WARFARIN: MANAGEMENT OF OUT-OF-RANGE INRs

OBJECTIVE:
To provide practical strategies supported by the best available evidence for managing out-of-range international normalized ratios (INRs) for patients on long-term warfarin therapy.

BACKGROUND:
1. Warfarin can be challenging to manage due to its narrow therapeutic range, variable dose-response among patients and common interactions with drugs, diet, alcohol, and other factors.
2. In patients who are taking warfarin, thromboembolic events and bleeding are strongly related to the time in therapeutic range (TTR). This is the proportion of treatment time that the INR is within the target therapeutic range (typically 2.0 to 3.0 or 2.5-3.5 for patients with mechanical mitral valve replacements).
3. Clinicians may underdose warfarin due to a perceived greater risk of harm from bleeding associated with supratherapeutic INR values. However, subtherapeutic anticoagulation has been shown to increase the frequency and severity of thromboembolic events.
4. Good INR control, defined arbitrarily as a TTR >60%, may be best achieved by appropriately addressing both high and low INR values using a consistent approach (paper based dosing nomogram or computerized decision support program).

APPROACH TO OUT-OF-RANGE INR VALUES:
1. For each out-of-range INR value, attempt to identify the cause. See the section below, “Summary of Common Causes of Out-of-Range INRs”.
   - Ask the patient the following:
     - Tell me what warfarin doses you’ve taken in the past 2 weeks. The patient may have mistakenly taken a different dosage regimen than what was prescribed.
     - Have you missed any doses in the past week? How do you ensure that all doses have been taken? Do you use a calendar to record doses? A pill box?
     - Have you started or stopped any medication or supplements (prescription or non-prescription) recently? Any dose changes of your medications? Do you take Tylenol? How many per day?
     - How is your appetite? Have you been eating regularly? Have there been any recent changes in your diet?
     - How often and how much alcohol do you drink? Do you drink just on weekends?
     - Overall, how has your health been? Any infection? Fever? Diarrhea? Flu? Recent cold?
2. Determine whether a one-time change in the dose is all that is required or if a change in the maintenance dose is required or both.
• A change in the maintenance dose should be considered if there are at least two consecutive out-of-range INR values (in the same direction) in a patient with previously stable, in-range INRs and for which there is no identified temporary cause.
• A one-time change in the dose is appropriate for patients in which a transient cause is identified.

MANAGING SINGLE OUT-OF-RANGE INR VALUES
• For patients with previously in-range INR values who present with a single slightly out-of-range INR (e.g. INR 0.5 above or below the target range), there are two management options:
  1. Continue current maintenance dose and repeat INR in 1-2 weeks, OR
  2. Make a one-time dose change (increase or hold by ½ to 1 single dose) and resume current maintenance dose. Repeat INR in 1-2 weeks
• The specific approach is influenced by the magnitude of the out-of-range value, previous experience of similar values in the patient and whether the patient has strong risk factors for thrombosis/stroke or bleeding.

MAINTENANCE DOSING ALGORITHMS:
There are many warfarin dosing algorithms available. Physicians should become familiar with one approach in order to develop experience and consistency in making dosing changes.

One example of an available computer decision support tool is INR Online® http://www.inronline.ca/

The Figure below is a sample, paper-based Maintenance Dosing Algorithm published by the American Society of Hematology (2014) for the management of non-bleeding patients taking warfarin. This algorithm is based on making a dose change as a percentage of the total weekly dose. This nomogram serves as a guide and does not replace clinical judgment.
SUMMARY OF COMMON CAUSES FOR OUT-OF-RANGE INRS:

Table 1 and Table 2 summarize common causes and management strategies for low and high INRs, respectively.

