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.

1. INITIATION OF ANTICOAGULATION
   A. Consider Warfarin versus direct thrombin inhibitor (Dabigatran) or Factor Xa inhibitors (Apixaban, Rivaroxaban, Edoxaban)
      1. Dabigatran or Factor Xa inhibitors are not recommended in patients with a mechanical heart valve.
      2. Dabigatran or the Factor Xa inhibitors are not recommended in patients with end-stage renal disease or on dialysis because of lack of clinical trial evidence, or patients with severe hepatic impairment.
   B. Provide all patients started on anticoagulation with education on the importance of medication compliance and signs and symptoms of bleeding or clotting.
   C. Patients starting Warfarin should be provided additional education early in therapy including:
      1. Indication and action of Warfarin
      2. INR (International Normalized Ratio) monitoring, dose adjustments and duration of therapy
      3. Possible side effects of Warfarin, including signs and symptoms of bleeding
      4. Drug interactions
      5. Dietary implications on Warfarin
      6. Special considerations on Warfarin: illness, interruption in therapy, or as indicated
      7. Importance of compliance with lab work, telephone calls, and appointments
   D. Bleeding risk must be assessed prior to initiation of Anticoagulation therapy. HAS-BLED scoring recommended.
   E. Baseline Hgb is assessed and followed annually. A low Hgb will be repeated in 6 months.
   F. Initiation of Warfarin at a dose of 4-6 mg daily is recommended, with smaller doses indicated for the elderly or debilitated patient. Loading doses are not recommended.
   G. Check initial INRs 3-4 days and 6-7 days after start of therapy.
      1. Warfarin peak effect may not be seen for 3-4 days.
      2. INR may not stabilize for 10-14 days.
   H. The dosing of Warfarin must be individualized according to the patient’s response to the drug as reflected by the INR.
   I. Warfarin may be begun concurrently with Low Molecular Weight Heparin (LMWH) or Unfractionated Heparin (UFH) and should be overlapped for 4 to 5 days.
      1. When the desired INR has been maintained for 1 day, the LMWH or UFH may be discontinued.

2. WARFARIN DOSAGE AND ADMINISTRATION
   A. Warfarin dosing must be individualized according to patient INR results.
   B. Individualized target INR ranges are determined according to the patient’s indication for anticoagulation and bleeding risk.
   C. Recommended INR range according to indication: see TABLE A.
D. Frequency of INR testing is variable over time, dictated by dose response and current clinical information.
   1. Check INR 1-2 times per week at start of therapy, until a therapeutic range is achieved and maintained for 2 consecutive tests.
   2. INR checks every 2-3 weeks is usually required for the next several weeks.
   3. 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.
   4. 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.

E. Dose Adjustments
   1. Response to Warfarin fluctuates over time, influenced by:
      a. Changes in other medications - ie; start of antibiotics - INR may need to be checked more often
      b. Intercurrent illness
      c. Dietary habits and changes in nutritional status
      d. Lifestyle habits including alcohol use, exercise, and travel
      e. Issues related to patient compliance
   2. Dose adjustments are best achieved by calculating the total weekly dose of Warfarin in milligrams per week and changing by only 5-15%
      a. Slight variations in the amount of daily doses are forgiven by the relatively long half-life of Warfarin.
      b. Using single-strength Warfarin tablets minimizes the opportunity for dosing errors.
      c. In general, when a dose has been changed, allow 7-14 days before scheduling the next INR.
      d. Instructions to patients must be clear, concise and simple.
   3. Management of subtherapeutic INR:
      a. For patients with a history of embolus or mechanical valve in the mitral position, notify the primary care provider upon the first INR that is 0.5 points below the target range. Increase Warfarin dose by 10-15% or as directed by PCP and recheck INR in 2-3 days.
      b. For patients with no history of embolus, notify primary care provider upon the second INR that is 0.5 points below the target range. Increase Warfarin dose by 10-15% and recheck INR in 2-3 days.
   4. INRs that are supratherapeutic will be managed consistently and safely: see TABLE B.

