>
</tr>
<tr>
<td>Apixaban</td>
<td>100 ml/min 12 hours</td>
<td>75 ml/min 24 hours</td>
<td>50 ml/min 36 hours</td>
</tr>
</tbody>
</table>

- Apixaban Warfarin Discontinue Apixaban and start warfarin 24 hours later3. If continuous anticoagulation desired, initiate
- Warfarin LMWH or Heparin
- Dabigatran LMWH or Heparin
- Rivaroxaban or Apixaban

- Warfarin INR (2-3) Discontinue warfarin and start dabigatran or apixaban when INR <2.0
- Warfarin INR (>3) Discontinue warfarin and start rivaroxaban when INR >3.0
- LMWH or Heparin Discontinue LMWH or Heparin when INR >1.5. All LMWH

- Apixaban 1 mg/kg intravenous over 15 minutes; and 1 mg/kg oral at next dose
- Rivaroxaban 15 mg or 20 mg oral

- Dabigatran 150 mg intravenous or 150 mg oral

- Aspirin, clopidogrel, and prasugrel inhibit platelet function for lifetime of the platelets. Inhibitors takes 7-10 days to resolve as new platelets are generated.

5. Reversal of Antithrombotic Agents

- Must consider indication for use in decision to reverse
- Ticagrelor may be useful for determining the appropriate dose of warfarin. To minimize this phenomenon, measure INR at apixaban trough.

- Reversal of Antithrombotic Agents

- Discontinue anticoagulant 1-5 days prior to procedure
- Consider platelet transfusion prior to risk bleeding procedures
- HasHTi

- C. Converting Between Anticoagulants

- Patient care and does not establish a fixed set of rules that preempt physician judgment.

- 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://journal.publications.chestnet.org/issue.aspx?journalid=99&issueid=23443 or refer to the Practice Guidelines section of the ASH website at www.ash.org/practaguide/eres. You may also contact the ASH Department of Quality Improvement Programs at 202-776-0544.

- © 2014 by the American Society of Hematology. All rights reserved.

- Images courtesy of Kenneth Mann, PhD, and Matthew Whellan, MS.

- Look for this pocket guide as a downloadable app by searching “ASH Guides” in the iTunes store or Android market.
C. Converting Between Anticoagulants

<table>
<thead>
<tr>
<th>Agent*</th>
<th>Half-Life</th>
<th>Parenteral Dosing for Reversal</th>
<th>Action</th>
<th>Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin (INR 2-3)</td>
<td>Dalteparin or Apixaban</td>
<td>Discontinue warfarin and start dalteparin or apixaban when INR ≤2.0</td>
<td><strong>Antihemostatic</strong></td>
<td>Protamine sulfate at 0.5 mg per 100 units dalteparin in previous 8 hours or LMWH or Heparin while maintaining anti-Xa level.</td>
</tr>
<tr>
<td>Warfarin (INR 2-3)</td>
<td>Tinzaparin</td>
<td>Discontinue warfarin and start tinzaparin when INR ≤2.0</td>
<td><strong>Antihemostatic</strong></td>
<td>Protamine sulfate at 0.5 mg per 100 units tinzaparin in previous 8 hours or LMWH or Heparin while maintaining anti-Xa level.</td>
</tr>
<tr>
<td>LMWH or Heparin</td>
<td>Dalteparin</td>
<td>Start dalteparin 0.25 mg 2 hours before administration of last LMWH/Heparin dose or 0.25 mg at same time as discontinuation of intravenous heparin.</td>
<td><strong>Antihemostatic</strong></td>
<td>Protamine sulfate at 0.5 mg per 100 units dalteparin in previous 8 hours or LMWH or Heparin while maintaining anti-Xa level.</td>
</tr>
<tr>
<td>LMWH or Heparin</td>
<td>Apixaban, Rivaroxaban, or Dabigatran (INR 2-3)</td>
<td>Discontinue LMWH or heparin and initiate intravenous heparin with at least 6 mg/kg heparin over 2 hours to maintain PT within targeted range.</td>
<td><strong>Antihemostatic</strong></td>
<td>Protamine sulfate at 0.5 mg per 100 units LMWH or heparin in previous 8 hours or LMWH or Heparin while maintaining anti-Xa level.</td>
</tr>
</tbody>
</table>

