Preventing Stroke in Patients with Atrial Fibrillation

A Structured Warfarin Management Plan

Managing warfarin therapy should follow a structured plan, whether it is taking place in a specialized anticoagulation clinic, a family doctor’s or specialist’s office, or other care setting.

Things to consider when developing a structured plan of care:
- Patient follow-up
- Ongoing patient education
- INR monitoring (every 4–12 weeks once stable)
- Caregiver engagement
- Dose adjustments (using nomogram/dosing tool)
- Other health care professionals involved in care/patient education
- Monitoring for complications and side effects

Out-of-Range INRs¹ – A Step-By-Step Approach

**STEP 1**

Note the INR target. Is your patient symptomatic for the INR?
- If the INR is high, is your patient exhibiting signs and/or symptoms of bleeding?
- If the INR is low, is your patient exhibiting signs and/or symptoms of a stroke or other clot?

IF YES: provide appropriate emergency/urgent care.
IF NO: proceed to Step 2.

**STEP 2**

Is your patient at risk of becoming symptomatic for the INR?
- If the INR > 10, hold the warfarin, give single oral dose of vitamin K 2.5 mg to 5 mg; ↓ weekly warfarin dose by 20%. Resume once INR is in the therapeutic range. Recheck INR in 2 days.
- If the INR is low, consider bridging with low-molecular-weight heparin if the patient is at high risk of a clot.

**STEP 3**

Is sub-/supratherapeutic INR a result of a permanent or transient cause?
- Transient causes: e.g., missed/extra dose, gastroenteritis, antibiotics, recent ↑ alcohol intake
  - Consider dose correction; e.g., hold or give extra dose and ↑ INR monitoring frequency
- Permanent causes: e.g., lifestyle change, change in a chronic medication
  - Consider a change in weekly dose and ↑ INR monitoring frequency

Example² of a Validated Nomogram for the Maintenance of Warfarin

<table>
<thead>
<tr>
<th>Target INR</th>
<th>Action</th>
<th>Target INR</th>
</tr>
</thead>
<tbody>
<tr>
<td>2–3</td>
<td>Extra dose, ↑ weekly dose by 10%–20%</td>
<td>2.5–3.5</td>
</tr>
<tr>
<td>1.5–1.9</td>
<td>↑ weekly dose by 5%–10%</td>
<td>2–2.4</td>
</tr>
<tr>
<td>2–3</td>
<td>No change</td>
<td>2.5–3.5</td>
</tr>
<tr>
<td>3.1–3.5</td>
<td>↓ weekly dose by 5%–10%</td>
<td>3.6–4</td>
</tr>
<tr>
<td>3.6–4.9</td>
<td>Hold 1 dose, ↓ weekly dose by 10%–20%</td>
<td>4.1–4.9</td>
</tr>
<tr>
<td>5–9</td>
<td>Hold 2 doses, ↓ weekly dose by 10%–20%</td>
<td>5–9</td>
</tr>
<tr>
<td>&gt; 9</td>
<td>Urgent evaluation</td>
<td>&gt; 9</td>
</tr>
</tbody>
</table>

- Do not adjust warfarin dose based on one asymptomatic, unexplained, out of range maintenance INR ≤ 0.5 +/- target.
- Recheck INR in 1–2 weeks.

The Bottom Line

Warfarin has been used for more than 60 years, and is safe and effective in preventing stroke and other complications in patients with Afib.

- Warfarin is the recommended first-line therapy for preventing stroke in patients with Afib.
- Warfarin is proven to be a safe, effective, and cost-effective first choice for therapy.
- Many patients taking warfarin do well on the medication. For these patients, there is no evidence to support switching therapies.
- Managing warfarin therapy should follow a structured plan, whether it is taking place in a specialized anticoagulation clinic, a family doctor’s or specialist’s office, or other care setting.
- Patient self-testing and self-management of INRs may be an option for some patients, but is not recommended for most.

A Note on Cost:

Cost of warfarin is $0.06/day.
Cost of warfarin + INR monitoring is $1.16/day.

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1. INRs = International Normalized Ratio
2. Many nomograms are available. If another validated nomogram is already in use in your care setting, there is no need to change.
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NOACs

Dabigatran (Pradaxa)
- 150 mg twice daily
- 110 mg twice daily if > 80, or > 75 with other bleeding risk factor(s)

Rivaroxaban (Xarelto)
- 20 mg once daily
- 15 mg once daily if creatinine clearance is 30-50 mL/min

Apixaban (Eliquis)
- 5 mg twice daily
- 2.5 mg twice daily if at least 2 of:
  - age > 80
  - weight < 60 kg
  - serum creatinine > 133 µmol/L

Monitoring NOAC Therapy:

Even though INR testing is not required, careful and regular monitoring of patients taking NOACs is necessary.

Patients taking NOACs should be monitored for:
- Adherence to treatment (the NOACs have shorter half-lives than warfarin, possibly increasing the risk of stroke and other blood clots with missed doses)
- Renal function at baseline and at least annually (may require dose adjustment or an alternate drug)
- Bleeding (e.g., change in bleeding risk over time, plan for management of bleeding)
- Side effects (e.g., GI)
- Drug interactions
  - Fewer known interactions than warfarin, but clinical experience lacking, and no way to adjust dose to compensate
  - Strong inhibitors of P-glycoprotein are contraindicated (e.g., ketoconazole)
  - Strong inhibitors of CYP3A4 are contraindicated with rivaroxaban and apixaban (e.g., azaoles, ritonavir)
  - Caution with CYP3A4 and P-glycoprotein inducers (e.g., rifampin, phenytoin, carbamazepine, St. John's wort) and inhibitors (e.g., verapamil, amiodarone, dronedarone, quinidine) with rivaroxaban and apixaban
  - Food interactions (e.g., grapefruit juice inhibits CYP3A4)

A Note on Cost:
Cost of NOACs is ~$3/day.

NOAC Cautions

NOACs may not be appropriate for patients with:
- Poor renal function
- Higher risk of dyspepsia (especially for dabigatran) or GI bleeding
- Recent stroke
- Concerns about drug costs

For many new drugs, evidence is limited for populations that were excluded from the original trials. For NOACs, these include:
- Pregnancy and lactation
- Liver disease
- Conditions that increase risk of hemorrhage
- Previous GI bleed
- Cancer
- Aneurysm
- NSAID therapy
- Anemia
- HIV
- Cardiac and valve abnormalities including patients with valvular AFib

The Bottom Line

- New oral anticoagulants are a second-line option for some patients with non-valvular AFib not doing well on warfarin.
- Compared with warfarin, the benefits of new oral anticoagulants or NOACs are small. The estimated number of patients who would avoid a stroke or other blood clot if treated with a new drug rather than warfarin was 1 to 9 people for every 1,000 patients treated per year.
- Bleeding risks for patients treated with the newer drugs compared with warfarin were similar overall, with a modest decrease in intracranial bleeding and a small increase in GI bleeding. A systematic review showed that there is no reversal agent or proven management strategy if bleeding occurs with the new drugs.
- The newer drugs are more expensive than warfarin and little is known about their long-term safety.

AFib = atrial fibrillation; CYP3A4 = cytochrome P450 3A4; GI = gastrointestinal; INR = International Normalized Ratio; NOACs = new oral anticoagulants; NSAID = non-steroidal antiinflammatory drug.