TABLE A
OPTIMAL THERAPEUTIC RANGE AND DURATION OF ANTICOAGULATION

<table>
<thead>
<tr>
<th>Indication</th>
<th>Target INR Range</th>
<th>Duration</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persistent or Paroxysmal Atrial Fibrillation/Flutter</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>CHADS-VASc scoring: 1 point each for CHF, HTN, age &gt; 65, Diabetes Mellitus, Vascular Disease, or female gender; 2 points for TIA or CVA and age &gt;75</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low risk of stroke with CHADS-VASc score =0</td>
<td>2.0-3.0 Chronic</td>
<td></td>
<td>Suggest anticoagulation over ASA or combination therapy with ASA and Clopidogrel (Plavix)</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Indication</th>
<th>Target INR Range</th>
<th>Duration</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>High risk of stroke with CHADS-VASc score = 2</td>
<td>2.0-3.0</td>
<td>Chronic</td>
<td>Recommend anticoagulation. If unable to take anticoagulation, recommend ASA and Clopidogrel</td>
</tr>
<tr>
<td>Atrial fibrillation/ flutter with mitral stenosis</td>
<td>2.0-3.0</td>
<td>Chronic</td>
<td>Recommend anticoagulation</td>
</tr>
<tr>
<td>Atrial fibrillation/ flutter, CHADS-VASc = 1 or more, with stable CAD or &gt; 1 yr. post -intervention</td>
<td>2.0-3.0</td>
<td>Chronic</td>
<td>Suggest anticoagulation alone rather than in combination with ASA</td>
</tr>
<tr>
<td>Atrial fibrillation/flutter, CHADS-VASc = 0 to 1, with CAD first year after BMS, DES, or ACS.</td>
<td>2.0-3.0</td>
<td>Chronic</td>
<td>Suggest dual antiplatelet therapy rather than triple therapy. At 12 months, suggest anticoagulation as for atrial fib with stable CAD.</td>
</tr>
<tr>
<td>Atrial fibrillation/flutter, CHADS-VASc = 2 or more, with CAD, first 3-12 months after BMS or DES.</td>
<td>2.0-3.0</td>
<td>Chronic</td>
<td>Suggest anticoagulation with dual antiplatelet drugs. At 12 months, suggest anticoagulation as for atrial fib with stable CAD.</td>
</tr>
</tbody>
</table>

**Cardioembolic Stroke**

- With risk factors for stroke (AF, CHF, LV dysfx, mural thrombus, hx TIA/CVA, TE) | 2.0-3.0 | Chronic | |
- After embolic event on anticoag | 2.0-3.0 | Chronic | Add antiplatelet therapy |

**Left Ventricular Dysfunction**

- EF<30% | 2.0-3.0 | Chronic | |
- Transient, following MI | 2.0-3.0 | 3 months | And ASA 81 mg daily |
- After embolic event on anticoag | 2.0-3.0 | Chronic | Add antiplatelet therapy |

**Myocardial Infarction**

- After Anterior MI | 2.0-3.0 | 3 months | And ASA 81 mg daily |
- After Inf MI with transient risks (AF, CHF, LV dysfx, mural thrombus, Hx TE) | 2.0-3.0 | 3 months | And ASA 81 mg daily |
- After initial Tx w/ persistent risk | 2.0-3.0 | Chronic | And ASA 81 mg daily |

**Thromboembolism (DVT, PE) (Preceded by UFH/ LMWH for minimum 5 days until INR>2)**

For DVT, add elastic compression stockings with 30-40 mmHg at ankle for 2 yrs. Treatment/ prevention of recurrence (including calf vein and upper extremity DVT)

- Transient risk factors | 2.0-3.0 | 3 months | |
- Idiopathic episode | 2.0-3.0 | 6-12 months | Consider chronic therapy |
- Recurrent DVT | 2.0-3.0 | Chronic | |
- With malignancy | 2.0-3.0 | Chronic | Precede LMWH x3-6mos |
- Hypercoagulable state | 2.0-3.0 | 6-12 months | Consider chronic therapy |
- 2 or more thrombophilic cond | 2.0-3.0 | 12 months | Consider chronic therapy |
- Antiphospholipid Antibody Syn. | 2.0-3.0 | 12 months | Consider chronic therapy |
- -w/recurrent DVT or other risk | 2.5-3.5 | 12 months | Consider chronic therapy |
- Chronic thromboembolic pulmonary HTN | 2.0-3.0 | Chronic | |
- Cerebral venous sinus thrombosis | 2.0-3.0 | 3-6 months | |
- Prevention post arthroplasty | 2.0-3.0 | 6 weeks or while decreased mobility | |

