REVIEW

AMIR JAFFER, MD*
Medical Director, Anticoagulation Clinic, and the IMPACT (Internal Medicine Preoperative Assessment and Consultation) Center, The Cleveland Clinic. The Anticoagulation Clinic currently cares for more than 1,600 patients on warfarin.

LEE BRAGG, PharmD†
Coordinator, Anticoagulation Clinic, Department of General Internal Medicine and Department of Pharmacy, The Cleveland Clinic

Practical tips for warfarin dosing and monitoring

ABSTRACT

Patients on warfarin and their physicians must constantly balance the risks of bleeding and clotting. We offer practical tips for safe and effective warfarin therapy, based on the practices of the Anticoagulation Clinic of The Cleveland Clinic.

KEY POINTS

Warfarin should usually be started at a dose of 5 mg per day. A 10-mg dose more frequently results in a supratherapeutic international normalized ratio (INR).

Amiodarone, fluconazole, metronidazole, trimethoprim-sulfamethoxazole, and many other drugs inhibit the metabolism of warfarin.

Asking if any medication changes have occurred since the last INR may be too vague: inquire more specifically about prescription drugs, over-the-counter drugs, and herbal and natural remedies.

The INR should be checked at least four times during the first week of therapy and then less frequently, depending on the stability of the INR.

In general, a missed dose of warfarin is reflected in the INR within about 2 to 5 days after the dose is missed.

PATIENT INFORMATION
What you need to know about your warfarin therapy, page 372

*The author has indicated that he is on the speakers' bureau of the Bristol-Myers Squibb (formerly DuPont Pharmaceutical) and Aventis corporations. He is also a consultant to Aventis and AstraZeneca and has received grant or research support from AstraZeneca.
†The author has indicated that he has received grant or research support from DuPont Pharmaceuticals.

PATIENTS WHO TAKE WARFARIN (Coumadin) walk a tightrope between bleeding and clotting—and a hundred things can tip the balance. It's a difficult drug to use, with a narrow therapeutic index, but 60 years after it was introduced it is still the mainstay of oral anticoagulant treatment. More than 2 million North Americans take it, and this number continues to grow with our aging population.[1]

Only a minority of these patients are managed by anticoagulation clinics, despite evidence that patients managed by anticoagulation clinics have fewer bleeding and thromboembolic events than those who receive usual medical care,[2,3] and their international normalized ratios (INRs) are in the therapeutic range a greater percentage of the time.[4–7]

Therefore, everyone who prescribes warfarin, whether a cardiologist, family physician, or internist, needs to understand:

- Warfarin's mechanism of action
- Its pharmacokinetics and pharmacodynamics
- Its multiple interactions with other drugs, diet, and disease states
- How to use the INR to determine the dose of warfarin and monitor its anticoagulant effect.

In the pages that follow we offer some practical tips on the art and science of using warfarin safely and effectively.

MECHANISM OF ACTION

Warfarin, a coumarin derivative, inhibits clotting by limiting hepatic production of the biologically active vitamin K-dependent clotting factors (activated factors II, VII, IX, and X). Normally, the precursors of these factors undergo a carboxylation reaction to be con-

Downloaded from www.ccjm.org on April 25, 2024. For personal use only. All other uses require permission.

TABLE 1

What to tell a patient taking warfarin

Indicate the reason for starting warfarin and how it relates to clot formation
Review the trade name and generic name of the drug and discuss how warfarin works
Discuss the potential duration of therapy
Explain the need for frequent INR testing and the target INR appropriate for the patient's treatment
Describe the common signs and symptoms of bleeding
Describe the common signs and symptoms of a thrombotic event
Outline precautionary measures to decrease trauma or bleeding
Discuss the influence of dietary vitamin K
Discuss potential drug interactions (prescription, over-the-counter, herbal)
Discuss the need to avoid or limit alcohol consumption
Explain need for birth control measures for women of childbearing age
Stress the importance of notifying all their health care providers (physicians, dentists, etc) that they are taking warfarin
Ask patient to notify the anticoagulation provider when dental, surgical, or invasive procedures and hospitalization are scheduled or occur unexpectedly
Ask patient to notify anticoagulation provider of any change in warfarin tablet color, shape, or markings
Specify when to take warfarin and what to do if they miss a dose
Instruct patient about the importance of carrying identification (ID card; medical alert bracelet/necklace)

Warfarin can paradoxically exert a procoagulant response by interfering with proteins C and S

verted to their activated forms. Warfarin, as a vitamin K antagonist, interferes with this reaction. The reduction in the amount and activity of these factors produces the anticoagulant response.

However, warfarin also interferes with production of the body's natural anticoagulants, protein C and protein S, and can therefore sometimes exert a procoagulant response.[8]

PHARMACOKINETICS AND PHARMACODYNAMICS

Warfarin is a racemic mixture of a right-handed and a left-handed stereoisomer, designated R and S. This racemic mixture has a half-life of approximately 36 to 42 hours. The S-isomer is five times more potent as a vitamin K antagonist than the R-isomer.[9]

Absorption of warfarin is rapid and complete. It is highly protein bound (> 98%), primarily to albumin. Only the free drug is pharmacologically active.[10] If the serum albumin level is low (such as in the nephrotic syndrome), the free fraction of warfarin is increased, but so is its plasma clearance.[11] Therefore, such conditions are not likely to lead to significant changes in the INR.

The hepatic metabolism of the two isomers differs, with clinically significant implications for drug interactions. The S-isomer is primarily metabolized by cytochrome P450 2C9 (and to a lesser degree by P450 3A4) and is eliminated in the bile. The R-isomer, in contrast, is primarily metabolized by cytochrome P450 1A2 and P450 3A4 and is excreted in the urine as inactive metabolites.