Table 1: Common Causes of Low INRs and Management Strategies

<table>
<thead>
<tr>
<th>COMMON CAUSES OF LOW INRS</th>
<th>MANAGEMENT STRATEGIES</th>
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| MISSED DOSES, NON-COMPLIANCE, or errors in dosing | • Review the doses of warfarin actually taken over the past several weeks  
• Use strategies to improve compliance: pill box, warfarin pill box or pharmacy-prepared blister packs, warfarin dosing calendar, patient education, simplify dosing regimen |
| UNDERDOSING | • Be aware that underdosing provides less protection against thrombosis but is still associated with bleeding. Bleeding risk is the same |
Table 2: Common Causes of High INRs and Management Strategies

<table>
<thead>
<tr>
<th>COMMON CAUSES OF HIGH INRS</th>
<th>MANAGEMENT STRATEGIES</th>
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</thead>
<tbody>
<tr>
<td><strong>DRUG INTERACTIONS</strong></td>
<td></td>
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<tr>
<td>Prescription: phenytoin,</td>
<td>• Temporary drug</td>
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<tr>
<td>carbamazepine, barbiturates,</td>
<td>interaction: temporary</td>
</tr>
<tr>
<td>rifampin, azathioprine</td>
<td>warfarin hold or dose</td>
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<tr>
<td>Non-prescription: green tea,</td>
<td>reduction</td>
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<tr>
<td>ginseng, St. John’s Wort</td>
<td>• Chronic drug</td>
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<tr>
<td></td>
<td>interaction: reduce</td>
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<tr>
<td></td>
<td>maintenance dose and</td>
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<td></td>
<td>increase frequency of</td>
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<td></td>
<td>INR tests until new</td>
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<td></td>
<td>stable INR is achieved</td>
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<tr>
<td></td>
<td>• Although many drugs</td>
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<td></td>
<td>may interact with</td>
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<td></td>
<td>warfarin, avoidance of</td>
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<tr>
<td></td>
<td>either warfarin or the</td>
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<tr>
<td></td>
<td>interacting drug is</td>
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<tr>
<td></td>
<td>usually not required**</td>
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</table>
### ALTERED HEALTH STATES

- Fever, acute illness, diarrhea, reduced food intake
- Uncontrolled hyperthyroidism
- CHF exacerbation

- Temporarily reduce the dose and increase the frequency of INR testing until the patient’s health stabilizes

### MALNUTRITION

(vitamin K deficiency)

- Encourage patient to consume regular meals, including those containing vitamin K. Consider meal replacement beverage.
- Reduce maintenance dose of warfarin and increase frequency of monitoring

### ALCOHOL

- A one-time moderate to large amount of alcohol (more than 2 drinks) will transiently increase the INR (e.g. weekend party).
- Continue usual maintenance dose

### NON-COMPLIANCE OR ERRORS IN DOSING

(The patient mistakenly took a different dosage regimen than was prescribed)

- Review the doses of warfarin actually taken over the past several weeks
- Use strategies to improve compliance: pill box, warfarin dosing calendar, patient education, simplify dosing regimen

### *Most common drugs that can increase INR:*

- Antibiotics: sulfamethoxazole/trimethoprim, metronidazole, quinolones (ciprofloxacin, levofloxacin), amoxicillin, erythromycin, clarithromycin, azithromycin
- Azole antifungals: fluconazole, miconazole, voriconazole
- Cardiac drugs: amiodarone, some statins (fluvastatin), fenofibrate
- Acetaminophen >1 g/day
- Levothyroxine dose increases – full effect observed after 4-6 weeks of dose change

### ANTIPLATELET AGENTS:

Antiplatelet agents (acetylsalicylic acid (ASA), clopidogrel, prasugrel, ticagrelor) and Non-steroidal Anti-Inflammatory Drugs (NSAIDs) significantly increase the risk of bleeding when combined with warfarin but generally do not change the INR. The indication and clinical necessity of using these agents should be carefully weighed against the increased bleeding risk, and should be avoided unless specifically indicated. Refer to the Clinical Guide: “Warfarin” for more information.

### OTHER RELEVANT THROMBOSIS CANADA CLINICAL GUIDES:
• Warfarin
• Warfarin: Point-of-Care INR Monitoring

REFERENCES:


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