Clinical Practice Guideline for Anticoagulation Management

This guideline is to inform practitioners of the Standard of Care for providing safe and effective anticoagulation management for ambulatory patients.

INITIATION OF DIFFERENT TYPES OF ANTICOAGULANTS:

1. Non-Vitamin K Antagonist Oral Anticoagulants (NOACs), also referred to as Direct Oral Anticoagulants (DOACs):
   A. Factor Xa Inhibitors (blocks the action of a certain natural substance that helps blood clots to form):
      1) apixaban (Eliquis):
         • Preferred for Stage 4 or 5 CKD or Dialysis patients.
         • Less dependent on kidney function for clearance than other NOACs.
         • Approved for severe hepatic impairment.
      2) rivaroxaban (Xarelto)
      3) edoxaban (Lixiana)
      4) betrixaban (Bevyxxa)
      5) edoxaban (Savaysa)
   B. Direct Thrombin Inhibitor (prevents blood clots from forming in the body):
      1) dabigatran (Pradaxa)

*Both Factor Xa Inhibitors and dabigatran are NOT recommended in patients with:
   o a mechanical heart valve
   o End-Stage Renal Disease (ESRD) or on dialysis due to lack of clinical trial evidence
   o Severe hepatic impairment
   o Seizures; many seizure medications can decrease the serum concentration of these anticoagulant medications; anti-seizure medications that should not be used in combination with NOACs/DOACs include: phenytoin, fosphenytoin, carbamazepine
   o HIV, on protease inhibitor-based antiretroviral therapy
   o BMI > 40 or weight > 120 kg

*Possible Contraindications to Anticoagulation are Presented in a Table

2. Vitamin K Antagonists (inhibits the synthesis of Vitamin K dependent clotting factors):
   A. warfarin (Coumadin)

3. Provide all patients started on anticoagulation with education on the importance of medication compliance and s/s of bleeding or clotting.

*Common Questions from Patients about the Different Oral Medicines used to Prevent or Treat Blood Clots
4. Patients starting warfarin should be provided additional education early in therapy including:
   A. Indication and action of warfarin.
   B. INR (International Normalized Ratio) monitoring, dose adjustments and duration of therapy.
   C. Possible side effects of warfarin, including s/s of bleeding.
   D. Drug interactions.
      *Medications that Interfere with the Effect of warfarin
   E. Dietary implications on warfarin.
      *Amount of Vitamin K in Different Foods
   F. Special considerations on warfarin: Illness, Interruption in Therapy
   G. Importance of Compliance with lab work, telephone calls, and appointments.

5. Bleeding risk must be assessed prior to initiation of Anticoagulation therapy.
   HAS-BLED scoring recommended.
      *HAS-BLED Bleeding Risk Score

6. Baseline Hgb is assessed and followed annually. A low Hgb will be repeated in 6 months.

WARFARIN DOSAGE AND ADMINISTRATION:
1. The goal of warfarin is to decrease the clotting tendency of blood and not to prevent clotting completely. Therefore, the dose of warfarin is adjusted to maintain the clotting time within a target range, based on the results of periodic blood tests.

2. Warfarin dosing must be individualized according to patient INR results
   A. Initiation of warfarin at a dose of 4-6 mg daily is recommended, with smaller doses indicated for the elderly or debilitated patient.
   B. Loading doses are NOT recommended.
      *Warfarin initiation nomogram

3. Individualized target INR ranges are determined according to the patient’s indication for anticoagulation and bleeding risk; majority of indications have a goal INR=2-3 (Afib and VTE), patients with mechanical heart values may require goal INR=2.5-3.5

4. Frequency of INR testing is variable over time, dictated by dose response and current clinical information:
   A. Check INR 1-2 times per week at start of therapy, until a therapeutic range is achieved and maintained for 2 consecutive tests.
   B. Warfarin peak effect may not be seen for 3-4 days; INR may not stabilize for 10-14 days.
   C. INR checks every 2-3 weeks is usually required for the next several weeks.
   D. INR tests at no greater than 1-month intervals are recommended for patients who have achieved a stable therapeutic INR unless specified by referring provider.
   E. Caution is recommended against frequently adjusting warfarin doses for slightly out-of-range results, (i.e. within 0.3 of range); instead repeat the INR in a week.

