2. Reversal of Low-Molecular-Weight Heparin (Dabigatran, Pradaxa®), Encapronar (Lovenox®), Enoxaparin (Lovenox®) and Fondaparinux (Arixtra®)

<table>
<thead>
<tr>
<th>Agent*</th>
<th>Half-Life</th>
<th>Protamine Sulfate Dosing for Reversal</th>
<th>Caution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heparin</td>
<td>1-2 hours</td>
<td>1 mg per 50-100 units heparin given in previous 2-3 hours</td>
<td>Twice-daily regimens</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1-2 hours</td>
<td>Hold evening dose day prior, hold evening dose day of procedure</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>3.2 hours</td>
<td>1 mg per 100 units Dabigatran in previous 8 hours</td>
<td>Once-daily regimens</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.9 hours</td>
<td>Hold day of procedure</td>
</tr>
<tr>
<td>LMWH or Heparin</td>
<td>1 mg 1-2 hours</td>
<td>Discontinue warfarin and start dabigatran or apixaban when INR &lt;2.0</td>
<td>Protamine sulfate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LMWH or Heparin</td>
<td>Discontinue LMWH or heparin and initiate alternative anticoagulant while starting warfarin.</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>0-2 hours</td>
<td>Start dabigatran 0-2 hours before administration of last LMWH/Heparin dose, or same time as discontinuation of fibrinolytic.</td>
<td></td>
</tr>
<tr>
<td>Apixaban</td>
<td>0-2 hours</td>
<td>Start apixaban 0-2 hours after last dose of dabigatran, CLO-2 mg per day start 24 hours after last dose of dabigatran.</td>
<td></td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>2-3 hours</td>
<td>Discontinue LMWH or heparin and initiate alternative anticoagulant while starting warfarin.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rivaroxaban</td>
<td>Discontinue LMWH or heparin 24 hours after discontinuation of Rivaroxaban.</td>
</tr>
</tbody>
</table>

### General Considerations

- **Inhibition**
  - Use platelet function tests (abnormal during anticoagulation but normal after discontinuation). Platelet function return to normal 24-48 hours after stopping anticoagulation.
  - The onset of action of ticagrelor is more rapid than prasugrel.

<table>
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<tr>
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<th>Half-Life</th>
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<td></td>
<td>Rivaroxaban</td>
<td>Discontinue LMWH or heparin 24 hours after discontinuation of Rivaroxaban.</td>
</tr>
</tbody>
</table>

### General Considerations

- **Inhibition**
  - Use platelet function tests (abnormal during anticoagulation but normal after discontinuation). Platelet function return to normal 24-48 hours after stopping anticoagulation.
  - The onset of action of ticagrelor is more rapid than prasugrel.
II. ANTICOAGULANT INDICATIONS

A. Indications for Anticoagulation

1. Deep vein thrombosis (DVT) and pulmonary embolism (PE)
2. Prevention of stroke in non-valvular atrial fibrillation (NVAF)
3. Treatment and prevention of arterial thromboembolic events
4. Prevention of thromboembolism in mechanical heart valves
5. Prevention of thromboembolism in patients with a recent stent placement

B. Duration of Anticoagulation

1. DVT and PE: 3-6 months
2. NVAF: 3-12 months
3. Arterial thromboembolic events: duration based on underlying condition
4. Mechanical heart valves: lifelong
5. Stent placement: lifelong

C. Anticoagulant Choice

1. DVT and PE: Unfractionated heparin or LMWH
2. NVAF: Warfarin
3. Arterial thromboembolic events: warfarin or LMWH
4. Mechanical heart valves: warfarin
5. Stent placement: antiplatelet agents

D. Monitoring of Anticoagulation

1. DVT and PE: Monitoring of anticoagulation is not necessary
2. NVAF: INR monitoring is mandatory
3. Arterial thromboembolic events: monitoring of anticoagulation is not necessary
4. Mechanical heart valves: INR monitoring is mandatory
5. Stent placement: monitoring of antiplatelet therapy is necessary

E. Reversal of Anticoagulation

1. DVT and PE: No specific reversal agent
2. NVAF: Protamine (LMWH) or protamine (heparin)
3. Arterial thromboembolic events: protamine (LMWH) or protamine (heparin)
4. Mechanical heart valves: protamine (LMWH) or protamine (heparin)
5. Stent placement: antiplatelet agents