Since the S-isomer is much more potent than the R-isomer, medications that inhibit or induce the P450 2C9 pathway lead to the most significant drug interactions. Most drug interactions that affect the R-isomer are not significant.[8]

STARTING WARFARIN

Warfarin is commonly used to decrease the risk of systemic arterial thromboembolism (eg,

Downloaded from www.ccjm.org on April 25, 2024. For personal use only. All other uses require permission.

stroke) in patients with atrial fibrillation or flutter or prosthetic valves. It is also used to prevent recurrent venous thromboembolism in patients with deep vein thrombosis or pulmonary embolism. Less commonly, it is used for secondary prevention after myocardial infarction.

When starting anticoagulation therapy, it is always important to review the risks and benefits with the patient. The decision should incorporate the patient's medical, social, dietary, and medication history, level of education and understanding, health beliefs, and adherence to prior therapy.[12] Subsequently, the patient should be thoroughly educated about warfarin (**TABLE 1**; also see "What you need to know about your warfarin therapy," page 372) upon initiation of therapy and periodically thereafter.

A system, either written or electronic, should be developed for documenting and recording test results, patient encounters, and return visits. Nomograms[13–16] and computer programs[17–19] are available to guide dosing.

Importance of the INR

The INR was developed in 1982 by the World Health Organization's Expert Committee on Biologic Standardization in response to variations in thromboplastin sensitivity and different ways of reporting the prothrombin time across the world.[8] Inappropriate management can lead to subtherapeutic or supratherapeutic INR values, increasing the risk of acute or recurrent thromboembolic episodes or bleeding episodes, respectively.

For most indications, the therapeutic INR range is 2.0 to 3.0. Exceptions are when warfarin is used for secondary prevention after a myocardial infarction or for patients with high-risk mechanical prosthetic heart valves, in which case the range is 2.5 to 3.5.

Heparin as a bridge to warfarin

In conditions such as acute venous thromboembolism, patients should receive unfractionated heparin or low-molecular-weight heparin during the first few days of warfarin therapy as a "bridge," as warfarin may take up to 5 days to achieve its antithrombotic effect. This is because prothrombin (activated factor II) has a long elimination half-life: 60 hours. In addition, a randomized clinical trial[20] showed higher rates of recurrent venous thromboembolism and mortality without this bridge.

However, in some conditions such as atrial fibrillation, warfarin is often started on an outpatient basis without overlap with heparin. This poses the theoretical risk of creating a hypercoagulable state as protein C levels fall, but this has not been substantiated except in patients with known protein C deficiency or another hypercoagulable condition.[21]

Start with 5 mg

Warfarin should be started at a dose of 5 mg per day. Randomized trials[22,23] have shown that patients are more likely to have a therapeutic INR 3 to 5 days after starting warfarin with a 5-mg dose than with a 10-mg dose. Also, a 10-mg dose more frequently results in supratherapeutic INR values.

We recommend a lower starting dose in:

- Elderly patients
- Those with low body weight or low albumin levels
- Patients with congestive heart failure or liver disease
- Patients taking certain medications,[21] eg, amiodarone, trimethoprim-sulfamethoxazole, or metronidazole.

If a patient has taken warfarin in the past, we resume his or her previous steady-state dose without INR monitoring during the first few days of therapy.

In acute thrombo-embolism, give heparin when starting warfarin

Raise the INR gradually

The INR response after starting warfarin is variable and highly dependent on the half-lives of the vitamin K-dependent clotting factors. The initial increase in the INR (the *anticoagulant effect*) is primarily a response to decreased levels of circulating factor VII, which is the factor with the shortest half-life—approximately 6 hours.[21] Factor IX also has a relatively short half-life.

On the other hand, the *antithrombotic effect* (the body's ability to prevent further thrombus formation) may not be achieved for up to 5 days. This effect depends on the clearance of circulating prothrombin, which, as we said, has an elimination half-life of about 60 hours.

Therefore, although higher starting doses of warfarin (> 5 mg) may lead to rapid increases in the INR, a rapid increase in the INR after one or two doses should not necessarily

Downloaded from www.ccjm.org on April 25, 2024. For personal use only. All other uses require permission.

be viewed as a good response, since this is simply a reflection of the anticoagulant effect. Rather, the goal should be to gradually increase the INR to achieve the antithrombotic effect. This avoids overshooting the INR range in the first several days of therapy and may lessen the risk of inducing a paradoxical hypercoagulable state.[8]

GENERIC WARFARIN VS COUMADIN

Whether a generic formulation of warfarin can be used instead of brand-name Coumadin is controversial.

In the 1980s, Boston City Hospital, in a cost-saving attempt, substituted generic amorphous warfarin sodium for crystalline warfarin sodium (Coumadin) in its pharmacy.[24,25] The substitution led to loss of anticoagulation control as evidenced by increases in patient visits and dosage adjustments and less time in the therapeutic range. Amorphous warfarin was subsequently withdrawn from the US market.

At least three generic formulations of warfarin are approved by the US Food and Drug Administration (FDA) and are felt to be substitutable for Coumadin.

A rapid anticoagulant effect does not equal an antithrombotic effect

A health maintenance organization that previously dispensed only Coumadin added generic warfarin (Barr Laboratories, Pomona, New York) to its pharmacy shelves.[26] About 80% of the patients changed to generic warfarin, and the substitution did not significantly affect INR control, adverse events (ie, thromboembolism or bleeding), or number of dose changes.

In our practice, if a patient starts on Coumadin, we continue to prescribe it. However, if a patient wants generic warfarin because it is cheaper, we make this change but monitor the INR more frequently in the first few weeks of the transition.

FREQUENCY OF MONITORING

The College of American Pathologists recommends the INR be checked at least four times during the first week of therapy and then less frequently, depending on the stability of the INR.[27] We recommend checking the INR daily or every other day until it is in the therapeutic range for 2 consecutive days.

