Warfarin has been used for over 60 years & is approved for multiple indications e.g. stroke prevention in atrial fibrillation, heart valve disease/replacement, venous thromboembolism prophylaxis & treatment, post-myocardial infarction/acute coronary syndrome, etc. When appropriately managed in compliant stable patients, warfarin is safe & effective. Safety & effectiveness ↑ as time in therapeutic range ↑.

**MANAGEMENT PEARLS**
- Use a validated nomogram for initiating & maintaining warfarin. Nomograms have been shown to ↑ time in therapeutic range (TTR) see Tables 1 & 2. CADTH, CHEST'12, 3
- Extend the frequency of international normalized ratio (INR) monitoring to q12wks in pts who have had stable INRs for ≥3 mos. CHEST'12 ensure pt will report any drug changes between INRs.
- In pts maintained on warfarin, do not adjust dose based on an asymptomatic, single, unexplained e.g. no drug/dietary intake, out-of-range INR ≤0.5 ± target range; recheck in 1-2 wks. 2,4
- If concomitant use of a drug that alters INR cannot be avoided, ↑ INR monitoring & reactively (not proactively) adjust the dose in response.

**INITIATING WARFARIN** see Tables 1 & 2
- Collect INR on Day 1 only if no baseline available; INR on Day 2 usually not needed.
- Target INR - for most: 2.5 (acceptable range = 2 - 3) - for mechanical mitral valve replacement: 3 (acceptable range 2.5 - 3.5)
- Consider dispensing in strengths that accommodate dose changes e.g. 1, 2, 3 & 5mg.
- Use one of the following regimens when starting warfarin; consider the patient’s risk factors for clotting or extension of existing clot & bleeding: 5,6

<table>
<thead>
<tr>
<th>1)</th>
<th>Warfarin 2-3mg po daily x 2 days, Day 3 INR, subsequent doses based on INRs</th>
</tr>
</thead>
<tbody>
<tr>
<td>•</td>
<td>Consider in pts who may be more sensitive to warfarin, e.g. elderly, debilitated, malnourished, HF, liver dx, ↑ risk of bleeding or taking medications known to ↑ INR.</td>
</tr>
<tr>
<td>•</td>
<td>There is no validated nomogram for this regimen, but can use same % ↑or ↓ as outlined in Table 1 (e.g. 3mg Day 1 &amp; 2, with a Day 3 INR of &lt;1.5→ give either 3mg or 6mg).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2)</th>
<th>Warfarin 5mg po daily x 2 days, Day 3 INR, subsequent doses based on INRs</th>
</tr>
</thead>
<tbody>
<tr>
<td>•</td>
<td>Consider in pts who may be more sensitive to warfarin, e.g. elderly, debilitated, malnourished, HF, liver dx, ↑ risk of bleeding or taking medications known to ↑ INR.</td>
</tr>
<tr>
<td>•</td>
<td>There is no validated nomogram for this regimen, but can use same % ↑or ↓ as outlined in Table 1 (e.g. 3mg Day 1 &amp; 2, with a Day 3 INR of &lt;1.5→ give either 3mg or 6mg).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3)</th>
<th>Warfarin 10mg po daily x 2 days, Day 3 INR, subsequent doses based on INRs</th>
</tr>
</thead>
<tbody>
<tr>
<td>•</td>
<td>Consider in pts who may be more sensitive to warfarin, e.g. elderly, debilitated, malnourished, HF, liver dx, ↑ risk of bleeding or taking medications known to ↑ INR.</td>
</tr>
<tr>
<td>•</td>
<td>There is no validated nomogram for this regimen, but can use same % ↑or ↓ as outlined in Table 1 (e.g. 3mg Day 1 &amp; 2, with a Day 3 INR of &lt;1.5→ give either 3mg or 6mg).</td>
</tr>
</tbody>
</table>

**FREQUENCY OF INR MONITORING**
- **Initiating warfarin:** see 3 options/examples to the left; in general, week 1: Baseline, Day 3 & 5, week 2: 2 INRs, then weekly INRs until stable x 2 weeks, then q2weeks until stable x 1 month, then monthly INRs. If stable x 3 months → INR up to q12 weeks CHEST'12 ensure patient will report any changes in drug therapy between INRs.
- **Warfarin dose changes:** check INR weekly until stable.
- **Starting, stopping or changing the dose of an interacting drug:** check INR in 4-6 days after the change. ↑ Monitoring duration for drugs with long t½ or onset e.g. amiobaronne.

