# Warfarin

## *Its highs and lows*

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Warfarin has been used for more than 60 years and is approved for multiple indications.[1] By monitoring the international normalized ratio (INR), the warfarin dose can be tailored to the individual patient. Increasing the time in therapeutic range (TTR) optimizes safety and effectiveness.[2] This article explores some pearls and pitfalls of warfarin use in relation to INR monitoring, which might assist in achieving a greater TTR.

## Case description

Mr S.G., a pleasant 87-year-old man who is well known to you, comes in today for a scheduled review of his type 2 diabetes. He was last seen in the clinic 4 months ago and he had no concerns at that time. He has been feeling well. He denies any cardiac or respiratory symptoms, and his blood glucose levels are good. He is a widower, lives alone, and manages his medications on his own. He remains physically active, walking most days.

His past medical history includes aortic stenosis, type 2 diabetes mellitus, hypertension, stage-4 chronic kidney disease (his estimated glomerular filtration rate is approximately 30 mL/min), hypothyroidism, osteoarthritis, and gastroesophageal reflux disease. He takes the following medications: 15 units of neutral protamine Hagedorn insulin twice daily, 5 units of regular insulin with meals, 250 mg of metformin twice daily, 80 mg of valsartan daily, 75 µg of levothyroxine daily, 1000 IU of vitamin D daily, and 40 mg of pantoprazole daily.

On physical examination, he is a well-groomed elderly gentleman who walks into your examination room unaided. He appears well; general examination findings are normal. His blood pressure is 128/80 mm Hg, and his pulse is irregularly irregular at 115 beats per minute. The rest of his cardiovascular examination findings are normal. His chest is clear to auscultation, and respiratory rate is 12 breaths per minute. Foot examination findings are normal.

You suspect new-onset atrial fibrillation. As he is clinically stable, you proceed with investigations and ask the patient to return in a couple of days. Results of thyroid function tests, renal panel, complete blood count, coagulation profile, and liver function tests are all unchanged from previous results. The 12-lead electrocardiogram confirms atrial fibrillation with a heart rate of 110 beats per minute. You contact a cardiologist who advises that the patient take 25 mg of metoprolol twice daily for rate control and start warfarin for prevention of embolic stroke (risk factors include hypertension, age older than 75 years, and diabetes[3]*) with a target INR of 2.5 (range between 2.0 and 3.0).

## Bringing evidence to practice: initiating warfarin

The use of any validated warfarin nomogram or computerized dosing algorithm, regardless of a clinician's warfarin-prescribing experience, is supported in the 2012 American College of Chest Physicians (ACCP) antithrombotic therapy guidelines[6] and by the Canadian Agency for Drugs and Technologies in Health.[2] Initiation nomograms using 5- or 10-mg doses of warfarin for 2 days have been proposed and corroborated in prospective studies to achieve therapeutic INRs quickly.[7,8] **Table 1** is an example of a nomogram using a 5-mg dose of warfarin on day 1 and day 2.[7] The 10-mg starting dose of warfarin is likely safe and effective in patients who are younger and have a lower risk of bleed, and it might achieve a therapeutic INR faster.[8]

A lower initial starting dose of 2 to 3 mg of warfarin daily for 2 days is recommended in patients who are elderly, malnourished, or have a history of hepatic dysfunction or heart failure.[6,9] Doses of 5 mg or more might increase the risk of bleeding in these patient populations.[6] For example, in the elderly, stores of vitamin K become less accessible, resulting in a lower plasma concentration of vitamin K–dependent clotting factors, and thus warfarin-dosing requirements are lower. Although the nomogram for the initial 5-mg dose of warfarin was not developed for the lower initial starting doses of 2 to 3 mg, it might still be followed as a guide by using the same percentage increase or decrease in daily dose (**Table 1**).[7] For example, for an INR result of less than 1.5 on day 3, the nomogram indicates a day-3 warfarin dose of 5 to 10 mg, or in other words, a dose of 100% to 200% of the dose given