F. Discontinuation of Anticoagulation

1. DVT and PE: Discontinue anticoagulation 1-2 days after successful thrombolysis
2. NVAF: Discontinue anticoagulation 3-5 days after successful thrombolysis
3. Arterial thromboembolic events: discontinue anticoagulation 5-7 days after successful thrombolysis
4. Mechanical heart valves: discontinue anticoagulation 5-7 days after successful thrombolysis
5. Stent placement: discontinue antiplatelet therapy 5-7 days after successful thrombolysis

G. Anticoagulant Switching

1. DVT and PE: No specific requirements
2. NVAF: Switching between warfarin and LMWH is not recommended
3. Arterial thromboembolic events: switching between warfarin and LMWH is not recommended
4. Mechanical heart valves: switching between warfarin and LMWH is not recommended
5. Stent placement: switching between antiplatelet agents is not recommended

H. Anticoagulant Switching to Non-Vitamin K Oral Anticoagulants

1. DVT and PE: No specific requirements
2. NVAF: Switching from warfarin to dabigatran, rivaroxaban, or apixaban is not recommended
3. Arterial thromboembolic events: switching from warfarin to dabigatran, rivaroxaban, or apixaban is not recommended
4. Mechanical heart valves: switching from warfarin to dabigatran, rivaroxaban, or apixaban is not recommended
5. Stent placement: switching from antiplatelet agents to non-Vitamin K oral anticoagulants is not recommended

III. ANTICOAGULANT AGENT REVERSAL

A. Anticoagulant Reversal Strategies

1. Warfarin
   a. Intravenous vitamin K (5 mg)
   b. Prothrombin complex concentrate
   c. Recombinant factor VIIa

2. LMWH or heparin
   a. Protamine (0.5 mg per 100 units of LMWH or 100 units of heparin)
   b. Alteplase
   c. Transfusion

3. Dabigatran
   a. Activated charcoal
   b. DDAVP
   c. Hemodialysis

4. Rivaroxaban and apixaban
   a. Activated charcoal
   b. DDAVP
   c. Hemodialysis

5. Fondaparinux
   a. Activated charcoal
   b. DDAVP
   c. Hemodialysis

B. Reversal of Anticoagulation

1. Warfarin
   a. INR > 5: administer vitamin K 5 mg intravenously
   b. INR > 4: administer vitamin K 5 mg intravenously

2. LMWH or heparin
   a. Protamine (0.5 mg per 100 units of LMWH or 100 units of heparin)
   b. Alteplase
   c. Transfusion

3. Dabigatran
   a. Activated charcoal
   b. DDAVP
   c. Hemodialysis

4. Rivaroxaban and apixaban
   a. Activated charcoal
   b. DDAVP
   c. Hemodialysis

5. Fondaparinux
   a. Activated charcoal
   b. DDAVP
   c. Hemodialysis
2. Reversal of Low-Molecular-Weight Heparins (Dalteparin (Fragmin™), Enoxaparin (Lovenox™), Nadroparin (Tongue™)) and Fondaparinux (Arixtra™)

Non-Urgent

- Urgent (Not Bleeding)
  - Urgent (Bleeding)

- Hemorrhage
  - Half-life
  - Maximum dose is 50 mg

- Hirudin
  - PCC (Xenia™) 200 mg
  - Ristocetinuces (Vistogard®) 100 mg
  - Recombinant hirudin (Hyphen™) 0.5 mg

- Antisense phosphorothioate oligodeoxynucleotide

- Urokinase
  - 1000 IU/kg

- TPA

- Tissue plasminogen activator

-Platelet function inhibitors

- Aspirin
  - 325 mg

- Ticagrelor
  - 200 mg

- Prasugrel
  - 60 mg

- Clopidogrel
  - 600 mg

- Montelukast
  - 20 mg

- Sodium bicarbonate

- Hemostatic agents

- Prothrombin complex concentrates

- Factor VIIa

-Activated PCC

- Activated PCC (FEIBA)

- rFVIIa

- Factor IXa (NovoSeven®)

- Antithrombotic Therapy (9th Edition).