**MANAGEMENT OF SUB-/SUPRATHERAPEUTIC INRS** see Figure & Table 3
- Interpretation of INR requires many considerations:
  - trend & time since last INR, duration of current dose 
  - full therapeutic effect may take 5-7 days
  - changes in medications (starting, stopping & changes in doses) of interacting medications, see Managing Warfarin Drug Interactions on the next page
  - factors that may ↑ INR: acute illnesses e.g. diarrhea, fever, ↑ in alcohol intake
  - factors that may ↓ INR: edema, ↑ vitamin K intake (e.g. garden harvest), ↑ physical activity level
  - patients with heart failure, diabetes & acute GI illness may experience INR instability 8
- See Figure: Stepwise approach for sub-/supratherapeutic INRs

**FIGURE: STEPWISE APPROACH FOR SUB-/SUPRATHERAPEUTIC INRS**
- Step 1: Note indication for warfarin & target INR. Is the patient symptomatic for the INR? If INR high, are there signs/symptoms of bleeding? Consider risk (platelet count, bleeding disorders)!
  - If INR is low, are there signs &/or symptoms of a stroke or VTE? If yes, provide appropriate emergent/urgent care. If no, proceed to Step 2.
- Step 2: Is the patient at risk of becoming symptomatic for the INR? If the INR >10: hold warfarin, & give vitamin K 2.5-5mg ampule po x1.
  - ACC‘17: Vit K 5-10mg IV if major/life threatening bleed; Vit K 2-5mg po/iv if not major bleed
  - ↓ weekly warfarin dose by 20% & resume once INR in therapeutic range. Re-check INR in ~2 days. Next day INR will likely still be elevated. Avoid IM vitamin K.
  - If the INR is low, consider bridging with LMWH if the patient is at high risk of a clot.
- Step 3: Identify if sub-/supratherapeutic INR is a result of a permanent or transient cause.
  - **Transient causes:** e.g. missed/extra dose, gastroenteritis, course of antibiotics, recent ↑ alcohol intake
  - Consider dose correction e.g. hold or give extra dose & ↑ INR monitoring frequency
  - **Permanent causes:** e.g. lifestyle change, change in a chronic medication
  - Consider a change in weekly dose see Table 3 below & ↑ INR monitoring frequency

- Vitamin K 100-200 mcg po daily may help stabilize INR in pts with unexplained fluctuating INRs, but lacks evidence for routine use. Tablets are available at health food stores (e.g. GNC).
- High vitamin K doses can cause warfarin resistance for ~1 week.

**TABLE 1: INITIATING WARFARIN - EXAMPLE OF A VALIDATED NOMOGRAM FOR 5mg Day 1 & 2 & INR 2-3**

<table>
<thead>
<tr>
<th>INR</th>
<th>Day 3 (mg)</th>
<th>Day 4 (optional INR)</th>
<th>Day 5 (optional INR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤0.5</td>
<td>5</td>
<td>10</td>
<td>≤0.5</td>
</tr>
<tr>
<td>0.5-1</td>
<td>2.5</td>
<td>5</td>
<td>2.5</td>
</tr>
<tr>
<td>1-1.5</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**TABLE 2: INITIATING WARFARIN - VALIDATED NOMOGRAM FOR 10mg Day 1 & 2 & INR 2-3**

| Warfarin 10mg x Day 1 & Day 2: |
|---|---|
| • | −likely safe & effective for outpatients not at high risk of bleeding CHEST’12 |
| • | −may achieve therapeutic INR faster 7 |

<table>
<thead>
<tr>
<th>Day 3 INR</th>
<th>Day 3 &amp; 4 (optional INR)</th>
<th>Day 5</th>
<th>Day 5, 6 &amp; 7 (optional INR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤1</td>
<td>1,5, 15</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>1.1-3</td>
<td>10, 10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>3.1-5</td>
<td>5, 5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>≥5</td>
<td>≥5</td>
<td>≥5</td>
<td>≥5</td>
</tr>
</tbody>
</table>