**Valvular Disease**

- Aortic valve disease with mobile atheroma or aortic plaque>4mm | 2.0-3.0 | Chronic | |
- Mitral valve prolapse, regurg, or annular calcification with AF or hx. systemic embolus | 2.0-3.0 | Chronic | |
- Recurrent TIA on ASA tx | 2.0-3.0 | Chronic | |
<table>
<thead>
<tr>
<th>Indication</th>
<th>Target INR Range</th>
<th>Duration</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatic mitral valve disease with AF, hx. Systemic embolus or LA &gt;5.5 cm</td>
<td>2.0-3.0</td>
<td>Chronic</td>
<td></td>
</tr>
<tr>
<td>S/P embolic event on anticoag</td>
<td>2.0-3.0</td>
<td>Chronic</td>
<td>Add ASA 81 mg daily</td>
</tr>
<tr>
<td><strong>Valve Replacement: Bioprosthetic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aortic</td>
<td>2.0-3.0</td>
<td>3 months</td>
<td>Then ASA 81 mg daily</td>
</tr>
<tr>
<td>Mitral</td>
<td>2.0-3.0</td>
<td>3 months</td>
<td>Then ASA 81 mg daily</td>
</tr>
<tr>
<td>Aortic or Mitral</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With LA thrombus</td>
<td>2.0-3.0</td>
<td>&gt;3 months</td>
<td>Then ASA 81 mg daily</td>
</tr>
<tr>
<td>Hx systemic embolus</td>
<td>2.0-3.0</td>
<td>3-12 months</td>
<td>Then ASA 81 mg daily</td>
</tr>
<tr>
<td>With A fib</td>
<td>2.0-3.0</td>
<td>Chronic</td>
<td></td>
</tr>
<tr>
<td>Following systemic embolism</td>
<td>2.0-3.0</td>
<td>Chronic</td>
<td>Add ASA 81 mg daily</td>
</tr>
<tr>
<td><strong>Valve Replacement: Mechanical</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aortic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bileaflet, St. Jude</td>
<td>2.0-3.0</td>
<td>Chronic</td>
<td></td>
</tr>
<tr>
<td>Bileaflet Carbomedics/tilting disk Medtronic Hall -in NSR, with nl EF, &amp; nl LA size</td>
<td>2.0-3.0</td>
<td>Chronic</td>
<td></td>
</tr>
<tr>
<td>-all others</td>
<td>2.5-3.5</td>
<td>Chronic</td>
<td></td>
</tr>
<tr>
<td>Tilting disk, other brands</td>
<td>2.5-3.5</td>
<td>Chronic</td>
<td></td>
</tr>
<tr>
<td>Ball &amp; cage, caged disk</td>
<td>2.5-3.5</td>
<td>Chronic</td>
<td>With ASA 81 mg daily</td>
</tr>
<tr>
<td>Mitral</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bileaflet or tilting disk</td>
<td>2.5-3.5</td>
<td>Chronic</td>
<td></td>
</tr>
<tr>
<td>Ball and cage/caged disk</td>
<td>2.5-3.5</td>
<td>Chronic</td>
<td>With ASA 81 mg daily</td>
</tr>
<tr>
<td>With additional risk factors or following TE event</td>
<td>2.5-3.5</td>
<td>Chronic</td>
<td>With ASA 81 mg daily</td>
</tr>
</tbody>
</table>

**TABLE B**

**MANAGEMENT OF SUPRATHERAPEUTIC INR:**

<table>
<thead>
<tr>
<th>INR</th>
<th>Symptoms</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; target range and ≤ 5</td>
<td>No significant bleeding</td>
<td>Lower or omit dose, resume therapy at a lower dose when INR therapeutic. Monitor INR more frequently.</td>
</tr>
<tr>
<td>&gt; 5 but &lt; 9</td>
<td>No significant bleeding</td>
<td>Omit next 1-2 doses and monitor INR. Resume at a lower dose when INR in target range. Consider Vitamin K 1-2.5 mg orally, particularly if at increased risk of bleeding. Notify PCP.</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. Recommendations: Hold Warfarin. Give Vitamin K orally or 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>
3. ANTI COAGULANT PERIOPERATIVE MANAGEMENT / BRIDGING

A. Bridging anticoagulation is not recommended for patients on direct thrombin or Factor Xa inhibitors.
1. 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.
2. 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.
3. For patients on Pradaxa with Creatinine Clearance <50mL/min, stop the drug 3-5 days before the procedure.
4. Resume anticoagulation after the surgery or procedure as soon as adequate hemostasis has been established.