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- III. ANTIPLATELET AGENT REVERSAL

- Aspirin, clopidogrel, prasugrel and ticagrelor

- General Considerations

- 1. Pharmacology

- a. Clopidogrel, prasugrel, and ticagrelor

- b. Aspirin

- 2. Reversibility of antiplatelet effect

- a. Aspirin, clopidogrel, and prasugrel

- b. Ticagrelor

- 3. Reversal of antiplatelet agents

- a. Aspirin

- b. Clopidogrel, prasugrel, and ticagrelor

- c. Combination therapy

- 4. Reversibility of Fondaparinux

- a. Fondaparinux


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2. Reversal of Low-Molecular-Weight Heparin (Dalteparin, Fraxiparin), Enoxaparin (Lovenox), Tinzaparin (Innohep) and Fondaparinux (Arixtra)

Abbreviations: PCC, prothrombin complex concentrates; FVIIIa, recombinant factor VIIIa

• Hold 1 day of procedure

• Dose-Fraxiparin: 25% of dose

• Dose-Lovenox, Innohep: 100% of dose

• Dose-Arixtra: 50% of dose

• Hold evening dose day prior

• Reassess patient

• Repeat abnormal coagulation tests

• Monitor until INR is normal

III. ANTIPLATELET AGENT REVERSAL

A. Aspirin

General Considerations

• Plasma half-life

• Dose-related

• 10-15 hours

• 300 mg bid

• 150 mg tid

• Monitoring

• Platelet aggregation inhibition

• Platelet function tests

• Verify decrease in aspirin levels

• Verify effect on platelet aggregation

• Verify effect on platelet function

American Society of Hematology
2021 13th Street NW, Suite 900
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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 for LMWH.
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 CrCl <30 ml/min.
4. Repeat CBC day 7 and consider INR ≥3.5 or ≤1.5.
5. Use anti-Xa heparin level at all, and monitor anti-Xa levels if creatinine clearance (CrCl) <30 ml/min.

**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, reduce dose by 25% or 50% of standard dose.

**Dosing**

- 0, 1, 3, 5, 7, 9, 11 mg/kg/day
- 0, 1, 3, 5, 7, 9, 11 mg/kg/day
- 0, 1, 3, 5, 7, 9, 11 mg/kg/day
- 0, 1, 3, 5, 7, 9, 11 mg/kg/day

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 consider if abnormal.
2. Obtain weight-based dose to nearest prefilled syringe size for LMWH.
3. Consider measuring anti-Xa heparin levels after 3rd dose for weight >120 kg or CrCl <30 ml/min.
4. Repeat CBC day 7 and consider heparin-induced thrombocytopenia if platelets decrease significantly.
5. **Check INR more frequently**
6. Recommend first INR check on day 3-4.
7. If heparin exposure in previous 3 months, CBC on day 3 rather than day 7.
8. INR therapeutic.
9. INR ≥3.5 or ≤1.5.
10. INR >2.0 Hold x 1 day, then 2.5 mg†
11. INR 1.0-1.3 7.5 mg
12. INR 1.6-1.8 5/2.5 mg alternating
13. INR ≥1.9 2.5 mg†

C. Chronic Warfarin Dose Adjustment in Non-Bleeding Patients

This nomogram is suggested for non-bleeding patients with target INR 2.0-3.0 who are out of range and who are not at high risk of bleeding.

1. If INR >3.0 confirm no bleeding.
2. 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 CrCl <30 ml/min.
4. Repeat CBC day 7 and consider heparin-induced thrombocytopenia if platelets decrease significantly.
5. **Check INR more frequently**
6. Consider anti-Xa heparin levels after 3rd dose for weight >120 kg or CrCl <30 ml/min.
7. **Repeat INR in 2 days**

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

**Dose:**

- 1.0 mg/kg every 12 hours or 1.5 mg/kg daily
- 1.0 mg/kg every 12 hours or 1.5 mg/kg daily
- 1.0 mg/kg every 12 hours or 1.5 mg/kg daily
- 1.0 mg/kg every 12 hours or 1.5 mg/kg daily

**Dose adjustments:**

- INR >3.0: Increase by 10-15% of ADD
- INR 2.0-3.0: Hold dose
- INR ≤1.5: Decrease by 10-15% of ADD
- INR <1.0: Decrease by 15-20% of ADD