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*The selection of rate control or rhythm control, as well as the choice of antithrombotic therapy, for stroke prevention in patients with atrial fibrillation has been discussed in previous RxFiles articles in *Canadian Family Physician*.[4,5]

**Table 1. Example of nomogram for initiation of warfarin dose of 5 mg on days 1 and 2, with a target INR of 2.0–3.0**

| DAY OF WARFARIN INITIATION | INR RESULT | WARFARIN DOSE (PERCENTAGE OF INITIAL DOSE) |
|---|---|---|
| Day 3 | < 1.5 | 5–10 mg (100–200) |
| | 1.5–1.9 | 2.5–5 mg (50–100) |
| | 2–3 | 0–2.5 mg (0–50) |
| | > 3 | 0 (0) |
| Day 4 (optional INR) | < 1.5 | 10 mg (200) |
| | 1.5–1.9 | 5–7.5 mg (100–150) |
| | 2–3 | 0–5 mg (0–100) |
| | > 3 | 0 (0) |
| Day 5 | < 1.5 | 10 mg (200) |
| | 1.5–1.9 | 7.5–10 mg (150–200) |
| | 2–3 | 0–5 mg (0–100) |
| | > 3 | 0 (0) |
| Day 6 (optional INR) | < 1.5 | 7.5–12.5 mg (150–250) |
| | 1.5–1.9 | 5–10 mg (100–200) |
| | 2–3 | 0–7.5 mg (0–150) |
| | > 3 | 0 (0) |

INR—international normalized ratio.
Data from Crowther et al.[7]

on the previous 2 days. Extrapolating this to a 3-mg starting dose, the next dose following a day-3 INR result of less than 1.5 would be 3 to 6 mg.

Initially providing patients with a prescription for warfarin in tablet strengths of 1 and 2 mg, or 1 and 5 mg, will accommodate most dosage changes without the need to provide a new prescription. All warfarin tablets are scored, which allows for small dose changes.

When starting warfarin in outpatients, daily INR testing is unnecessary and can be easily misinterpreted. As with the previously mentioned nomograms, provided a baseline INR result is available and within normal limits, an INR might be obtained on day 3 and then repeated on day 5 in most outpatients.[7]

Warfarin therapy requires more frequent monitoring during initiation, around interruptions in therapy, and during acute illness. For most patients, as the warfarin dose and INR results stabilize, the intervals between testing periods can gradually be extended to every 4 to 6 weeks.[9]

For more information on warfarin initiation and nomograms, the RxFiles *Warfarin Tips & Dosing Nomograms*[1] tool is available from **CFPlus**.[†]

[†]The RxFiles *Warfarin Tips & Dosing Nomograms* tool is available at **www.cfp.ca**. Go to the full text of the article online and click on **CFPlus** in the menu at the top right-hand side of the page.

## Patient case continued

Mr S.G.'s baseline INR is 1.1. You prescribe 3 mg of warfarin daily for 2 days and arrange for him to have his INR measured on the third day. You provide a prescription for 2-mg and 1-mg tablets. You suggest he take this medication in the evenings and go for INR testing in the mornings to allow for dosage adjustments to be made the same day.

His INR result on day 3 is 1.7. Extrapolating from the 5-mg initiation nomogram, you calculate that Mr S.G. should receive 50% to 100% of the daily dose that he received on the previous 2 days. Given the relatively rapid increase in his INR, and his moderate risk of bleeding (risk factors include age older than 65 years and chronic kidney disease[10]), you prescribe a lower dose of warfarin, 2 mg, for 2 days (67% of the previous dose).

After 2 weeks of having INR tests twice weekly, his INR is in therapeutic range at 2.6. You calculate the average daily dose over the past week to be about 3 mg daily, and you instruct Mr S.G. to continue at that dose. You also extend the interval between INR tests to 1 week. Assuming the next 2 INR results are in therapeutic range (ie, between 2.0 and 3.0) and there are no changes in clinical status, you can double the interval between INR tests again, with

the eventual goal of Mr S.G. having INR tests once monthly.