**TABLE 3: MAINTENANCE OF WARFARIN – EXAMPLE VALIDATED NOMOGRAM**

<table>
<thead>
<tr>
<th>Target INR 2-3</th>
<th>Action</th>
<th>Target INR 2.5-3.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1.5</td>
<td>Extra dose, ↑ weekly dose by 10-20%</td>
<td>&lt;2</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 20%</td>
<td>4.1-4.9</td>
</tr>
<tr>
<td>5-9</td>
<td>Hold 2 doses, ↓ weekly dose by 20%</td>
<td>5-9</td>
</tr>
<tr>
<td>≥9</td>
<td>Urgent evaluation</td>
<td>≥9</td>
</tr>
</tbody>
</table>

Do not adjust warfarin dose based on 1 asymptomatic, unexplained, out-of-range maintenance INR ≤0.5 ± target range. Recheck INR in 1-2 wks.
WARFARIN TIPS & DOSING NOMOGRAMS

WARFARIN DOSING
- For confirmed or suspected DVT or PE, start warfarin on day 1 (see options under “Initiating Warfarin” above).
  - When cross-covering with parenteral anticoagulant e.g. heparin or LMWH, even if INR > 2, a minimum 5 days of overlap is required regardless of initial dosing; i.e. warfarin + LMWH x 5 days & until INR > 2.
  - When initiating warfarin, INR may be elevated before fully anticoagulated? hypercoagulable due to protein C deficiency, 1/3 = 6 hours.
- With these 2 things in mind: the higher the dose the higher the potential to overshoot the INR, possibly prompting early discontinuation of LMWH before true anticoagulation effect of warfarin has taken effect.
- The average warfarin dose is 4-6 mg daily (daily range ±0.5 – ±225 mg), & has an inverse relationship with age (e.g. 6.3 mg daily in 50 yrs, 3.6 mg daily in 70 yrs) 12
- Is there an upper limit for warfarin doses? Probably not, however, if ↑ & otherwise inexplicable, investigate absorption or non-compliance → deliberate or inadvertent e.g. verify dose using colours of tablets.
- Generic Taro-Warfarin tablet strengths & colours:

MANAGING WARFARIN DRUG INTERACTIONS
- Avoid interacting drugs when possible, e.g. verify indications, select non-/less interacting alternatives.
- Assume there is an interaction with any drug start, stop, or dose change. May need to check ≥2 references; many inclusion/omission conflicts across major references.
- Review of 4 references: 3 common combinda & the warfarin’s product monograph. Collectively, 648 total drug & food interactions → only 50 common to all 4 references. 14
- Warfarin interactions can be divided into 2 categories:
  1) Interactions that cause a change in INR: e.g. amiodarone delayed x days/weeks/months, antiepileptics, antimicrobials especially cotrimoxazole, ciprofloxacin, metronidazole, corticosteroids. If combination cannot be avoided, ↑ INR monitoring & reactively adjust dose in response. Empiric dosage adjustments rarely necessary & are less predictable than the interaction itself.
  2) Interactions that ↑ risk of bleed or clot without affecting INR: e.g. NSAIDs, antiplatelets, hormone therapy. These interactions require a balance of the risk (bleeding, clotting) with the benefit of therapy.
- Most/any antibiotic can interact with warfarin by disrupting normal GI flora, thereby disrupting vitamin K conversion/cycle.
- Very few, if any, combinations are absolutely contraindicated.

WARFARIN MONITORING
- Less experienced clinicians may benefit more from using a nomogram, BUT even most high-capacity anticoagulation clinics e.g. 100s of patients use a nomogram.
- Anticoagulation Clinics may improve TTR absolute ↑ ≥8%.
- Patient self-monitoring/self-testing has some supporting evidence ↓ clots & bleeds but is reserved for special cases +/−motivation /training/education; ensure device regulated by Health Canada: Medical Devices Active Licenses Search www.hc-sc.gc.ca/dhp-mps/md-im/lien/mdlic-eng.php
- Pharmacogenetic testing likely helps predict dose, but is reserved for special cases.
- The average time in therapeutic range (TTR) = 60% to 70%.
- TTR effect: ↓ intracranial hemorrhage, ↓ DVT or PE, ↓ stroke/TIA, ↓ heart failure, ↓ mortality.