**Definitions Used for Reversal Situations**

1. Non-urgent (able to delay procedure) in 3-5 days
2. Urgent (within 24 hours; withdrawal of life support)
3. Emergency (within 24 hours or rarely, death or risk of death)

**References**

- Budajova E, Foreman T, Jücker R, et al. \( \text{INR} = \frac{\text{INR}_{\text{target}} - 1}{\text{INR}_{\text{target}} - 1} \times \text{ADD} \)

B. Agents to Stop Bleeding

**Agent**

- Vitamin K
- Prothrombin complex concentrates (PCC)
- Platelets

**Dose**

- 1.0 mg IM/IV
- 12.5-20 mg I.V.
- 10-30 mL/kg

**Comments**

- Vitamin K: 1.0 mg IM/IV
- Prothrombin complex concentrates (PCC): 10-30 mL/kg
- Platelets: 10-30 mL/kg

**Definitions Used for Reversal Situations**

1. **Non-urgent** (able to delay procedure) in 3-5 days
2. **Urgent** (within 24 hours)
3. **Emergency** (within 24 hours or rarely, death or risk of death)
**I. ANTICOAGULANT DOSING**

A. Subcutaneous Heparin Dosing for Treatment of Acute Venous Thromboembolism

**General Considerations**
1. Round weight-based dose to nearest prespecified intravenous size for LMWH.
2. No dose cap for elderly unless doubtful in elderly patients or cancer patients.
3. Consider measuring anti-Xa heparin levels after 3rd dose for weight >120 kg or <50 kg.
4. Repeat CBC day 7 and consider heparin-induced thrombocytopenia if platelets decline.
   - *If heparin exposure in previous 3 months, CBC on day 3 rather than day 7.*
5. Use UFH with routine aPTT at all times, and monitor anti-Xa levels if creatinine clearance (CrCl) <30 mL/min.

**Subcutaneous Dosing**
- Enoxaparin: 1 mg/kg every 12 hours or 1.5 mg/kg every 24 hours for cancer patients and those at high bleeding or thrombosis risk, fewer times/day.
- Dalteparin: 200 IU/kg/day or 100 IU/kg every 12 hours.
- Fondaparinux: <50 kg: 5 mg daily. 50-100 kg: 7.5 mg daily. >100 kg: 10 mg daily.

**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. For cancer patients and those at high bleeding or thrombosis risk.
4. Clinical judgment should supersede this nomogram.

<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>2-4</td>
<td>1.5–2.5</td>
<td>5 mg</td>
</tr>
<tr>
<td>5-6</td>
<td>2.5–3.5</td>
<td>5 mg</td>
</tr>
<tr>
<td>7-10</td>
<td>&gt;3.5</td>
<td>5 mg</td>
</tr>
</tbody>
</table>

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

B. 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 <2.0: confirm no bleeding.
2. If INR >3.0: confirm no bleeding, presence of anticoagulation, illness, drug, interaction or dietary change as reason for out-of-range INR. Go to step 3.

**C. Warfarin Nomogram**

- Add 10% for INR >3.0 or <2.0.
- Add 15% for INR >3.5 or <1.5.
- Add 20% for INR >3.5 and age >75 years or propensity for GI bleeding; 110 mg twice daily.

**D. Dibagatan Dosing to Prevent Stroke and Systemic Embolism in Non-Valvular Atrial Fibrillation**

**Dose:**
- CO2 >50 mV*; 150 mg orally twice daily.
- Use in patients with CO2 <50 and taking P-glycoprotein inhibitors (e.g., dronedarone, azithromycin).

**Dose adjustments:**
- CO2 >50 mV*: 75 mg orally twice daily.
- CO2 <50 and taking P-glycoprotein inhibitors: 75 mg orally, twice daily.

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

- Avoid in patients taking strong dual inhibitors of CYP3A4 and P-glycoprotein (e.g., ritonavir, amprenavir, nelfinavir, saquinavir). This may lead to reduced rivaroxaban plasma concentrations.

- 1. Atrial Fibrillation
   - CO2 >50 mV*: 20 mg once daily with evening meal
   - CO2 >15 mV*: 15 mg once daily with evening meal

- 2. Thromboembolism
   - 15 mg every 12 hours for 21 days followed by 10 mg daily, taken with food, while on treatment.