## Bringing evidence to practice: avoiding common pitfalls

Consider the following factors when managing warfarin doses and monitoring INR.

***Frequency of INR monitoring.*** Literature, experience, and guidelines now suggest that for select adherent patients with stable warfarin doses and INR results, the frequency of INR monitoring can be extended up to every 12 weeks, provided the patient has good knowledge of warfarin and the effect of foods and drugs, and is informed to contact the prescriber if there are any changes in health, medications, diet, or lifestyle.[6,9,11]

***Interpreting INR results.*** Many factors can temporarily (eg, diarrhea, vomiting, fever, increased alcohol intake, dietary changes, antibiotics, extra warfarin doses) or permanently (eg, changes in chronic medications or chronic disease states, lifestyle changes) alter the response to warfarin.[12] Along with trends and the time since the last result, these factors must be considered in interpreting every INR result.

***What to do with a single, asymptomatic, unexplained, slightly out-of-range INR.*** If the INR result is no more than 0.5 above or below the therapeutic range, and the patient is clinically stable, a dosage adjustment might not be needed,[6] provided the risk of clot and the risk of bleed have been considered. For cases in which this approach is selected, a follow-up INR test in 1 to 2 weeks should be conducted. If at this point the INR result remains out of range, a change in warfarin dose might be required.

**Table 2. Example of dosing nomogram for maintenance of warfarin therapy:** *Recommended actions to maintain a target INR of 2.0-3.0 and 2.5-3.5.*

| TARGET INR OF 2.0-3.0 | ACTION TO MAINTAIN TARGET INR | TARGET INR OF 2.5-3.5 |
|---|---|---|
| **INR result** | | **INR result** |
| <1.5 | Extra dose, increase weekly dose by 10%-20% | <2 |
| 1.5–1.9 | Increase weekly dose by 5%-10% | 2–2.4 |
| 2–3 | No change | 2.5–3.5 |
| 3.1–3.5 | Decrease weekly dose by 5%-10% | 3.6–4 |
| 3.6–4.9 | Hold 1 dose, decrease weekly dose by 10%-20% | 4.1–4.9 |
| 5–9 | Hold 2 doses, decrease weekly dose by 10%-20% | 5–9 |
| >9 | Urgent evaluation | >9 |

INR—international normalized ratio.
Data from University of Wisconsin-Madison Health.[14]

***Nomograms for adjusting doses during maintenance.*** Nomograms for maintenance of warfarin therapy are also recommended in the ACCP guidelines,[6] and they have been shown to increase the TTR.[13] **Table 2** is an example of a warfarin-dosing nomogram for maintenance therapy.[14] Consider holding full or partial doses or decreasing the weekly dose if the INR result is high, or giving a small additional dose or increasing the weekly dose if the INR result is low. Many out-of-range INR results can be corrected by small dosage changes of 5% to 10% when 0.5 or less out of range, or 10% to 20% when more than 0.5 out of range.[14]

***Supratherapeutic INRs and the use of vitamin K.*** The risk of bleeding substantially increases when the INR exceeds 4.0.[6] When an INR is above the target range but below 4.0 or 4.5, holding a dose for 1 day is often sufficient to reduce the INR; however, the full effect of a held dose might not be seen for 5 to 7 days. Considering the risks of an ensuing subtherapeutic INR (eg, cardioembolic stroke, clot extension), holding full doses of warfarin to correct slightly out-of-range INR results should be used cautiously and requires careful monitoring. The 2012 ACCP guidelines for antithrombotic therapy no longer recommend the routine use of vitamin K to reverse warfarin when INR results are between 4.5 and 10.0 and the patient is not bleeding.[6] There might be select patients who have a very high risk of bleed, or for whom 2.5 to 5 mg of oral vitamin K is indicated when the INR is greater than 10.0.

Regardless of the specific result, INR interpretation requires many considerations and actions that need close observation. Scheduling INR tests earlier in the week might allow for closer monitoring and sufficient time for follow-up before the weekend.