**1.** Fondaparinux has no specific antidote

**2.** Rivaroxaban affects INR, so INR measurements made during coadministration with rivaroxaban the PT. These tests may be prolonged when dabigatran and rivaroxaban are used at recommended doses but they do not affect the PT activity. Therapeutic levels of warfarin may not elevate the PT. To measure anticoagulant activity, the scoring clotting time (ECT) or dilution thrombin time (DDT) is useful for dalteparin and chromogenic anti-factor Xa assay using validated calibrators and controls may be used for marcouin and apixaban.

**3.** Reversal of anticoagulant effect
- Apixaban, clopidogrel, and prasugrel inhibit platelet function for lifetime of the platelets. Inhibition takes 7-10 days to resolve as new platelets are produced.
- Ticagrelor is a reversible inhibitor, so platelet function normalizes after drug clearance. Hold a minimum of 5 days to resolve effect. Unclear if platelet transfusion will be effective in reversing effect when given within 5-7 days of last dose.
- Circulating drug or active metabolites can inhibit transfused platelets.
- Must consider indication for use in decision to reverse
- Risk of coronary stent closure (which can be lethal) within 3 months of bare metal stent implantation; period of risk is likely longer for drug eluting stents.

**4.** Reversal of Dabigatran, Rivaroxaban or Apixaban

**Non-urgent:** Hold further four to five half-lives for recommended duration. Consider longer times for major surgery, placement of spinal or epidural catheter or port.

**Urgent:**
- Hold evening dose day prior
- Hold at least 24 hours
- Hold 48 hours

**5.** Half-life
- **Enoxaparin (Lovenox®):** 3.9 hours • 1 mg per 100 units in previous 8 hours
- **Dalcetaparin (Fondaparinux®):** 2.2 hours • 1 mg per 100 units in previous 8 hours
- **Tinzaparin (Innohep®):** 3.9 hours • 1 mg per 100 units in previous 8 hours
- **Heparin:** 4.5 hours • 1 mg per 1 mg heparin in previous 8 hours
- **Dabigatran:** 12 hours • 1 mg per 100 units dabigatran in previous 8 hours
- **Apixaban:** 7-10 hours • 1 mg per 100 units apixaban in previous 8 hours
- **Rivaroxaban:** 7-10 hours • 1 mg per 100 units rivaroxaban in previous 8 hours
- **Dabigatran present:** 5-9 hours
- **Rivaroxaban present:** 4-5 hours
- **Apixaban present:** 6-7 hours

**6.** Half-life is longer with subcutaneous administration for all agents so may require monitoring with PT (heparin) or anti-Xa level (LMWH) every 3 hours with repeat protamine (0.5 mg per 0.5 mg heparin in previous 8 hours) or LMWH in previous 8 hours.

**7.** Half-life can be increased by concomitant use of warfarin or other anticoagulants.

**8.** Clinical Practice Guidelines (9th Edition).

**9.** Available from the American Society of Hematology.

**10.** You may also contact the ASH Department of Quality Improvement Programs at 202-776-0544.

**11.** Adapted in part from the American College of Chest Physicians Evidence-Based Clinical Practice Guidelines on Antithrombotic and Thrombolytic Therapy (9th Edition).

**12.** 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://journal.publications.chestnet.org/issue.aspx?journalid=99&issueid=23443 or refer to the Practice Guidelines section of the ASH website at www.ash.org/practiceguidelines. You may also contact the ASH Department of Quality Improvement Programs at 202-776-0544.

**13.** © 2014 by the American Society of Hematology. All rights reserved.

**14.** Images courtesy of Kenneth Mann, PhD, and Matthew Whelihan, MS.
**I. ANTICOAGULANT DOERING**

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

**General Considerations**
- 1. Round weight-based dose to nearest prediluted syringe size for U.H.M.
- 2. No dose cap for elderly except elderly delirious in cancer patients.
- 3. Consider measuring anti-Xa heparin levels after 3rd dose for weight >120 kg or >300 lb.
- 4. Repeat CBC day 7 and consider heparin-induced thrombocytopenia if platelets decline.
- 5. If heparin exposure exceeds in 3 months, B.C.H. on day 3 rather than 7.