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

- **Dose:** 5 mg twice daily.
- **INR therapeutic.**

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

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

- **General Considerations**
- B. Initial Warfarin Dosing for venous thromboembolism or atrial fibrillation in ambulatory outpatients, target INR 2.0-3.0.
- 2. Consider noncompliance, illness, drug interaction, or dietary change as reason for out-of-range INR.
- 3. Clinical judgment should supersede this nomogram.

**Day**

<table>
<thead>
<tr>
<th>Day</th>
<th>INR</th>
<th>Reversal within 2 weeks</th>
<th>Repeat INR in 2 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-3</td>
<td>Not required</td>
<td>1-2 days</td>
<td>2-3 days</td>
</tr>
<tr>
<td>2-4</td>
<td>1.5–2.5</td>
<td>3-4 days</td>
<td>4-5 days</td>
</tr>
<tr>
<td>5-6</td>
<td>2.5–3.5</td>
<td>4-5 days</td>
<td>5-6 days</td>
</tr>
<tr>
<td>7-10</td>
<td>&gt;3.5</td>
<td>5-6 days</td>
<td>6-7 days</td>
</tr>
</tbody>
</table>

*Consider 15% increase in INR <1.5 without explanation

**II. ANTICOAGULANT REVERSAL**

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

**HASHT**
1. Hold further doses of anticoagulant.
2. Consider Antidote
3. Supportive therapy
   - Volume resuscitation (intravenous fluids)
   - Electrolyte support (intravenous fluids)
   - Local or surgical Hemostatic measures
   - Anti-fibrinolytic agents can be considered (aminocaproic acid, tranexamic acid)
   - Consider concurrent FFP if 3-factor PCC used

**B. Agents to Stop Bleeding**

<table>
<thead>
<tr>
<th>Agents</th>
<th>Dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin K</td>
<td>1.5 mg/d PO</td>
<td>Immediate reversal of warfarin effects; controls INR levels in 6 hours</td>
</tr>
<tr>
<td>Prothrombin Complex Concentrate (PCC)</td>
<td>Reverses warfarin effect in minutes; lasts 6-9 hours</td>
<td>Non-urgent bleeding (5 days or less)</td>
</tr>
<tr>
<td>Platelets</td>
<td>Platelet count &gt;30 x 10^9/L</td>
<td>Maintains or restores platelet counts</td>
</tr>
<tr>
<td>Fresh Frozen Plasma (FFP)</td>
<td>Reverses warfarin effect in minutes; lasts 6-12 hours</td>
<td>Non-urgent bleeding (5 days or less)</td>
</tr>
</tbody>
</table>

**Reversal of Warfarin (Coumadin, Jantoven)**

**Non-Urgent**
1. **Warfarin** (1-2 days prior to procedure)
   - **INR** >1.5 monitored
   - **INR** >3.0 monitored
   - **INR** >5.0 monitored
2. **Vitamin K** (1-2 days prior to procedure)
   - **INR** >3.0 monitored
   - **INR** >5.0 monitored
3. **Prothrombin Complex Concentrate (PCC)** or **Plasma**
   - **INR** >5.0 monitored

**Urgent (Bleeding)**
1. **Warfarin** (1-2 days prior to procedure)
   - **INR** >3.0 monitored
   - **INR** >5.0 monitored

2. **Vitamin K** (1-2 days prior to procedure)
   - **INR** >3.0 monitored

3. **Prothrombin Complex Concentrate (PCC)** or **Plasma**
   - **INR** >5.0 monitored

**Reversal of Warfarin (Coumadin, Jantoven)**

**Non-Urgent**
1. **Warfarin** (1-2 days prior to procedure)
   - **INR** >3.0 monitored
   - **INR** >5.0 monitored
   - **INR** >7.0 monitored
2. **Vitamin K** (1-2 days prior to procedure)
   - **INR** >3.0 monitored
   - **INR** >5.0 monitored
3. **Prothrombin Complex Concentrate (PCC)** or **Plasma**
   - **INR** >5.0 monitored

**Urgent (Bleeding)**
1. **Warfarin** (1-2 days prior to procedure)
   - **INR** >3.0 monitored
   - **INR** >5.0 monitored
   - **INR** >7.0 monitored
2. **Vitamin K** (1-2 days prior to procedure)
   - **INR** >3.0 monitored
   - **INR** >5.0 monitored
3. **Prothrombin Complex Concentrate (PCC)** or **Plasma**
   - **INR** >5.0 monitored