Once the INR is in the therapeutic range for 2 consecutive days, it should be checked every 3 to 5 days. When the INR and warfarin dose remain stable for 1 week, the INR should be checked weekly. Once the INR and warfarin dose remain stable for an additional 2 to 3 weeks, the testing interval can be extended to every 4 weeks.[21]

MAINTENANCE THERAPY

Once a patient makes the transition from the initial dosing phase to the maintenance phase, more consideration to the multiple factors that may affect the INR should be given when interpreting low or high INR values. The key is to individualize the dosage according to these factors and the target INR range.

The ideal regimen should provide the same dose every day, but this is not always possible. Warfarin comes in many tablet strengths: 1, 2, 2.5, 3, 4, 5, 6, 7.5, and 10 mg. Still, for some patients, a given tablet strength might not be enough while the next higher tablet strength may be too much.

In this situation one needs to give different doses on different days of the week. It is better if the doses are similar rather than greatly different. For example, if a patient were taking warfarin 2 mg daily except 4 mg on Monday and Friday using 2-mg tablets, it would be reasonable to change the dosage to 3 mg daily except 2 mg on Monday, Wednesday, and Friday if the INR tended to fluctuate regularly. The patient would still receive 18 mg/week, but with less variability in the day-to-day dose. Obviously, this type of regimen may not work for every patient, as it could be confusing or the patient may have difficulty splitting tablets. Nevertheless, the point is that the warfarin dosage needs to be individualized.

In most cases, alternating doses (eg, 2.5 mg alternating with 5 mg) or repeating doses (eg, 2.5 mg, then 2.5 mg, then 5 mg) should be avoided, as they provide different total weekly doses of warfarin.

Before changing the dosage

Before adjusting the dosage of warfarin, one should evaluate previous warfarin doses, previ-

Downloaded from www.ccjm.org on April 25, 2024. For personal use only. All other uses require permission.

ous INR results, and whether anything else in the patient's condition or regimen has changed. Patients should be asked about:

- **Adherence.** Did they miss any doses?
- **Changes in other medications.** Asking if any medication changes have occurred since the last INR may be too vague—it may be necessary to inquire more specifically: Did you start any prescription drugs, over-the-counter drugs, or herbal or natural remedies since your last visit? Did you stop any of these? Did the dosage of any of these change? Any of these can alter warfarin's action.
- **Current vitamin K consumption,** including foods, vitamins, and supplements.
- **Concomitant illnesses.** Patients with medical conditions that may affect warfarin such as congestive heart failure or thyroid dysfunction should be asked about disease-specific symptoms or medication changes.

Although it is not necessary in every instance to ask about recent illness, remember that illness can affect the INR in several ways. Fever, vomiting, or diarrhea can affect the INR. Ill patients may reduce their intake of vitamin K. Antibiotics may alter the response to warfarin.[28–30]

Dosage adjustment based on INR

Once an appropriate evaluation of the patient is completed, you should determine whether a dosage adjustment is necessary. Depending on how far above or below the target INR range the current value is, it may not be necessary to adjust the dosage at all. Some authors recommend the dosage be changed whenever two consecutive INR values are out of the target INR range[31] or whenever two consecutive values are more than 0.3 units above or below the target INR range.[32]

In most cases, if the dosage needs to be adjusted, then it should be adjusted by 5% to 20% of the total weekly dose,[17] depending on the current INR, the previous dose, and any changes identified that may have been the cause for the INR to be too high or too low.

For example, suppose a patient with atrial fibrillation taking warfarin 35 mg/week has an INR of 1.7 (target range 2.0–3.0). He previously had therapeutic INRs for 3 months. During the interview you learn that his dosage of amiodarone was decreased approximately 3 weeks ago. As this is a logical explanation for the current subtherapeutic INR, a weekly dosage adjustment of approximately 10% would be appropriate, ie, bringing his dosage to 38 mg/week—say, 5 mg on Monday, Wednesday, Friday, and Sunday and 6 mg on Tuesday, Thursday, and Saturday. If a second patient in the exact same scenario had an INR of 1.5, a weekly adjustment of closer to 20% would be more appropriate, ie, bringing his dosage to 42 mg/week—6 mg/day.

CAUSES OF HIGH OR LOW INRs

Many things can cause the INR to become high or low. This is not intended to be an exhaustive review of all such causes but to provide a concise overview. Since there are multiple causes to consider, you should not assume that one patient's response to a particular effect will hold true for all subsequent patients. This highlights the need for a thorough assessment of any abnormal INR value and an individualized approach to dosage adjustments and follow-up monitoring of the INR.

Drug interactions

Of the many causes of high or low INR values, the most common that are likely to lead to significant changes in the INR and increase the propensity for bleeding or clotting are drug interactions.

Drug interactions with warfarin can be defined as either pharmacokinetic or pharmacodynamic. Pharmacokinetic interactions involve alterations in the absorption, protein binding, and hepatic metabolism of warfarin. Conversely, pharmacodynamic interactions affect the tendency for bleeding or clotting through either antiplatelet effects or increases or decreases in vitamin K catabolism.

Pharmacokinetic interactions. Few medications affect the absorption of warfarin. The most widely cited example is cholestyramine, and this interaction may be minimized or avoided by separating the doses of warfarin and cholestyramine by 2 to 6 hours.[33]

Interactions involving protein binding displacement are few and usually of minimal significance, since a compensatory increase in plasma clearance of warfarin occurs with any increase in unbound warfarin concentrations.

Check the INR every 1–2 days until it is in the therapeutic range for 2 consecutive days

Downloaded from www.ccjm.org on April 25, 2024. For personal use only. All other uses require permission.