B. 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:
1. Embolic stroke or systemic embolic event within the previous 12 weeks.
2. Mechanical mitral valve
3. Mechanical aortic valve and additional stroke risk factors.
4. Atrial fibrillation and very high risk of stroke (eg. CHADS-VASc score of 5 or more, stroke systemic embolism within the previous 12 weeks).
5. Venous thromboembolism (VTE) within the previous 12 weeks.
6. Previous thromboembolism during interruption of chronic anticoagulation.

C. Schedule of bridging therapies
1. Stop Warfarin 5 days before surgery
2. Monitor INR closely pre-and post-procedure to time bridging therapy.
3. Begin LMWH or UFH when INR falls below 2.0.
4. If the INR remains elevated (>1.5) 1-2 days before surgery, Consider Vitamin K 1-2 mg PO.
5. Administer last dose of LMWH 24 hours before surgery.
6. Stop UFH 4 hours before surgery.
7. Resume Warfarin 12-24 hours after surgery and when there is adequate hemostasis.
8. For low bleeding risk surgery, resume LMWH/ UFH after 24 hours, when hemostasis is secured and continue until INR is at least 2.0.
9. 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.

D. Dosing of LMWH: Lovenox (Enoxaparin)
1. Therapeutic: 1.0 mg/kg BID or 1.5 mg/ kg daily
   a. Severe renal impairment (creatinine clearance < 30) 1 mg/kg daily
2. Low Dose: 30 mg SC BID
3. For patients receiving once daily therapeutic dose LMWH, the last dose 24 hours before surgery should be half the daily dose instead of the entire daily dose.

E. Reversal of Warfarin for Urgent Surgery or Procedure
1. Vitamin K 2.5-5 mg IV or PO
2. For most urgent reversal, fresh frozen plasma or other prothrombin concentrate in addition to Vitamin K 2.5-5 mg.
3. Patients receiving Aspirin, Clopidogrel, or both undergoing surgery, and have excessive or life-threatening perioperative bleeding, suggest transfusion of platelets or other prohemostatic agents.
F. Reversal of direct oral anticoagulants:
   1. Reversal of Dabigatran may be achieved using Idarucizumab (Praxbind).
   2. A reversal agent for Factor X inhibitors is not yet FDA approved. If the last dose has been within 2 hours, oral activated charcoal may be used. If the last dose has been over 2 hours, consider use of Prothrombin Complex Concentrate (Kcentra).

G. Minor dental procedures (fillings, crowns, bridges, root canal, cleaning, single or double extraction, scaling, and polishing): continue anticoagulant and Aspirin

H. Minor dermatologic procedures: continue anticoagulant and Aspirin

I. Cataract removal: continue anticoagulant and Aspirin

J. Interruption of Antiplatelet therapy (Aspirin, Clopidogrel, Ticagrelor, Presugrel)
   1. In patients with drug-eluting coronary stents who require surgery within 12 months of stent placement, recommend continuing dual antiplatelet therapy.
   2. In patients with bare-metal coronary stents who require surgery within 6 weeks of stent placement, recommend continuing dual antiplatelet therapy.
   3. 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.
   4. For patients not at high risk for cardiac events, stop Aspirin or antiplatelet therapy. 5 days before surgery; resume 24 hours after surgery when hemostasis is adequate.
   5. For patients at high risk for cardiac events, scheduled for noncardiac surgery, continue Aspirin, stop other antiplatelet therapy 5 days prior to surgery.
   6. Inpatients scheduled for CABG, continue Aspirin, or if interrupted, restart within 6-48 hours after CABG. Stop antiplatelet therapy 5 days before surgery.

K. 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.

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.

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Medical Associates Clinic & Health Plans

3/2/18