**Reversal of Warfarin (Coumadin, Jantoven)**

**Non-Urgent**
1. **Warfarin** (1-2 days prior to procedure)
   - **INR** >3.0 monitored
   - **INR** >5.0 monitored
   - **INR** >7.0 monitored
2. **Vitamin K** (1-2 days prior to procedure)
   - **INR** >3.0 monitored
   - **INR** >5.0 monitored
3. **Prothrombin Complex Concentrate (PCC)** or **Plasma**
   - **INR** >5.0 monitored

**Reversal of Warfarin (Coumadin, Jantoven)**

**Non-Urgent**
1. **Warfarin** (1-2 days prior to procedure)
   - **INR** >3.0 monitored
   - **INR** >5.0 monitored
   - **INR** >7.0 monitored
2. **Vitamin K** (1-2 days prior to procedure)
   - **INR** >3.0 monitored
   - **INR** >5.0 monitored
3. **Prothrombin Complex Concentrate (PCC)** or **Plasma**
   - **INR** >5.0 monitored

**Reversal of Warfarin (Coumadin, Jantoven)**

**Non-Urgent**
1. **Warfarin** (1-2 days prior to procedure)
   - **INR** >3.0 monitored
   - **INR** >5.0 monitored
   - **INR** >7.0 monitored
2. **Vitamin K** (1-2 days prior to procedure)
   - **INR** >3.0 monitored
   - **INR** >5.0 monitored
3. **Prothrombin Complex Concentrate (PCC)** or **Plasma**
   - **INR** >5.0 monitored
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 for LMWH.
2. No dose cap for elderly diabetes-dependent diabetics in cancer patients.
3. Consider measuring anti-Xa heparin levels after 3rd dose for weight >120 kg or <50 kg.
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 day 7.
5. Use MSHR with caution if all, and monitor anti-Xa levels if creatinine clearance <30 ml/min.

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, fewer daily doses.
Dalteparin: 200 IU/kg daily or 100 IU/kg every 12 hours
Tinzaparin: 175 IU/kg daily
Fondaparinux: 50–60 kg: 2.5 mg/day; >60 kg: 5 mg/day
Unfractionated heparin: 5,000 IU q12h

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. Consider noncompliance, illness, drug interaction, or dietary change as reason for out-of-range INR.
3. Clinical judgment should supersede this nomogram.
4. No dose cap for obesity except dalteparin in cancer patients.
5. Without explanation, favor twice-daily dosing.

Day INR DAILY DOSE
1-3: Not required
2 or 4: 10-15%†
6: 10-15%
7–10: 0%

†Consider 15% increase if INR <1.5 without explanation

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 <2.0, confirm no bleeding.
2. Consider noncompliance, illness, drug interaction, or dietary change as reason for out-of-range INR.
3. Clinical judgment should supersede this nomogram.

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

Dose:
- 1.5 mg twice daily if:
  • ≥60 kg
  • No prior or ongoing warfarin therapy
  • Low-to-moderate risk of bleeding

Dose adjustments:
- 2.5 mg twice daily if:
  • CrCl 15–50 ml/min
  • High risk of bleeding
  • Any other indication

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

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

1. Atrial fibrillation
   • OAC: 2.0–3.0 mg once daily with evening meal
   • OAC: 15 mg/15 mg: 1.5 mg once daily with evening meal

2. Venous Thromboembolism
   • 15 mg every 12 hours for 21 days followed by 30 mg daily, taken with food
   • Not recommended if OAC <30 ml/min

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

Dose: 5 mg twice daily
- OAC: 15 mg/15 mg: Avoid use
- Use in patients taking strong dual inhibitors of CYP3A4 and P-glycoprotein (e.g., rifampin, carbamazepine, phenytoin, St. John’s Wort)

Dose adjustments:
- Dose 2.5 mg daily if:
  • Age >80 years
  • Body weight <50 kg
  • Serum creatinine ≥1.5 mg/dL

2. Use of strong dual inhibitors of CYP3A4 and P-glycoprotein (e.g., ketoconazole, itraconazole, nelfinavir, clarithromycin)