5. **Dose Adjustments:**
   A. Response to warfarin fluctuates over time, influenced by:
      1) Changes in other medications (ie; start of antibiotics); INR may need to be checked more often.
      2) Inter-current illness
3) Dietary habits and changes in nutritional status.
4) Lifestyle habits including alcohol use, exercise, and travel:
   a. Limit alcohol to 1-2 servings per day.
   b. A serving of alcohol is equal to:
      I.) 1 Beer (12 ounces)
      II.) 1 glass of Wine (5 ounces)
      III.) 1.5 ounces of Spirits
   c. Avoid drinking excessive amounts of alcohol over a short period of time (with a single meal) because this can affect the INR and increase the risk of injury and serious bleeding.
5) Issues related to patient compliance

B. Dose adjustments are best achieved by calculating the total weekly dose of warfarin in milligrams per week and changing by only 5-15%:
   1) Slight variations in the amount of daily doses are forgiven by the relatively long half-life of warfarin.
   2) Using single-strength warfarin tablets minimizes the opportunity for dosing errors.
   3) In general, when a dose has been changed, allow 7-14 days before scheduling the next INR.
   4) Instructions to patients must be clear, concise and simple.

**Adjustment of maintenance warfarin dosing based on the RE-LY trial**

<table>
<thead>
<tr>
<th>INR</th>
<th>Adjustment in total mg of warfarin per week</th>
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<tbody>
<tr>
<td>≤1.5</td>
<td>Increase dose by 15% of weekly dose</td>
</tr>
<tr>
<td>1.5 to 1.99</td>
<td>Increase dose by 10% of weekly dose</td>
</tr>
<tr>
<td>2 to 3</td>
<td>No change</td>
</tr>
<tr>
<td>3.01 to 4</td>
<td>Decrease dose by 10% of weekly dose</td>
</tr>
<tr>
<td>4.01 to 4.99</td>
<td>HOLD ONE dose; restart with dose decreased by 10% of weekly dose</td>
</tr>
<tr>
<td>5 to 8.99</td>
<td>HOLD until INR 2-3; restart with dose decreased by 15% of weekly dose</td>
</tr>
</tbody>
</table>

The table provides an algorithm for monitoring and adjustment of maintenance warfarin dosing with a goal of maintaining the INR between 2 and 3. The maintenance dose algorithm requires that INR measurements are made at a maximum interval of every four weeks, with at least weekly monitoring for out of range INRs (<2 or >3). All percent changes in warfarin dosage are adjusted based on the current INR value and calculated based upon the sum of the previous seven days of warfarin doses (also known as mg of warfarin per week). The increase or decrease in warfarin dose per week is distributed over the following week, preferably as evenly as possible to avoid large fluctuations.

C. INRs that are supratherapeutic will be managed consistently and safely: see TABLE A

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**TABLE A**

<table>
<thead>
<tr>
<th>INR</th>
<th>Symptoms</th>
<th>Recommendations</th>
</tr>
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<tbody>
<tr>
<td>&gt; Target range</td>
<td>No significant</td>
<td>Lower or omit dose, resume therapy at a lower dose when INR is</td>
</tr>
<tr>
<td>and ≤ 5</td>
<td>bleeding</td>
<td>therapeutic. Monitor INR more frequently.</td>
</tr>
<tr>
<td>&gt; 5 but &lt; 9</td>
<td>No significant</td>
<td>Omit next 1-2 doses and monitor INR. Resume at a lower dose when INR is</td>
</tr>
<tr>
<td></td>
<td>bleeding</td>
<td>in target range. Consider Vitamin K (1-2.5 mg) orally, particularly if at</td>
</tr>
<tr>
<td></td>
<td></td>
<td>increased risk of bleeding. Notify PCP.</td>
</tr>
<tr>
<td>INR Elevation</td>
<td>Bleeding Status</td>
<td>Action</td>
</tr>
<tr>
<td>---------------</td>
<td>----------------</td>
<td>--------</td>
</tr>
<tr>
<td>&gt; 9</td>
<td>No significant bleeding</td>
<td>Hold warfarin. Consider Vitamin K (1, 2.5, 5, or 10 mg) orally, particularly if at increased risk of bleeding. With Vitamin K (5-10 mg), expect INR to be reduced substantially by 24-48 hours. Monitor more frequently. Resume therapy at lower dose when INR therapeutic. Notify PCP.</td>
</tr>
<tr>
<td>Any INR elevation</td>
<td>Significant bleeding</td>
<td>Send patient to the ER. <strong>Recommendations:</strong> Hold warfarin. Give Vitamin K orally or via slow IV infusion, supplemented with Fresh Frozen Plasma or Prothrombin Complex Concentrate, depending on the urgency of the situation. Recombinant Factor VIIa may be considered as alternative to Prothrombin Complex Concentrate. Notify PCP.</td>
</tr>
</tbody>
</table>