**Subcutaneous Dosing**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Time</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enoxaparin</td>
<td>1 mg/kg daily</td>
<td>Subcutaneously</td>
<td>Monitor anti-Xa levels if creatinine clearance (CrCl) &gt; 50 mL/min.</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>&lt; 50 kg: 7.5 mg daily</td>
<td>50-100 kg: 10 mg daily</td>
<td>&gt;100 kg: 15 mg daily</td>
</tr>
</tbody>
</table>

**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. No dose cap for obesity except dalteparin in cancer patients.
- 3. Consider measuring anti-Xa heparin levels after 3rd dose for weight >120 kg or >300 lb.

**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. If INR >3.0, consider diabetes, illness, drug interaction or dietary reason as cause for out-of-range INR.
3. Clinical judgment should supersede this nomogram.

**Day INR DAILY DOSE**

1-3 25-50 units/kg IV (lower doses studied)

2 or 4 25-50 units/kg IV (lower doses studied)

5-10 10-30 mL/kg (maximum 50 mL/kg) IM

11-15 5-8 whole FFP

>15 1 unit/kg bolus

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

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

**Dosing**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Time</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enoxaparin</td>
<td>1 mg/kg daily</td>
<td>Subcutaneously</td>
<td>Monitor anti-Xa levels if creatinine clearance (CrCl) &gt; 50 mL/min.</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>&lt; 50 kg: 7.5 mg daily</td>
<td>50-100 kg: 10 mg daily</td>
<td>&gt;100 kg: 15 mg daily</td>
</tr>
</tbody>
</table>


**II. ANTICOAGULANT REVERSAL**

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

**Dosing**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Time</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enoxaparin</td>
<td>1 mg/kg daily</td>
<td>Subcutaneously</td>
<td>Monitor anti-Xa levels if creatinine clearance (CrCl) &gt; 50 mL/min.</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>&lt; 50 kg: 7.5 mg daily</td>
<td>50-100 kg: 10 mg daily</td>
<td>&gt;100 kg: 15 mg daily</td>
</tr>
</tbody>
</table>


**B. Agents to Stop Bleeding**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>10 mg IV PO</td>
<td>• Rapid, complete INR correction in warfarin-treated patients</td>
</tr>
<tr>
<td>Heparin</td>
<td>50-100 units/kg IV (lower doses studied)</td>
<td>• Hold 1 day, decrease by 10–15% †</td>
</tr>
<tr>
<td>Fibrinolytics</td>
<td>1 g IV half-hourly</td>
<td>• Place platelet count at 10 x 10^9/L, S. John’s Wort.</td>
</tr>
<tr>
<td>Tranexamic acid</td>
<td>50-100 units/kg IV (lower doses studied)</td>
<td>• Place platelet count at 10 x 10^9/L, S. John’s Wort.</td>
</tr>
<tr>
<td>Vitamin K</td>
<td>10-30 mg PO</td>
<td>• Place platelet count at 10 x 10^9/L, S. John’s Wort.</td>
</tr>
</tbody>
</table>

**References**
- **HASHTI**
- **J Thromb Haemost 2012; 10(8):1657-1665.**
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 3.0-3.5:
   - Decrease by 15% of ADD.
   - 1.0-1.3: 5 mg po
   - 1.4-1.7: 7.5 mg po
   - 1.8-2.0: 10 mg po
   - 2.1-2.5: 15 mg po

2. If INR >3.5:
   - No guidance is suggested for this INR range.

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

Dose: 200 mg orally, twice daily

Dose adjustments:

- For cancer patients and those at high bleeding or thrombosis risk, favor twice-daily dosing
- For patients with creatinine clearance 15-30 ml/min, use 150 mg once daily with evening meal
- Avoid use in patients taking strong dual inhibitors of CYP3A4 and P-glycoprotein

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

Dose:

- For patients taking strong dual inhibitors of CYP3A4 and P-glycoprotein (e.g., rifampin, carbamazepine, phenytoin, St. John’s Wort), this may lead to reduced rivaroxaban plasma concentrations.