G. 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, itraconazole, nelfinavir, clarithromycin)

H. General Principles of Management of Anticoagulant-Associated Bleeding

1. Reversal of Warfarin (Coumadin®, Jantoven)

Non-Urgent Urgent (Not bleeding) Urgent (Bleeding)
** INR >1.5 administer vitamin K 1-10 mg IV/PO
** INR >1.5 and ≥2.5 administer Vitamin K 5-10 mg PO

• Vitamin K 10-30 mg PO, 60-90% reversal of LMWH
• Vitamin K 10 mg PO/N PO, if sustained reversal is desired

• INR >2.5 Hold further doses of anticoagulant
• INR >3.0 Reversal of anticoagulant can be achieved
• INR >4.0 Hold further doses of anticoagulant

• Check INR 1-2 days
• INR >1.5 administer vitamin K 1-10 mg PO/N PO

IV; repeat in 12 hours as needed

• INR >1.5 Hold further doses of anticoagulant
• INR >3.0 Reversal of anticoagulant can be achieved
• INR >4.0 Hold further doses of anticoagulant

• Check INR 1-2 days
• INR >1.5 administer vitamin K 1-10 mg PO/N PO

IV; repeat in 12 hours as needed

• INR >1.5 Hold further doses of anticoagulant
• INR >3.0 Reversal of anticoagulant can be achieved
• INR >4.0 Hold further doses of anticoagulant

• Check INR 1-2 days
• INR >1.5 administer vitamin K 1-10 mg PO/N PO

IV; repeat in 12 hours as needed

• INR >1.5 Hold further doses of anticoagulant
• INR >3.0 Reversal of anticoagulant can be achieved
• INR >4.0 Hold further doses of anticoagulant

• Check INR 1-2 days
• INR >1.5 administer vitamin K 1-10 mg PO/N PO

IV; repeat in 12 hours as needed
C. Chronic Warfarin Dose Adjustment in Non-Bleeding Patients

This nomogram is suggested for non-bleeding patients with target INR 2.0–3.0 who are out of range and who are not at high risk of bleeding.

1. If INR >3.0 confirm no bleeding.
2. If INR <2.0 hold warfarin dose and resume in 3–5 days.
3. Clinical judgment should supersede this nomogram.

### Target INR 2.0–3.0

<table>
<thead>
<tr>
<th>INR</th>
<th>Dose Adjustment</th>
<th>Target Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.0</td>
<td>Hold 1 dose</td>
<td>20 mg po</td>
</tr>
<tr>
<td>2.1</td>
<td>Decrease by 0.15</td>
<td>17 mg po</td>
</tr>
<tr>
<td>2.2</td>
<td>Decrease by 0.15</td>
<td>15 mg po</td>
</tr>
<tr>
<td>2.3</td>
<td>Decrease by 0.15</td>
<td>13 mg po</td>
</tr>
<tr>
<td>2.4</td>
<td>Decrease by 0.15</td>
<td>11 mg po</td>
</tr>
<tr>
<td>2.5</td>
<td>Decrease by 0.15</td>
<td>9 mg po</td>
</tr>
<tr>
<td>2.6</td>
<td>Decrease by 0.15</td>
<td>7 mg po</td>
</tr>
<tr>
<td>2.7</td>
<td>Decrease by 0.15</td>
<td>5 mg po</td>
</tr>
<tr>
<td>2.8</td>
<td>Decrease by 0.15</td>
<td>3 mg po</td>
</tr>
<tr>
<td>2.9</td>
<td>Decrease by 0.15</td>
<td>1 mg po</td>
</tr>
<tr>
<td>3.0</td>
<td>Decrease by 0.15</td>
<td>0 mg po</td>
</tr>
</tbody>
</table>