**ANTICOAGULANT PERIOPERATIVE MANAGEMENT / BRIDGING:**

1. Bridging anticoagulation is NOT recommended for patients on Direct Thrombin or Factor Xa Inhibitors.
   - A. Stop Direct Thrombin or Factor Xa anticoagulant at least 48 hours prior to elective procedure or invasive procedures with a moderate or high risk of significant bleeding.
   - B. Stop Direct Thrombin or Factor Xa anticoagulant at least 24 hours prior to elective surgery or invasive procedures with a low risk of bleeding or where the bleeding would be noncritical in location and easily controlled.
   - C. For patients on Pradaxa with creatinine clearance <50mL/min, stop the drug 3-5 days before the procedure.
   - D. Resume anticoagulation after the surgery or procedure as soon as adequate hemostasis has been established.

2. Bridging anticoagulation may be appropriate in patients on warfarin who have a very high thromboembolic risk who will have prolonged interruption of their anticoagulant. Individual patient comorbidities that increase bleeding risk may also need to be considered because an increased postoperative bleeding risk may be a reason to avoid bridging. We suggest the use of bridging in individuals on warfarin for one of the following conditions:
   - A. Embolic Stroke or systemic embolic event within the previous 12 weeks.
   - B. Mechanical Mitral Valve
   - C. Mechanical Aortic Valve and additional stroke risk factors.
   - D. Atrial Fibrillation and very high risk of stroke (eg. CHADS-VASc score of 5 or more, Stroke systemic Embolism within the previous 12 weeks).
   - E. Venous Thromboembolism (VTE) within the previous 12 weeks.
   - F. Previous Thromboembolism during interruption of chronic anticoagulation.

3. Schedule of Bridging Therapies:
   - A. Stop warfarin 5 days before surgery
   - B. Monitor INR closely pre-and post-procedure to time bridging therapy.
   - C. Begin LMWH or UFH when INR falls below 2.0.
   - D. If the INR remains elevated (>1.5) 1-2 days before surgery, consider Vitamin K (1-2 mg) PO.
   - E. Administer last dose of LMWH 24 hours before surgery.
   - F. Stop UFH 4 hours before surgery.
   - G. Resume warfarin 12-24 hours after surgery and when there is adequate hemostasis.
   - H. For low bleeding risk surgery, resume LMWH/ UFH after 24 hours, when hemostasis is secured and continue until INR is at least 2.0.
   - I. For major or high bleeding risk surgery, delay the resumption of therapeutic-dose LMWH/UFH
for 48-72 hours, or give low-dose LMWH/UFH, considering bleeding risk and adequacy of postoperative hemostasis for each patient individually.

4. Dosing of LMWH: Lovenox (enoxaparin):
   A. **Therapeutic:** 1.0 mg/kg BID or 1.5 mg/kg daily
      1) Severe renal impairment (creatinine clearance < 30ml/min) 1 mg/kg daily
   B. **Prophylactic Dose:** 30 mg SC BID or 40 mg daily

5. Reversal of Warfarin for Urgent Surgery or Procedure:
   A. Vitamin K (2.5-5 mg) IV or PO.
   B. For most urgent reversal, Fresh Frozen Plasma or other Prothrombin Concentrate in addition to Vitamin K (2.5-5 mg).
   C. Patients receiving ASA, clopidogrel, or both undergoing surgery, and have excessive or life-threatening perioperative bleeding, suggest transfusion of platelets or other Prohemostatic Agents.