MANAGING WARFARIN FOOD INTERACTIONS
- Encourage consistent vitamin K intake.
- Empiric dose changes for altered vitamin K intake (e.g. garden season) are unpredictable, therefore monitor INR more frequently & adjust dose as required; exception: ↑ INR monitoring not necessary when previous fluctuations in vitamin K intake had little impact on INR.
- Anticoagulation bridging also see pages 15 & 16
- Anticoagulation bridging during warfarin interruption can be considered for patients at moderate to high risk of thrombosis. CHEST’12 See Perioperative chart pg 16.
- Due to the lack of high-quality evidence, CHEST’12, 15 the decision to bridge should be tailored to the patient & balance the risk of clotting & bleeding both the patient’s baseline risk & risk associated with the procedure:
  - Low risk of thrombosis e.g. CHADS<sub>2</sub> score 0-2 without hx of stroke/TIA, VTE >12 months ago with no other risk factors & non/minimally-invasive procedures: continue warfarin.
  - Minor dental procedures: continue warfarin with topical prohemostatic agents, e.g. tranexamic acid 5mL (100mg/mL) po 5-10 minutes pre-procedure, & 3-4x/day for 1-2 days post-procedure. CHEST’12
  - Moderate risk of thrombosis e.g. CHADS<sub>2</sub> score 3-4, VTE >3-12 months ago: balance risk of bleeding & clotting. CHEST’12
  - High risk of thrombosis e.g. CHADS<sub>2</sub> score 5-6, VTE or stroke/TIA ≤3 months ago, mechanical valve (especially mitral): consider anticoagulant bridging (e.g. LMWH). CHEST’12

MANAGING WARFARIN DRUG INTERACTIONS continued
- Thyroid medications can cause counter-intuitive for some reactions:
  - Levothyroxine ↑ INR ↑ catabolism of clotting factors
  - Methimazole & propylthiouracil ↓ INR

RESTARTING WARFARIN POST-INTRACEREBRAL BLEED
- Retrospective cohort study 19 tertiary centres in Germany, 2006 to 12. 18 Warfarin restarted in 172/719 (23.9%), AF n=566, Mean CHADS<sub>2</sub> 2.5 & HASBLED 3.1, median INR 2.8 (IQR 2.3-3.5). Those who restarted warfarin had ↓ ischemic complications (5.2% [9/172] versus not on warfarin 15% [82/547], p=0.001), but bleeding & recurrent intracerebral hemorrhage non-statistically significant. Median time for warfarin resumption was 31 days (IQR 18-65). Consider restarting warfarin after 4-8 weeks. ESC’18

Note: Acenocoumarol SINTROM (1mg, 4mg; $30-$70) considered an alternative warfarin for those patients with warfarin intolerances, other than bleeding.

AF=atrial fibrillation ASA=acetylsalicylic acid DVT=deep vein thrombosis HF=heart failure GI=gastrointestinal INR=international normalized ratio LMWH=low molecular weight heparin NSAID=non-steroidal anti-inflammatory drugs PE=pulmonary embolism TIA=transient ischemic attack SK=Saskatchewan 6½=half-life TTR=time in therapeutic range VTE=venous thromboembolism yr=years old
REFERENCES FOR WARFARIN TIPS & DOSING NOMOGRAMS


17) Garcia P, Ruiz W, Loza Munarriz C. Warfarin initiation nomograms for venous thromboembolism. Cochrane Database Syst Rev. 2013 Jul 10;7:CD007699. In patients with acute thromboembolism (DVT or PE) aged 18 years or older, considerable uncertainty surrounds the use of a 10-mg or a 5-mg loading dose for initiation of warfarin to achieve an INR of 2.0 to 3.0 on the fifth day of therapy. Heterogeneity among analyzed studies limits certainty surrounding optimal warfarin initiation nomograms.