1. Initial Dosing
   - 2.5 mg po 15-90 minutes before evening meal

2. Repeat INR
   - For cancer patients and those at high bleeding or thrombosis risk, favor twice-daily dosing
   - For patients with creatinine clearance 15-30 ml/min, use 150 mg once daily with evening meal
   - Avoid use in patients taking strong dual inhibitors of CYP3A4 and P-glycoprotein

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

Dose: 5 mg twice daily

- For patients taking strong dual inhibitors of CYP3A4 and P-glycoprotein (e.g., rifampin, carbamazepine, phenytoin, St. John’s Wort), this may lead to reduced rivaroxaban plasma concentrations.

1. Initial Dosing
   - 2.5 mg po 15-90 minutes before evening meal

2. Repeat INR
   - For cancer patients and those at high bleeding or thrombosis risk, favor twice-daily dosing
   - For patients with creatinine clearance 15-30 ml/min, use 150 mg once daily with evening meal
   - Avoid use in patients taking strong dual inhibitors of CYP3A4 and P-glycoprotein

G. Anticoagulant Reversal

A. General Principles of Management of Anticoagulant-Associated Bleeding

- Hemorrhage usually requires coagulation factor levels <30%.
- Factor IX may only reach 50%.
- Short half-life may need repeat dosing after 8 hours.
- Large volume, can take hours to thaw and infuse.
- PCC or FFP before procedure.
- Vitamin K 5-10 mg
- Protamine
- Aminocaproic acid
- Factor IX may only reach 20%.
- Factor IX may only reach 50%.
- Short half-life may need repeat dosing after 8 hours.
- Large volume, can take hours to thaw and infuse.
- PCC or FFP before procedure.
- Vitamin K 5-10 mg
- Protamine
- Aminocaproic acid
- Factor IX may only reach 20%.
- Factor IX may only reach 50%.
- Short half-life may need repeat dosing after 8 hours.
- Large volume, can take hours to thaw and infuse.

B. Agents to Stop Bleeding

- Protamine
- Aminocaproic acid
- Factor IX may only reach 50%.
- Short half-life may need repeat dosing after 8 hours.
- Large volume, can take hours to thaw and infuse.
- PCC or FFP before procedure.
- Vitamin K 5-10 mg
- Protamine
- Aminocaproic acid
- Factor IX may only reach 50%.
- Short half-life may need repeat dosing after 8 hours.
- Large volume, can take hours to thaw and infuse.
- PCC or FFP before procedure.
### I. ANTICOAGULANT DOSING

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

**General Considerations**
- Round weight-based dose to nearest prefixed milligram size for LMWH.
- No dose cap for elderly unless dyspnea in cancer patients.
- Consider measuring anti-Xa heparin levels after 3rd dose for weight >100 kg or <50 kg.
- 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 day 7.

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

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

<table>
<thead>
<tr>
<th>Day</th>
<th>INR</th>
<th>DAILY DOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-3</td>
<td>Not required</td>
<td>5 mg*</td>
</tr>
<tr>
<td>3 or 4</td>
<td></td>
<td>15 mg</td>
</tr>
<tr>
<td>15-17</td>
<td>5 mg</td>
<td>5 mg every 8 hours</td>
</tr>
<tr>
<td>18-19</td>
<td>5 mg</td>
<td>2.5 mg twice daily</td>
</tr>
<tr>
<td>20</td>
<td>60 kg</td>
<td>1 dose/day, up to 2.5 mg</td>
</tr>
<tr>
<td>21-32</td>
<td>Increase by 0.5 mg/ADD</td>
<td>Increase by 0.5 mg/ADD</td>
</tr>
<tr>
<td>33-35</td>
<td>Increase by 1.0 mg/ADD</td>
<td>Increase by 1.0 mg/ADD</td>
</tr>
<tr>
<td>36-38</td>
<td>Increase by 1.5 mg/ADD</td>
<td>Increase by 1.5 mg/ADD</td>
</tr>
<tr>
<td>39-42</td>
<td>Increase by 2.0 mg/ADD</td>
<td>Increase by 2.0 mg/ADD</td>
</tr>
<tr>
<td>43 or 44</td>
<td>No Change</td>
<td>Decrease by 10% of ADD</td>
</tr>
<tr>
<td>45-48</td>
<td>Decrease by 10% of ADD</td>
<td>Decrease by 10% of ADD</td>
</tr>
<tr>
<td>49</td>
<td>1 dose/day, up to 2.5 mg</td>
<td>Increase by 1.0 mg/ADD</td>
</tr>
</tbody>
</table>

