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 empirically 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? If yes, how many? 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 new antibiotics? 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.
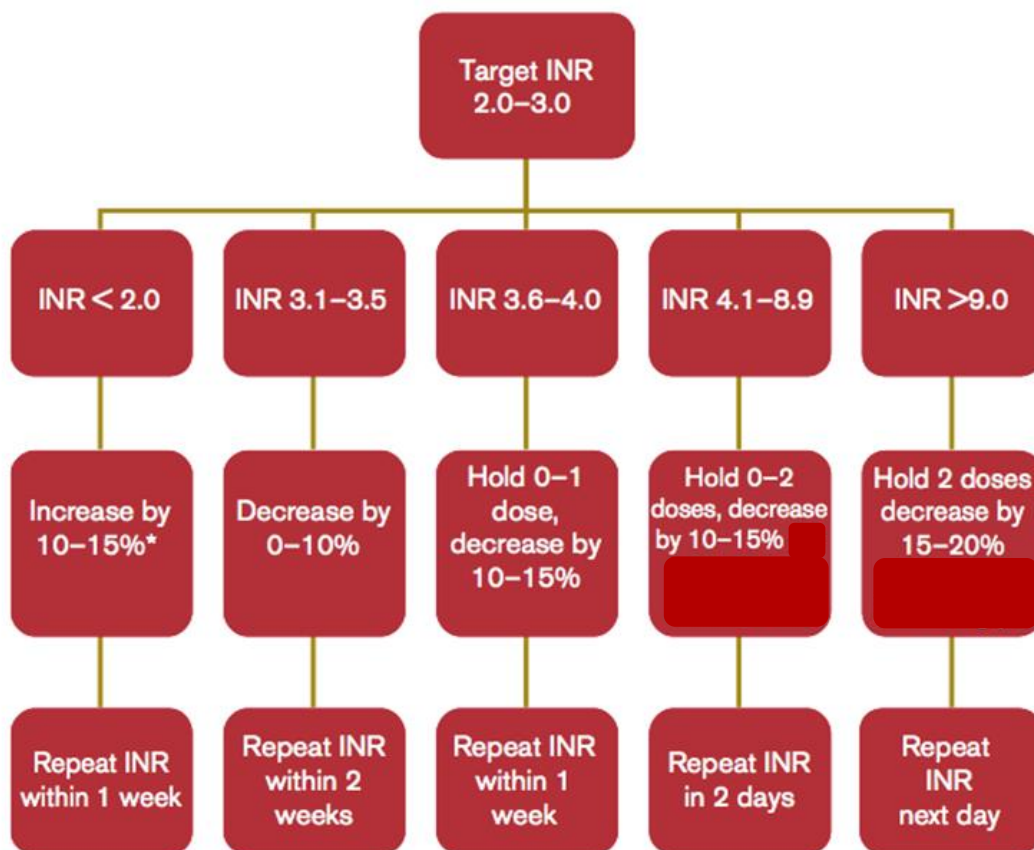
MAINTENANCE DOSING ALGORITHMS:

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 nomogram serves as a guide and does not replace clinical judgment.

Figure: Warfarin Dose Adjustment in Non-Bleeding Patients by % Dose Change of Total Weekly Dose (adapted from Cushman et al, 2014)

Target INR 2.0–3.0

INR < 2.0	INR 3.1–3.5	INR 3.6–4.0	INR 4.1–8.9	INR >9.0
Increase by 10–15%*	Decrease by 0–10%	Hold 0–1 dose, decrease by 10–15%	Hold 0–2 doses, decrease by 10–15%	Hold 2 doses decrease by 15–20%
Repeat INR within 1 week	Repeat INR within 2 weeks	Repeat INR within 1 week	Repeat INR in 2 days	Repeat INR next day

*Consider 15% increase if INR ≤1.5 without explanation

This algorithm is based on making a dose change as a percentage of the total weekly dose.

For patients with INRs of >4.5 but <10 and without clinically relevant bleeding, temporary cessation of VKA alone without the addition of vitamin K is suggested. Vitamin K may be given if INR >10, even in the absence of bleeding, depending on individual patient circumstances (e.g. risk factors for bleeding, risk for thrombosis if over-correction of INR, ability to have repeat INR testing).

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

COMMON CAUSES OF LOW INRS	MANAGEMENT STRATEGIES
MISSED DOSES, NON-COMPLIANCE, or ERRORS IN DOSING	• Review the doses of warfarin actually taken over the past several weeks.

	• If patient is receiving more than one strength of tablet, consider adjusting dose to enable use of a single strength to avoid confusion. • 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 similar with INRs 1.5-2.0 and 2.0-3.0, but risk of thrombosis rises quickly below INR 2.0. • Aim for an INR of 2.5. Aiming for 2.0 will lead to a higher chance of underdosing. • Increase the dose according to INR value.
CHANGE IN DIET/EXERCISE • Increased Vitamin K-rich foods (green leafy vegetables, soy, avocado, seaweed) • Meal replacement beverages containing vitamin K • Increased exercise	• Day-to-day and week-to-week variation in dietary vitamin K intake commonly results in variability in INR. • Do <u>not</u> advise patients to eat less vitamin K-rich foods. • Educate patient to maintain a **<u>consistent</u>**, healthy diet and lifestyle. • If INR is low and changes are long-term, increase the warfarin dose.
DRUG INTERACTIONS <u>Prescription</u>: examples include phenytoin, carbamazepine, barbiturates, rifampin, azathioprine, trazodone <u>Non-prescription</u>: examples include green tea, ginseng, St. John's Wort	• A change in INR is seen within 2 weeks of drug initiation. Increase maintenance dose of warfarin incrementally until stable maintenance dose is established. • Educate patient to maintain consistency. Avoid herbal supplements, extremes of "binging" and avoidance.

Table 2: Common Causes of HIGH INRs and Management Strategies

COMMON CAUSES OF HIGH INRS	MANAGEMENT STRATEGIES
DRUG INTERACTIONS*	• *Temporary drug interaction*: temporary warfarin hold or dose reduction. • *Chronic drug interaction*: reduce maintenance dose and increase frequency of INR tests until new stable INR is achieved. • **Although many drugs may interact with warfarin, avoidance of either warfarin or the interacting drug is usually <u>not</u> required.***
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 (atorvastatin and pravastatin are least likely to interact), fenofibrate
- Acetaminophen >1 g/day
- Levothyroxine dose changes– 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

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