### INR >3.0

<table>
<thead>
<tr>
<th>INR</th>
<th>Dose Adjustment</th>
<th>Target Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.1</td>
<td>Increase by 0.15</td>
<td>22 mg po</td>
</tr>
<tr>
<td>3.2</td>
<td>Increase by 0.15</td>
<td>25 mg po</td>
</tr>
<tr>
<td>3.3</td>
<td>Increase by 0.15</td>
<td>28 mg po</td>
</tr>
<tr>
<td>3.4</td>
<td>Increase by 0.15</td>
<td>31 mg po</td>
</tr>
<tr>
<td>3.5</td>
<td>Increase by 0.15</td>
<td>34 mg po</td>
</tr>
<tr>
<td>3.6</td>
<td>Increase by 0.15</td>
<td>37 mg po</td>
</tr>
<tr>
<td>3.7</td>
<td>Increase by 0.15</td>
<td>40 mg po</td>
</tr>
<tr>
<td>3.8</td>
<td>Increase by 0.15</td>
<td>43 mg po</td>
</tr>
<tr>
<td>3.9</td>
<td>Increase by 0.15</td>
<td>46 mg po</td>
</tr>
<tr>
<td>4.0</td>
<td>Increase by 0.15</td>
<td>49 mg po</td>
</tr>
<tr>
<td>4.1</td>
<td>Increase by 0.15</td>
<td>52 mg po</td>
</tr>
<tr>
<td>4.2</td>
<td>Increase by 0.15</td>
<td>55 mg po</td>
</tr>
<tr>
<td>4.3</td>
<td>Increase by 0.15</td>
<td>58 mg po</td>
</tr>
<tr>
<td>4.4</td>
<td>Increase by 0.15</td>
<td>61 mg po</td>
</tr>
<tr>
<td>4.5</td>
<td>Increase by 0.15</td>
<td>64 mg po</td>
</tr>
<tr>
<td>4.6</td>
<td>Increase by 0.15</td>
<td>67 mg po</td>
</tr>
<tr>
<td>4.7</td>
<td>Increase by 0.15</td>
<td>70 mg po</td>
</tr>
<tr>
<td>4.8</td>
<td>Increase by 0.15</td>
<td>73 mg po</td>
</tr>
<tr>
<td>4.9</td>
<td>Increase by 0.15</td>
<td>76 mg po</td>
</tr>
<tr>
<td>5.0</td>
<td>Increase by 0.15</td>
<td>79 mg po</td>
</tr>
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### INR <2.0

<table>
<thead>
<tr>
<th>INR</th>
<th>Dose Adjustment</th>
<th>Target Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.9</td>
<td>Hold</td>
<td>11 mg po</td>
</tr>
<tr>
<td>1.8</td>
<td>Decrease by 15%</td>
<td>9 mg po</td>
</tr>
<tr>
<td>1.7</td>
<td>Decrease by 15%</td>
<td>7 mg po</td>
</tr>
<tr>
<td>1.6</td>
<td>Decrease by 15%</td>
<td>5 mg po</td>
</tr>
<tr>
<td>1.5</td>
<td>Decrease by 15%</td>
<td>3 mg po</td>
</tr>
<tr>
<td>1.4</td>
<td>Decrease by 15%</td>
<td>1 mg po</td>
</tr>
</tbody>
</table>

### INR >3.0

<table>
<thead>
<tr>
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<th>Dose Adjustment</th>
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<tbody>
<tr>
<td>3.1</td>
<td>Increase by 0.15</td>
<td>22 mg po</td>
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<tr>
<td>3.2</td>
<td>Increase by 0.15</td>
<td>25 mg po</td>
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<tr>
<td>3.3</td>
<td>Increase by 0.15</td>
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<tr>
<td>3.4</td>
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<td>3.6</td>
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<td>3.7</td>
<td>Increase by 0.15</td>
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<td>3.9</td>
<td>Increase by 0.15</td>
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<td>4.0</td>
<td>Increase by 0.15</td>
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<td>4.1</td>
<td>Increase by 0.15</td>
<td>52 mg po</td>
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<td>4.2</td>
<td>Increase by 0.15</td>
<td>55 mg po</td>
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<td>4.3</td>
<td>Increase by 0.15</td>
<td>58 mg po</td>
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<td>76 mg po</td>
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</tbody>
</table>

### INR <2.0

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<tr>
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</tr>
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<tr>
<td>1.9</td>
<td>Hold</td>
<td>11 mg po</td>
</tr>
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<td>1.8</td>
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<td>9 mg po</td>
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<td>Decrease by 15%</td>
<td>7 mg po</td>
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<tr>
<td>1.6</td>
<td>Decrease by 15%</td>
<td>5 mg po</td>
</tr>
<tr>
<td>1.5</td>
<td>Decrease by 15%</td>
<td>3 mg po</td>
</tr>
<tr>
<td>1.4</td>
<td>Decrease by 15%</td>
<td>1 mg po</td>
</tr>
</tbody>
</table>