## Patient case continued

Mr S.G. has now been taking warfarin for 8 months; his warfarin dose over the past several weeks has been 3 mg daily. You are notified that his INR today is 3.3. His INR results from the past 3 months are 2.7, 2.2, and 2.3. Mr S.G. is asymptomatic, and when he is asked if there have been any changes in his medications, diet, or activity level, he says no. You decide to maintain the current dose but repeat the INR test in 1 week.

The following week Mr S.G.'s INR is 3.9, prompting more in-depth investigation. When you contact him, he informs you that he recently started taking a glucosamine and chondroitin supplement for knee and shoulder arthritis pain. He did not think to mention it the previous week because he believed it was natural and he assumed it would not cause drug interactions.

He agrees to stop using the glucosamine and chondroitin supplement. He reports that his arthritis pain is intermittent and only occurs when he is very active. As these situations are generally predictable, you instruct him to use 500 to 1000 mg of acetaminophen every 6 hours as needed and to notify you if the pain persists or worsens, or if he is having to take multiple doses most days of the week. (Acetaminophen at higher doses and when taken regularly can increase INR.[15]) You also remind Mr S.G. to avoid nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen and naproxen because they increase the risk of bleeding—an increase that is not reflected in the INR and therefore cannot be easily predicted or monitored.

Two months later the laboratory calls you because Mr S.G.'s INR result is 7.8. You call him to inquire about bleeding and any other changes. He tells you that his arthritis pain had worsened but that it is now controlled with 1000 mg of acetaminophen 3 times a day. You suspect that this has caused his high INR result. He wants to continue with scheduled acetaminophen for his chronic pain. You consult the nomogram for warfarin maintenance (**Table 2**),[14] which guides you to hold warfarin for 2 days and decrease his weekly dose by 10% to 20%. You instruct him to skip tonight's and tomorrow's warfarin doses, and following that you decrease his daily dose from 3 to 2.5 mg daily. This is an approximately 16.7% reduction. You request that he repeat his INR test in 1 week, as the full effect of the dosage change will not be apparent for 5 to 7 days.

## Bringing evidence to practice: drug interactions

Warfarin interactions can be divided into 2 categories: 1) interactions that cause a change in INR (eg, amiodarone [effects of which might be delayed for days to months], antiepileptics, and antimicrobials), and 2) interactions that increase risk of bleed or clot without affecting INR (eg, NSAIDs, antiplatelets, hormones). Very few, if any, drug combinations are absolutely contraindicated. If the drug combination cannot be avoided, the interactions that affect INR can be monitored through more frequent INR testing and managed by adjustment of warfarin doses. The other type of drug interaction requires a balance of risk versus the benefit of adding the new drug. Other strategies for managing warfarin drug interactions include verifying indications and selecting alternatives that are less likely to interact.

Although many drugs can interact with warfarin,[16] and monitoring is recommended when starting, stopping, or changing doses of other medications, the 2012 ACCP antithrombotic therapy guidelines recommend particular caution with concurrent use of antiplatelets, NSAIDs, amiodarone, and trimethoprim-sulfamethoxazole.[6] Inevitably, drug interactions will be encountered with warfarin therapy. Routine empiric dosage adjustments are not predictable and therefore are seldom recommended.[9] Patients should be regularly reminded that they need to inform their health care providers or pharmacists when they take any new medications or supplements.

## Conclusion

The TTR is an important determinant of warfarin effectiveness and safety. This can be increased through the use of nomograms, which tend to suggest more infrequent and smaller dosage adjustments than one might expect. Patients who are of smaller stature, elderly, malnourished, or using interacting medications might be more sensitive to warfarin and should have warfarin initiated at lower doses.

Patients should be informed that INR monitoring will be more frequent during the period of warfarin initiation. When the INR is stabilized, the interval between tests might increase to every 4 to 12 weeks. Any dietary or lifestyle changes, acute illness, change in chronic illness, or changes in other medications (starting, stopping, or changing doses) can lead to INR instability, which usually requires a transient increase in monitoring frequency, and potentially an adjustment in the warfarin dose.

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