TABLE 2

Common drug interactions with warfarin

DRUG AND INTERACTION	MECHANISM OF INTERACTION
Can increase the INR	
Acetaminophen[35–37]	Unknown*
Amiodarone[38,39]	2C9 inhibition†
Cimetidine[40,41]	Enzyme inhibition
Ciprofloxacin[42]	Enzyme inhibition
Clarithromycin[43,44]	Enzyme inhibition
Clofibrate[45,46]	Enzyme inhibition
Erythromycin[47,48]	Enzyme inhibition
Fluconazole[49,50]	2C9 inhibition†
Fluvastatin[51,52]	2C9 inhibition
Fluvoxamine[53]	Enzyme inhibition
Gemfibrozil[54]	Enzyme inhibition
Isoniazid[55]	Enzyme inhibition
Itraconazole[56]	Enzyme inhibition
Ketoconazole[57]	Enzyme inhibition
Lovastatin[58]	Enzyme inhibition
Metronidazole[59]	2C9 inhibition†
NSAIDs[76,77]	Platelet inhibition‡
Propafenone[60]	Enzyme inhibition
Simvastatin[61]	Enzyme inhibition
Tamoxifen[62,63]	Enzyme inhibition
Thyroid hormones[75]	Increased vitamin K catabolism
Tramadol[64,65]	Enzyme inhibition
Trimethoprim sulfamethoxazole[66]	2C9 inhibition†
Zafirlukast[67]	2C9 inhibition
Can decrease the INR	
Barbiturates[68,69]	Enzyme induction
Carbamazepine[70]	Enzyme induction
Dicloxacillin[71]	Enzyme induction
Methimazole[75]	Decreased vitamin K catabolism
Propylthiouracil[75]	Decreased vitamin K catabolism
Rifampin[74]	Enzyme induction
Initially increase, then decrease the INR	
Phenytoin[72,73]	Protein displacement/ enzyme induction

*Lesser effect
†Greater effect
‡Only reported with certain NSAIDs and appears to be dose-related

An example of a protein displacement interaction occurs with valproic acid.[34]

The most frequent and significant interactions involve the hepatic inhibition or induction of warfarin metabolism. Recall that warfarin is composed of two isomers, and the S-isomer is five times more potent than the R-isomer. Medications that inhibit or induce the cytochrome P450 2C9 pathway, the primary site of S-isomer metabolism, can lead to significant increases or decreases in the INR (TABLE 2).[35–77] A more comprehensive review on the subject is provided by Cropp and Bussey.[78]

In general, medications that cause enzyme induction of warfarin metabolism (and therefore reduce warfarin's action and lower the INR) have a gradual onset and offset that may take 1 to several weeks. The primary determinant of the onset and offset is the half-life of the inducing agent. The INR should be monitored frequently for several weeks when an enzyme inducer is started or stopped or when its dosage is changed.

Enzyme inhibitors of warfarin metabolism (which increase warfarin's action and raise the INR) are more numerous and are encountered more frequently. In general, the onset of effect for inhibitors is quicker than for inducers and may occur after only several doses of the inhibitor. Similarly, the offset tends to be quicker for inhibitors but again depends on the half-life of the medication. For example, amiodarone, with its extremely long half-life, may have an offset lasting several months.

Potential interactions between alternative therapies and warfarin have been reviewed elsewhere[79]; however, the most widely used natural therapies that can affect the INR are ginseng, garlic, and ginkgo biloba.

Adherence, missed doses

If the INR is high or low, the patient may not be adhering to the regimen. Confirm the actual dose taken: if the INR is high you want to rule out the possibility that the patient took a higher than prescribed dose.

Also, always ask patients about missing any doses of warfarin. In general, a missed dose of warfarin is reflected in the INR within about 2 to 5 days after the dose is missed. This could be important even if the INR value is in the therapeutic range. For example, a patient with a therapeutic INR value who reports missing a dose of warfarin 2 days ago would

Downloaded from www.ccjm.org on April 25, 2024. For personal use only. All other uses require permission.

very likely have had a supratherapeutic INR if he or she had not missed the dose. This is probably of greater concern for interpreting INR results of a patient recently started on warfarin.

Concomitant diseases

Certain diseases can influence anticoagulation control.[80]

Congestive heart failure can cause hepatic congestion of blood flow and inhibit warfarin metabolism. This can be troublesome in patients with frequent exacerbations of heart failure.

Hypothyroidism decreases the catabolism of the vitamin K clotting factors. Therefore, hypothyroidism of new onset or due to inadequate replacement therapy could be suspected if there is a general trend toward decreased INR values with a need for increased warfarin doses.

Hyperthyroidism, on the other hand, increases the catabolism of the vitamin K clotting factors and could be suspected if there is a general trend toward increased INR values with a need for decreased warfarin doses.[80]

Hepatic failure may significantly elevate the INR due to decreased production of clotting factors.

Vitamin K intake

Excessive vitamin K consumption can promote increased production of the vitamin K clotting factors, decreasing the anticoagulant response to warfarin.[28] Alternatively, decreased vitamin K consumption can increase the anticoagulant response to warfarin.

The foods that contain the highest amount of vitamin K per serving are the green leafy vegetables (eg, spinach, broccoli, turnip greens).[81] Unfortunately, many patients have been misinformed or otherwise believe that these foods should be avoided if they are taking warfarin.

It is true that, of the foods typically consumed in the average diet, the green leafy vegetables are most likely to cause fluctuations in the INR. However, these foods are very nutritious and may contribute to a healthy diet. It is much better to advise patients who eat or want to eat these types of foods to do so consistently and in moderation.

The key is to maintain a balanced amount of vitamin K in the diet. There is no evidence that consuming less vitamin K is more beneficial in maintaining anticoagulation control than consuming more. Therefore, patients should simply be instructed to avoid binge eating of vitamin K–rich foods and to report any dietary changes to their anticoagulation provider.

Vitamins and supplements may contain varying amounts of vitamin K and should be evaluated when a thorough dietary assessment is necessary.

Dispensing errors

As unlikely as it would seem, dispensing errors do occur and should be given consideration when evaluating high or low INR values. Simply asking the patient to verify the prescription label may be inadequate. Instead, the patient and the anticoagulation care provider should identify the tablet according to color and markings, as the prescription may have been labeled correctly but may contain the incorrect tablet strength.