### II. ANTICOAGULANT REVERSAL

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

**Dose:**
- Enoxaparin 30-50 mg or Fondaparinux 7.5 mg orally, twice daily.

**Dose Adjustments:**
- INR >5.0: 0–10% of ADD.
- INR >10.0: 0–20% of ADD.

**Definition of Reversal Situations**
- **Non-urgent**
  - Reversal is elective (procedures >5 days away)
  - Immediate reversal
- **Urgent (without bleeding)**
  - Reversal needed within hours
- **Urgent (with bleeding)**
  - Immediate reversal

### Chronic Warfarin Dose Adjustment in Non-Bleeding Patients

<table>
<thead>
<tr>
<th>Target INR</th>
<th>DAILY DOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.0-3.0</td>
<td><strong>Reversal within 2 weeks</strong></td>
</tr>
<tr>
<td>3.1-3.5</td>
<td>Hold 0–1 day, then decrease by 15% or less</td>
</tr>
<tr>
<td>3.6-4.0</td>
<td>Decrease by 10–15%*</td>
</tr>
<tr>
<td>4.1-4.9</td>
<td>Adjust INR by 0.1–0.2</td>
</tr>
<tr>
<td>&gt;5.0</td>
<td><strong>Hold further doses of anticoagulant</strong></td>
</tr>
</tbody>
</table>

**Definition of Reversal Situations**
- **Urgent (with bleeding)**
  - Immediate reversal
  - Reversal needed within hours

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

- **Dose:**
  - 2.5 mg for young healthy patients
  - 5-7.5 mg for young healthy patients
  - 2.5 mg for frailty, liver disease, malnutrition, drugs that enhance warfarin activity, or Asian ethnicity

**Rivaroxaban**
- 2.5 mg po q.d.
- 5 mg po q.d.
- 15 mg every 12 hours for 21 days followed by 2.5 mg po daily, taken with food.

**APixaban**
- 5 mg po q.d.
- 10 mg po q.d.

**Dabigatran**
- 75 mg po b.i.d.
- 150 mg po b.i.d.

- **Dose Adjustments:**
  - Age >75 years or body weight <50 kg
  - Liver dysfunction
  - CHF, renal failure

**Definitions Used for Reversal Situations**
- **Non-urgent**
  - Reversal is elective (procedures >5 days away)
- **Urgent (without bleeding)**
- **Urgent (with bleeding)**
  - Immediate reversal

### 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>11–13 mg N/1 PO</td>
<td>Vitamin K may cause bleeding and should not be administered orally.</td>
</tr>
<tr>
<td>Protamine sulfate</td>
<td>12.50–20 mg/200 mL IV</td>
<td>Full reversal of unfractionated heparin.</td>
</tr>
<tr>
<td>Platelets</td>
<td>1–8 apheresis or 5–8 whole blood units</td>
<td>Use for other indications currently off label.</td>
</tr>
<tr>
<td>Heparin flush (LMWH)</td>
<td>100–500 units/mL</td>
<td>Must be performed with antithrombin therapy.</td>
</tr>
<tr>
<td>FFP or PCC prior to procedure.</td>
<td>1.4%</td>
<td>Risk of thrombus 5–10%.</td>
</tr>
<tr>
<td>Reversal of Fondaparinux</td>
<td>1.4%</td>
<td>May increase risk of thrombosis.</td>
</tr>
<tr>
<td>Reversal of Factor Xa inhibitor (e.g., rivaroxaban, apixaban)</td>
<td>1.4%</td>
<td>Risk of thrombosis 1.4%; contraindicated with history of HIT.</td>
</tr>
<tr>
<td>Protamine</td>
<td>0.25–1 g/hr x 24 hrs</td>
<td>Large doses can cause warfarin resistance on resumption.</td>
</tr>
<tr>
<td>Protamine and vitamin K</td>
<td>0.25–1 g/hr x 24 hrs</td>
<td>May increase risk of thrombosis.</td>
</tr>
<tr>
<td>Warfarin (10–15 mg)</td>
<td>0.25–1 g/hr x 24 hrs</td>
<td>May increase risk of thrombosis.</td>
</tr>
<tr>
<td>Vitamin K 5–10 mg PO</td>
<td>0.25–1 g/hr x 24 hrs</td>
<td>May increase risk of thrombosis.</td>
</tr>
</tbody>
</table>