6. Reversal of Direct Oral Anticoagulants:
   A. Many patients presenting with minor bleeding may not require DOAC reversal. Given the short half-lives of these drugs, even short-term but unneeded interruption of therapy could result in avoidable thrombosis. Occasionally, bleeding that appears significant in fact is not (eg, some epistaxis or hemorrhoidal bleeds); in such cases, observation and local measures such as ice and pressure may allow resolution of the bleeding without requiring aggressive intervention.
   B. Coagulation testing is not used for determining the anticoagulation status of a patient receiving a DOAC. Specialized testing has limited availability/utility, as rapid turn-around time is not always guaranteed. Testing that may be useful when considering use of a reversal agent includes: anti-factor Xa heparin level (useful as a guide to the presence of a direct factor Xa inhibitor), quantitative factor Xa inhibitor levels, and quantitative dabigatran levels.
   C. Anticoagulation is considered to be fully reversed, after 5 half-lives have elapsed since the last dose; see **TABLE B** for half-lives of DOACs
   D. Major bleeding can be managed with the following reversal agents
      1. Reversal of dabigatran may be achieved using idarucizumab (Praxbind).
      2. Reversal of Factor X inhibitors may be achieved using andexantra alfa (AndexXa) or an unactivated 4-factor PCC (Kcentra). These agents are generally **only used** when there is imminent risk of death.
      3. For Factor Xa inhibitors, oral activated charcoal may be used if the last dose is within the following timeframes: rivaroxaban 8 hours, apixaban 6 hours, and edoxaban 2 hours; Factor Xa inhibitors **cannot** be dialyzed

7. Minor dental procedures such as fillings, crowns, bridges, root canal, cleaning, single or double extraction, scaling, and polishing:
   A. Continue anticoagulant and aspirin.

8. Minor dermatologic procedures:
   A. Continue anticoagulant and aspirin.

9. Cataract removal:
   A. Continue anticoagulant and aspirin.

10. Interruption of Antiplatelet therapy (aspirin, clopidogrel, ticagrelor, prasugrel):
A. In patients with drug-eluting coronary stents who require surgery within 12 months of stent placement, recommend continuing dual antiplatelet therapy.

B. In patients with bare-metal coronary stents who require surgery within 6 weeks of stent placement, recommend continuing dual antiplatelet therapy.

C. For patients with a coronary stent who have interruption of antiplatelet therapy before surgery, suggest no routine bridging with LMWH, UFH, Direct Thrombin Inhibitors, or IIb/IIIa Inhibitors.

D. For patients not at high risk for cardiac events, stop ASA or antiplatelet therapy 5 days before surgery. Resume 24 hours after surgery when hemostasis is adequate.

E. For patients at high risk for cardiac events, scheduled for non-cardiac surgery, continue ASA, and stop other antiplatelet therapy 5 days prior to surgery.

F. Inpatients scheduled for CABG, continue ASA, or if interrupted, restart within 6-48 hours after CABG. Stop antiplatelet therapy 5 days before surgery.

11. Special caution is warranted in all patients on anticoagulation undergoing epidural or spinal anesthesia or puncture. Hematomas have occurred that may result in long-term or permanent paralysis.

12. *Switching Between Oral Anticoagulants*

**TABLE B**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Half-life</th>
<th>Time after last dose to reach 5 half-lives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>12-17 hours</td>
<td>2.5 to 3.5 days after the last dose</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>5-9 hours</td>
<td>1 to 2 days after the last dose</td>
</tr>
<tr>
<td>Apixiban</td>
<td>8-15 hours</td>
<td>1.5 to 3 days after the last dose</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>6-11 hours</td>
<td>1.3 to 2 days after the last dose</td>
</tr>
<tr>
<td>Betrixaban</td>
<td>19-27 hours</td>
<td>4 to 5.5 days after the last dose</td>
</tr>
</tbody>
</table>

Half-lives noted here are for patients with normal renal function

**REFERENCES:**

- Bridging Anticoagulation in Patients who Require Temporary Interruption of Warfarin Therapy for an Elective Invasive Procedure or Surgery. American College of Cardiology, Published 06/22/2015.
- UpToDate “Atrial Fibrillation: Anticoagulant Therapy to Prevent Thromboembolism”; Authors: Dr. Warren J Manning, Dr. Daniel E Singer, Dr. Gregory YH Lip; Apr 2021; [https://www.uptodate.com/contents/atrial-fibrillation-anticoagulant-therapy-to-prevent-thromboembolism](https://www.uptodate.com/contents/atrial-fibrillation-anticoagulant-therapy-to-prevent-thromboembolism)
- UpToDate “Patient Education: Warfarin (Beyond the Basics)”; Authors: Russell D Hull, MBBS, MSc, Dr. David A Garcia, Sara R Vazquez, PharmD, BCPS, CACP; May 2021; [https://www.uptodate.com/contents/warfarin-beyond-the-basics](https://www.uptodate.com/contents/warfarin-beyond-the-basics)