IF THE INR IS TOO HIGH

Using the current literature,[21,82–89] we have developed guidelines (TABLE 3) for management of the supratherapeutic INR at our institution. We have also developed a checklist (TABLE 4) to evaluate for anticoagulation-associated bleeding, which we use in conjunction with our guidelines for every supratherapeutic INR.

Many warfarin patients mistakenly believe they must avoid green leafy vegetables

Give vitamin K 2.5 mg by mouth

The use of 1 mg of oral vitamin K has been shown to lower supratherapeutic INR values into range faster than placebo and with fewer major bleeding events.[88] Since US pharmacies do not carry 1-mg tablets of vitamin K, we prescribe a 5-mg tablet and have the patient break it in half to provide 2.5 mg of oral vitamin K.

Before prescribing oral vitamin K, we like to exclude laboratory error. Therefore, whenever it is possible to reconfirm the supratherapeutic INR, we do so.

In some situations we can almost predict that an elevated INR is an error. For example,

Downloaded from www.ccjm.org on April 25, 2024. For personal use only. All other uses require permission.

TABLE 3

Cleveland Clinic guidelines for managing patients with high INR values

INR > target range but < 5.0
- Assess for bleeding by completing the "Provider checklist for evaluation of anticoagulation-associated bleeding" (TABLE 4)
- **If no bleeding**
  - Lower or omit next warfarin dose; if INR is only minimally above therapeutic range or if temporary cause is identified and resolved (eg, acute alcohol ingestion), dose reduction may not be necessary
  - Resume warfarin at a lower maintenance dose if applicable
  - Evaluate INR in 7–14 days; may need to evaluate sooner if newly started on warfarin, new interacting medication started, suspected rising INR, or otherwise clinically indicated
- **If bleeding suspected**
  - Contact supervising physician, refer patient for medical evaluation

INR > 5.0 but < 9.0
- Assess for bleeding by completing the "Provider checklist for evaluation of anticoagulation-associated bleeding" (TABLE 4)
- **If no bleeding**
  - Evaluate patient for characteristics associated with increased risk of bleeding*; if patient has *no* characteristics associated with increased risk of bleeding, then omit next dose or two of warfarin and evaluate the INR in 24–48 hours
  - If patient has ≥ 1 characteristic associated with increased risk of bleeding, then omit next dose or two of warfarin *and* give oral vitamin K 2.5 mg
  - Evaluate INR in 24–48 hours
  - When INR < 5.0, resume warfarin at an appropriate maintenance dose and reevaluate INR in 3–5 days
- **If bleeding is suspected**
  - Contact supervising physician, refer patient for medical evaluation

INR > 9.0
- Assess for bleeding by completing the "Provider checklist for evaluation of anticoagulation-associated bleeding" (TABLE 4)
- Contact supervising physician
- Refer patient for medical evaluation and for administration of oral, subcutaneous, or intravenous vitamin K
- Hold warfarin therapy until INR < 5.0, then may resume warfarin at an appropriate maintenance dose and recheck INR in 3–5 days

---

***Characteristics associated with increased risk of bleeding**[21,82-89]
- History of past bleeding (cerebrovascular, gastrointestinal, other)
- Recent surgery
- Hypertension
- Cerebrovascular disease or history of stroke
- Serious heart disease or recent myocardial infarction
- Renal insufficiency (serum creatinine > 1.5 mg/dL)
- Age > 65 years
- Severe anemia (hematocrit < 30%)
- Concomitant medications that potentiate bleeding
- Diabetes

indwelling vascular catheters should not be used for drawing INR samples because they are flushed with heparin, but this still often happens. Therefore, if a patient with a vascular catheter or on hemodialysis has an elevated INR, we recheck the INR before prescribing oral vitamin K.

Although low-dose oral vitamin K has not been shown to induce warfarin resistance like high-dose subcutaneous or intravenous vitamin K, its injudicious use could be a problem in patients with a recent thromboembolic event or valve replacement by putting them at risk for recurrent thromboembolism.

BEFORE SURGERY

Many patients on long-term warfarin therapy need to undergo surgery or other procedures. This poses a problem, as the warfarin needs to be discontinued in many cases. We will address this topic in detail in an upcoming article in this journal.

Downloaded from www.ccjm.org on April 25, 2024. For personal use only. All other uses require permission.

TABLE 4

Provider checklist for evaluation of anticoagulation-associated bleeding

QUESTION	YES	NO	COMMENTS
Characteristics associated with increased risk of bleeding (TABLE 3)?	_____	_____	_____
Bruises without obvious cause?	_____	_____	_____
Fall or blow to the head?	_____	_____	_____
Severe and prolonged headache?	_____	_____	_____
Nosebleeds (prolonged or frequent)?	_____	_____	_____
Coughing up blood?	_____	_____	_____
Vomiting red blood or material that looks like coffee grounds?	_____	_____	_____
Bleeding heavily from gums after brushing teeth?	_____	_____	_____
Swelling and tenderness or pain in the abdomen?	_____	_____	_____
Severe, prolonged back pain, without obvious cause?	_____	_____	_____
Bowel movements that are loose or contain blood or that are black and bad smelling?	_____	_____	_____
Urine that contains red blood or that is dark brown?	_____	_____	_____
Heavy bleeding at menstrual periods, such as twice the usual flow?	_____	_____	_____
Prolonged bleeding from small cuts?	_____	_____	_____

FUTURE TRENDS

This is an exciting time in oral anticoagulation management.

Patient self-management may be an option for patients who are very adherent and capable. Handheld instruments are available that measure the INR with sufficient accuracy, and studies[6] show that patients can learn to manage their own anticoagulation therapy after several hours of teaching, leading to improved anticoagulation control and fewer adverse events.