### III. Warfarin Resistance

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>Increased sensitivity</td>
<td>Reversal is rarely necessary.</td>
</tr>
<tr>
<td>Vitamin K antagonists</td>
<td>Increased sensitivity</td>
<td>Reversal is rarely necessary.</td>
</tr>
<tr>
<td>Fibrinolytics</td>
<td>Increased sensitivity</td>
<td>Reversal is rarely necessary.</td>
</tr>
</tbody>
</table>

---

*23 mg for thrice daily, less malnourished, drugs that enhance warfarin activity, or Asian ethnicity; 5-7.5 mg for young healthy patients

---

**Check INR more frequently**

---

**INR target INR 2.0-3.0**

<table>
<thead>
<tr>
<th>INR range</th>
<th>Dose adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0–1.3</td>
<td>7.5 mg daily</td>
</tr>
<tr>
<td>1.6–1.8</td>
<td>5/2.5 mg alternating</td>
</tr>
<tr>
<td>1.9–2.0</td>
<td>Hold 1 day, then 2.5 mg†</td>
</tr>
<tr>
<td>&gt;2.0</td>
<td>Hold further doses of anticoagulant</td>
</tr>
</tbody>
</table>

---

**INR therapeutic.**
A. **Subcutaneous Heparin Dosing for Treatment of Acute Venous Thromboembolism**

**General Considerations**
1. Round weight-based dose to nearest predefined salting size for LMWH.
2. No dose cap for obesity except dalteparin for cancer patients.
3. Consider measuring anti-Xa heparin levels after 3 doses for weight >120 kg or >75 kg.
4. Repeat CBC day 7 and check heparin-induced thrombocytopenia if platelets decline.
   - If heparin exposure in previous 3 months, CBC on day 3 rather than day 7.
5. Use anti-Xa levels if all 3, and monitor anti-Xa levels if creatinine clearance (Ccr) <30 mL/min.

**Subcutaneous Dosing**
- Enoxaparin: 1 mg/kg every 12 hours or 1.5 mg/kg daily
- Unfractionated heparin: 333 IU/kg x 1, then 250 IU/kg every 12 hours
- Fondaparinux: 
  - <60 kg: 5 mg daily
  - 60-100 kg: 7.5 mg daily
  - >100 kg: 10 mg daily

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

**Anticoagulant Dosing**
- Dabigatran: 150 mg twice daily
- Apixaban: 5 mg twice daily
- Rivaroxaban: 10 mg once daily
- Edoxaban: 60 mg once daily
- Arixten: 5 mg once daily

**Dose Adjustments**
- Use of strong dual inhibitors of CYP3A4 and P-glycoprotein (e.g., ketoconazole, ritonavir, clarithromycin)
- Avoid use in patients taking P-glycoprotein inducers (e.g., rifampin, carbamazepine, phenytoin, St. John’s Wort).
- Do not administer apixaban in patients with both #1 and #2.

**Definitions Used for Reversal Situations**
- Non-urgent: elective (procedures >5 days away)
- Urgent (without bleeding): Immediate reversal
- Urgent (with bleeding): Immediate reversal to 7.8 +8.0
   - Increase by 15% if INR >1.5

**II. COAGULATION REVERSAL**

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

**Definitions Used for Reversal Situations**
- Non-urgent: elective (procedures >5 days away)
- Urgent (without bleeding): Immediate reversal