Point-of-care testing. In addition, the ease of use and availability of these instruments and computer programs to manage patients on warfarin not only has increased the use of point-of-care testing in existing anticoagulation clinics, but also has led to the establishment of new clinics. This model, where face-to-face interaction occurs using point-of-care testing, is termed the *near-patient testing model*.

So far there is little evidence the near-patient testing model leads to better outcomes than a telephone-based anticoagulation service. However, at our institution, where we manage patients in both these models, it is our experience that quicker, more efficient care is possible in the near-patient testing model. There may also be opportunity for reimbursement using this model, whereas none is available for telephone management. We are currently undertaking a study to evaluate these two models.

New antithrombotic agents are also being developed. Some parenteral direct thrombin inhibitors (DTIs) are already FDA-approved for heparin-induced thrombocytopenia, and oral DTIs are under investigation.

One such DTI is ximelagatran (Exanta), which is currently being compared with warfarin and other anticoagulants in phase II and III clinical trials. This drug has shown initial promise, and if the trials show similar efficacy and safety for preventing thromboembolism in conditions such as atrial fibrillation and venous thromboembolism, this drug may ultimately start to replace warfarin because of its advantages, ie, no need for monitoring and fewer drug interactions.

However, it will be awhile until warfarin is replaced in clinical practice.

Downloaded from www.ccjm.org on April 25, 2024. For personal use only. All other uses require permission.

REFERENCES

1. **Waterman AD, Banet G, Milligan PE, et al.** Patient and physician satisfaction with a telephone-based anticoagulation service. J Gen Intern Med 2001; 16:460–463.
2. **Wilt VM, Gums JG, Ahmed OI, et al.** Pharmacy-operated anticoagulation service: improved outcomes in patients on warfarin. Pharmacotherapy 1995; 15:732–739.
3. **Chiquette E, Amato AG, Bussey HI.** Comparison of an anticoagulation clinic and usual medical care: anticoagulation control, patient outcomes, and health care cost. Arch Intern Med 1998; 158:1641–1647.
4. **Foss MT, Schooch PH, Sintek CD.** Efficient operation of high-volume anticoagulation clinic. Am J Health Syst Pharm 1999; 56:443–449.
5. **Samsa GP, Matchar DB, Goldstein LB, et al.** Quality of anticoagulation management among patients with atrial fibrillation. Arch Intern Med 2000; 160:967–973.
6. **Sawicki PT, for the Working Group for the Study of Patient Self-Management of Oral Anticoagulation.** A structured teaching and self-management program for patients receiving oral anticoagulation: a randomized controlled trial. JAMA 1999; 281:145–150.
7. **Beyth RJ, Quinn L, Landefeld CS.** A multicomponent intervention to prevent major bleeding complications in older patients receiving warfarin. A randomized, controlled trial. Ann Intern Med 2000; 133:687–695.
8. **Hirsh J, Dalen JE, Anderson DR, et al.** Oral anticoagulants: mechanism of action, clinical effectiveness, and optimal therapeutic range. Chest 2001; 119(suppl):8S–21S.
9. **Breckenridge A, Orme M, Wesseling H, et al.** Pharmacokinetics and pharmacodynamics of the enantiomers of warfarin in man. Clin Pharmacol Ther 1974; 15:424–430.
10. **O'Reilly R.** Interaction of the anticoagulant drug warfarin and its metabolites with human plasma albumin. J Clin Invest 1969; 48:193–202.
11. **Ganeval D, Fischer AM, Barre J, et al.** Pharmacokinetics of warfarin in the nephrotic syndrome and effect on vitamin K dependent clotting factors. Clin Nephrol 1986; 25:75–80.
12. **Brandjes DP, Hejjboer H, Buller HR, et al.** Acenocoumarol and heparin compared with acenocoumarol alone in the initial treatment of proximal-vein thrombosis. N Engl J Med 1992; 327:1485–1489.
13. **Tait RC, Sefcick A.** A warfarin induction regimen for out-patient anticoagulation in patients with atrial fibrillation. Br J Haematol 1998; 101:450–454.
14. **Crowther MA, Harrison L, Hirsh J.** Warfarin: less may be better—in response. Ann Intern Med 1997; 127:333.
15. **Fennerty A, Dolben J, Thomas P, et al.** Flexible induction dose regimen for warfarin and prediction of maintenance dose. BMJ (Clin Res Ed) 1984; 288:1268–1270.
16. **Gedge J, Orme S, Hampton KK, et al.** A comparison of low dose warfarin induction regimen with the modified Fennerty regimen in elderly patients. Age Aging 2000; 29:31–34.
17. **Poller L, Wright D, Rowlands M.** Prospective comparative study of computer programs used for management of warfarin. J Clin Pathol 1993; 46:299–303.
18. **Vadher B, Patterson DL, Leaning M.** Evaluation of a decision support system for initiation and control of oral anticoagulation in a randomised trial. BMJ 1997; 314:1252–1256.
19. **White RH, Hong R, Venook AP, et al.** Initiation of warfarin therapy: comparison of physician dosing with computer-assisted dosing. J Gen Intern Med 1987; 314:1252–1256.
20. **Ansell JE, Buttaro ML, Thomas OV, et al.** Consensus guidelines for coordinated outpatient oral anticoagulation therapy management. Ann Pharmacother 1997; 31:604–615.
21. **Ansell J, Hirsh J, Dalen J, et al.** Managing oral anticoagulant therapy. Chest 2001; 119(suppl):22S–38S.
22. **Harrison L, Johnston M, Massicotte MP, et al.** Comparison of 5 mg and 10 mg loading doses in initiation of warfarin therapy. Ann Intern Med 1997; 126:133–136.
23. **Crowther MA, Ginsberg JB, Kearon C, et al.** A randomized trial comparing 5 mg and 10 mg warfarin loading doses. Arch Intern Med 1999; 159:46–48.
24. **DeCara JM, Croze S, Falk R.** Generic warfarin: a cost-effective alternative to brandname drug or a clinical wild card? Chest 1998; 113:261–263.
25. **Richton-Hewett S, Foster E, Apstein CS.** Medical and economic consequences of a blinded oral anti-coagulant brand change at a municipal hospital. Arch Intern Med 1988; 148:806–808.
26. **Milligan PE, Banet GA, Waterman AD, et al.** Substitution of generic warfarin for Coumadin in an HMO setting. Ann Pharmacother 2002; 36:764–768.
27. **Fairweather RB, Ansell J, Van den Besselaar AM, et al.** College of American Pathologists Conference XXXI on laboratory monitoring of anticoagulant therapy: laboratory monitoring of oral anticoagulant therapy. Arch Pathol Lab Med 1998; 122:768–781.
28. **Booth SL, Charnley JM, Saddowski JA, et al.** Dietary vitamin K1 and stability of oral anticoagulation: proposal of a diet with a constant vitamin K1 content. Thromb Haemost 1997; 77:504–509.
29. **Richards RK.** Influence of fever upon the action of 3,3-methylene bis-(4-hydroxycoumarin). Science 1943; 97:313–316.
30. **Udall JA.** Human sources and absorption of vitamin K in relation to anticoagulation. JAMA 1965; 194:127–129.
31. **Triplett DA.** Current recommendations for warfarin therapy. Use and monitoring. Med Clin North Am 1998; 82:601–611.
32. **Tiede DJ, Nishimura RA, Gastineau DA, et al.** Modern management of prosthetic valve anticoagulation. Mayo Clin Proc 1998; 73:665–680.
33. **Jahnchen E, Meinertz T, Gilfrich HJ, Kersting F, Groth U.** Enhanced elimination of warfarin during treatment with cholestyramine. Br J Clin Pharmacol 1978; 5:437–440.
34. **Guthrie SK, Stoysich AM, Bader G, Hilleman DE.** Hypothesized interaction between valproic acid and warfarin [letter]. J Clin Psychopharmacol 1995; 15:138–139.
35. **Hylek EM, Heiman H, Skates SJ, et al.** Acetaminophen and other risk factors for excessive warfarin anticoagulation. JAMA 1998; 279:657–662.
36. **Bell WR.** Acetaminophen and warfarin: undesirable synergy. JAMA 1998; 279:702–703.
37. **Eliason BC, Larson W.** Acetaminophen and risk factors for excess anticoagulation with warfarin. JAMA 1998; 280:696–697.
38. **Cheung B, Lam FM, Kumana CR.** Insidiously evolving, occult drug interaction involving warfarin and amiodarone. Br Med J 1996; 312:107–108.
39. **Kerin NZ, Blevins RD, Goldman L, et al.** The incidence, magnitude, and time course of the amiodarone-warfarin interaction. Arch Intern Med 1988; 148:1779–1781.
40. **Sax MJ, Randolph WC, Peace KE, et al.** Effect of two cimetidine regimens on prothrombin time and warfarin pharmacokinetics during long-term warfarin therapy. Clin Pharm 1987; 6:492–495.
41. **Toon S, Hopkins KJ, Garstan FM, et al.** Comparative effects of ranitidine and cimetidine on the pharmacokinetics and pharmacodynamics of warfarin in man. Eur J Clin Pharmacol 1987; 32:165–172.
42. **Ellis RJ, Mayo MS, Bodensteiner DM.** Ciprofloxacin-warfarin coagulopathy: a case series. Am J Hematol 2000; 63:28–31.
43. **Recker MW, Kier KL.** Potential interaction between clarithromycin and warfarin. Ann Pharmacother 1997; 31:996–998.
44. **Oberg KC.** Delayed elevation of international normalized ratio with concurrent clarithromycin and warfarin therapy. Pharmacotherapy 1998; 18:386–391.
45. **Eastham RD.** Warfarin dosage influenced by clofibrate plus age. Lancet 1973; 1:1450.
46. **Bjornsson TD, Meffin PJ, Blaschke TF.** Interaction of clofibrate with warfarin. I. Effect of clofibrate on the disposition of the optical enantiomorphs of warfarin. J Pharmacokinet Biopharm 1977; 5:495–505.
47. **Hassell D, Utt JK.** Suspected interaction: warfarin and erythromycin. South Med J 1985; 78:1015–1016.
48. **Weibert RT, Lorentz SM, Townsend RJ, et al.** Effect of erythromycin in patients receiving long-term warfarin therapy. Clin Pharm 1989; 8:210–214.
49. **Black DJ, Kunze KL, Wienkers LC, et al.** Warfarin-fluconazole. II. A metabolically based drug interaction: in vivo studies. Drug Metab Dispos 1996; 24:422–428.
50. **Ellis KW, Smith EA, Baddour LM.** Immediate potentiation of the hypoprothrombinemic response of warfarin by fluconazole. Infect Dis

Downloaded from www.ccjm.org on April 25, 2024. For personal use only. All other uses require permission.

Clin Prac 1999; 8:351–354.
51. **Trilli LE, Kelley CL, Aspinall SL, et al.** Potential interaction between warfarin and fluvastatin. Ann Pharmacother 1996; 30:1399–1402.
52. **Kline SS, Harrell CC.** Potential warfarin-fluvastatin interaction [letter]. Ann Pharmacother 1997; 31:790.
53. **Benfield P, Ward A.** Fluvoxamine: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in depressive illness. Drugs 1986; 32:313–334.
54. **Rindone JP, Keng HC.** Gemfibrozil-warfarin drug interaction resulting in profound hypoprothrombinemia. Chest 1998; 114:641–642.
55. **Rosenthal AR, Self TH, Baker ED, Linden RA.** Interaction of isoniazid and warfarin. JAMA 1977; 238:2177.
56. **Yeh J, Soo SC, Summerton C, Richardson C.** Potentiation of action of warfarin by itraconazole [letter]. BMJ 1990; 301:669.
57. **Smith AG.** Potentiation of oral anticoagulants by ketoconazole. BMJ 1984; 288:188–189.
58. **Ahmad S.** Lovastatin: warfarin interaction. Arch Intern Med 1990; 150:2407.
59. **O'Reilly RA.** The stereoselective interaction of warfarin and metronidazole in man. N Engl J Med 1976; 295:354–357.
60. **Kates RE, Yee YG, Kirsten EB.** Interaction between warfarin and propafenone in healthy volunteer subjects. Clin Pharmacol Ther 1987; 42:305–311.
61. **Mogyorosi A, Bradley B, Showalter A, et al.** Rhabdomyolysis and acute renal failure due to combination therapy with simvastatin and warfarin. J Intern Med 1999; 246:599–602.
62. **Tenni P, Lalich DL, Byrne MJ.** Life threatening interaction between tamoxifen and warfarin. BMJ 1989; 298:93–94.
63. **Lodwick R, McConkey B, Brown AM.** Life threatening interaction between tamoxifen and warfarin. BMJ 1987; 295:1141.
64. **Sabbe JR, Sims PJ, Sims MH.** Tramadol-warfarin interaction. Pharmacotherapy 1998; 18:871–873.
65. **Scher ML, Huntington NH, Vitillo JA.** Potential interaction between tramadol and warfarin [letter]. Ann Pharmacother 1997; 31:646–647.
66. **O'Reilly RA.** Stereoselective interaction of trimethoprim-sulfamethoxazole with the separated enantiomorphs of racemic warfarin in man. N Engl J Med 1980; 302:33–35.
67. **Morkunas A, Graeme K.** Zafirlukast-warfarin drug interaction with gastrointestinal bleeding [abstract]. J Toxicol Clin Toxicol 1997; 35:501.
68. **Udall JA.** Clinical implications of warfarin interactions with five sedatives. Am J Cardiol 1975; 35:67–71.
69. **Orme M, Breckenridge A.** Enantiomers of warfarin and phenobarbital. N Engl J Med 1976; 295:1482–1483.
70. **Massey EW.** Effect of carbamazepine on Coumadin metabolism [letter]. Ann Neurol 1983; 13:691–692.
71. **Mailloux AT, Gidal BE, Sorkness CA.** Potential interaction between warfarin and dicloxacillin. Ann Pharmacother 1996; 30:1402–1407.
72. **Nappi JM.** Warfarin and phenytoin interaction [letter]. Ann Intern Med 1979; 90:852.
73. **Taylor JW, Alexander B, Lyon LW.** Oral anticoagulant-phenytoin interactions. Drug Intell Clin Pharm 1980; 14:669–673.
74. **Heimark LD.** The mechanism of the warfarin-rifampin drug interaction in humans. Clin Pharmacol Ther 1987; 42:388.
75. **Hansten PD.** Oral anticoagulants and drugs which alter thyroid function. Drug Intell Clin Pharm 1980; 14:331–334.
76. **Chan TYK.** Adverse interactions between warfarin and nonsteroidal antiinflammatory drugs: mechanisms, clinical significance, and avoidance. Ann Pharmacother 1995; 29:1274–1283.
77. **Frazee LA, Reed MD.** Warfarin and nonsteroidal antiinflammatory drugs: why not? [editorial]. Ann Pharmacother 1995; 29:1289–1291.
78. **Cropp JS, Bussey HI.** A review of enzyme induction of warfarin metabolism with recommendations for patient management. Pharmacotherapy 1997; 17:917–928.
79. **Heck AM, DeWitt BA, Lukes AL.** Potential interactions between alternative therapies and warfarin. Am J Health Syst Pharm 2000; 57:1221–1230.
80. **Demirkan K, Stephens MA, Newman KP, Self TH.** Response to warfarin and other oral anticoagulants: effects of disease states. South Med J 2000; 93:448–455.
81. **Booth SL, Centurelli MA.** Vitamin K: a practical guide to the dietary management of patients on warfarin. Nutrition Reviews 1999; 57:288–296.
82. **Levine MN, Raskob G, Landefeld S, Kearon C.** Hemorrhagic complications of anticoagulant treatment. Chest 1998; 114(suppl):511S–523S.
83. **Beyth RJ, Quinn LM, Landefeld CS.** Prospective evaluation of an index for predicting the risk of major bleeding in outpatients treated with warfarin. Am J Med 1998; 105:91–99.
84. **Hylek EM, Chang Y, Skates SJ, et al.** Prospective study of the outcomes of ambulatory patients with excessive warfarin anticoagulation. Arch Intern Med 2000; 160:1612–1617.
85. **Weibert RT, Le DT, Rayser SR, et al.** Correction of excessive anticoagulation with low-dose oral vitamin K. Ann Intern Med 1997; 125:959–962.
86. **Duong TM, Plowman BK, Morreale AP, et al.** Retrospective and prospective analyses of the treatment of over anticoagulated patients. Pharmacotherapy 1998; 18:1264–1270.
87. **Taylor CT, Chester EA, Byrd DC, et al.** Vitamin K to reverse excess anticoagulation: a review of the literature. Pharmacotherapy 1999; 19:1415–1425.
88. **Crowther MA, Julian J, McCarty D, et al.** Treatment of warfarin-associated coagulopathy with oral vitamin K: a randomized controlled trial. Lancet 2000; 356:1551–1553.
89. **Patel RJ, Witt DM, Saseen JJ, et al.** Randomized, placebo-controlled trial of oral phytonadione for excessive anticoagulation. Pharmacotherapy 2000; 20:1159–1166.

ADDRESS: *Amir Jaffer, MD, Department of General Internal Medicine, A72, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195; e-mail jaffera@ccf.org.*

Downloaded from www.ccjm.org on April 25, 2024. For personal use only. All other uses require permission.