Warfarin Therapy: Evolving Strategies in Anticoagulation

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Warfarin is the oral anticoagulant most frequently used to control and prevent thromboembolic disorders. Prescribing the dose that both avoids hemorrhagic complications and achieves sufficient suppression of thrombosis requires a thorough understanding of the drug's unique pharmacology. Warfarin has a complex dose-response relationship that makes safe and effective use a challenge. For most indications, the dose is adjusted to maintain the patient's International Normalized Ratio (INR) at 2 to 3. Because of the delay in factor II (prothrombin) suppression, heparin is administered concurrently for four to five days to prevent thrombus propagation. Loading doses of warfarin are not warranted and may result in bleeding complications. Interactions with other drugs must be considered, and therapy in elderly patients requires careful management. Current dosing recommendations are reviewed, and practical guidelines for the optimal use of warfarin are provided.

Warfarin (Coumadin) is the most frequently prescribed oral anticoagulant, the fourth most prescribed cardiovascular agent and the overall eleventh most prescribed drug in the United States, with annual sales of approximately $500 million. Nonetheless, in 1995 the Agency for Healthcare Policy and Research (AHCPR) reported that warfarin is greatly underutilized for stroke prevention. The AHCPR noted that physicians are reluctant to prescribe warfarin, in part because they are not familiar with techniques for administering the drug safely and fear that the drug will cause bleeding. Patients treated with warfarin do require close monitoring to avoid bleeding, but it has been shown that the drug prevents 20 strokes for every bleeding episode that it causes.

Even though four decades have passed since warfarin was first used to prevent thromboembolic disease, studies continue to discover and refine techniques that make therapy with this agent safer and more effective. Because warfarin has a complex dose-response relationship, family physicians need to understand the drug's pharmacology. This article presents the rationale for published dosing recommendations and suggests practical guidelines for the use of warfarin therapy.
Goals of Anticoagulation

The goal of anticoagulant therapy is to administer the lowest possible dose of anticoagulant to prevent clot formation or expansion. The required degree of anticoagulation continues to evolve as studies provide more information about the efficacy and safety of lower doses. Current therapeutic goals for various disease states are summarized in Table 1.

By using the lowest possible required dose of warfarin, the physician can minimize the risk of bleeding while providing the benefits of anticoagulation. To achieve this goal, the physician must have a working knowledge of the pharmacologic, pharmacokinetic and pharmacodynamic properties of warfarin.

**TABLE 1**

Recommended Therapeutic Goals for Oral Anticoagulation

<table>
<thead>
<tr>
<th>Indication</th>
<th>INR</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prophylaxis of venous thrombosis for high-risk surgery</td>
<td>2 to 3</td>
<td>Clinical judgment</td>
</tr>
<tr>
<td>Treatment of venous thrombosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First episode</td>
<td>2 to 3</td>
<td>3 to 6 months*</td>
</tr>
<tr>
<td>High risk of recurrent thrombosis</td>
<td>2 to 3</td>
<td>Lifelong</td>
</tr>
<tr>
<td>Thrombosis associated with antiphospholipid antibody</td>
<td>3 to 4</td>
<td>Lifelong</td>
</tr>
<tr>
<td>Treatment of pulmonary embolism</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First episode</td>
<td>2 to 3</td>
<td>3 to 6 months</td>
</tr>
<tr>
<td>High risk of recurrent embolism</td>
<td>2 to 3</td>
<td>Lifelong</td>
</tr>
<tr>
<td>Prevention of systemic embolism</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tissue heart valves</td>
<td>2 to 3</td>
<td>3 months</td>
</tr>
<tr>
<td>Acute myocardial infarction (to prevent systemic embolism)†</td>
<td>2 to 3</td>
<td>Clinical judgment</td>
</tr>
<tr>
<td>Valvular heart disease (after thrombotic event or if the left atrium is greater than 5.5 cm)</td>
<td>2 to 3</td>
<td>Lifelong</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic or intermittent</td>
<td>2 to 3</td>
<td>Lifelong</td>
</tr>
<tr>
<td>Cardioversion</td>
<td>2 to 3</td>
<td>3 weeks before and 4 weeks after atrial fibrillation if normal sinus rhythm is maintained</td>
</tr>
<tr>
<td>Prosthetic heart valves</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aortic position</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mechanical</td>
<td>2.5 to 3.5‡</td>
<td>Lifelong</td>
</tr>
<tr>
<td>Bioprosthetic</td>
<td>2 to 3</td>
<td>Clinical judgment (3 months optional)</td>
</tr>
<tr>
<td>Mitral position</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mechanical</td>
<td>2.5 to 3.5‡</td>
<td>Lifelong</td>
</tr>
<tr>
<td>Bioprosthetic</td>
<td>2 to 3</td>
<td>3 months</td>
</tr>
</tbody>
</table>

INR=International Normalized Ratio.

*--One study suggested that 4 weeks may be an adequate duration of oral anticoagulant therapy in patients without continuing risk factors.

†--If oral anticoagulant therapy is elected to prevent recurrent myocardial infarction, an INR of 2.5 to 3.5 is recommended.

‡--Depending on the type of mechanical valve (i.e., caged ball or caged disk) and the valve position (mitral), some patients may benefit from INRs in the upper end of the range.

Information derived from references 4 through 9.

Pharmacology

Warfarin is an antagonist of vitamin K, a necessary element in the synthesis of clotting factors II, VII, IX and X, as well as the naturally occurring endogenous anticoagulant proteins C and S. These factors and proteins are biologically inactive without the carboxylation of certain glutamic acid residues. This carboxylation process requires a reduced vitamin K as a cofactor. Antagonism of vitamin K or a deficiency of this
vitamin reduces the rate at which these factors and proteins are produced, thereby creating a state of anticoagulation.

Therapeutic doses of warfarin reduce the production of functional vitamin K-dependent clotting factors by approximately 30 to 50 percent. A concomitant reduction in the carboxylation of secreted clotting factors yields a 10 to 40 percent decrease in the biologic activity of the clotting factors. As a result, the coagulation system becomes functionally deficient.10

**Pharmacokinetics**

A knowledge of the pharmacokinetics of warfarin is helpful in understanding the initial response to therapy. Warfarin can be detected in the plasma one hour after oral administration, and peak concentrations occur in two to eight hours.10

Warfarin is a racemic mixture of stereo isomers, which are 99 percent bound to albumin.11 The drug is metabolized in the liver and kidneys, with the subsequent production of inactive metabolites that are excreted in the urine and stool.10

The half-life of racemic warfarin ranges from 20 to 60 hours. The mean plasma half-life is approximately 40 hours, and the duration of effect is two to five days.10 Thus, the maximum effect of a dose occurs up to 48 hours after administration, and the effect lingers for the next five days.

**Pharmacodynamics and Dosing Considerations**

*Anticoagulant Activity.* The anticoagulant activity of warfarin depends on the clearance of functional clotting factors from the systemic circulation after administration of the dose. The clearance of these clotting factors is determined by their half-lives. The earliest changes in the International Normalized Ratio (INR) are typically noted 24 to 36 hours after a dose of warfarin is administered. These changes are due to the clearance of functional factor VII, which is the vitamin K-dependent clotting factor with the shortest half-life (six hours). However, the early changes in the INR are deceptive because they do not actually affect the body’s physiologic ability to halt clot expansion or form new thromboses.4

*Antithrombotic Effect.* The antithrombotic effect of warfarin, or the inability to expand or form clots, is not present until approximately the fifth day of therapy. This effect depends on the clearance of functional factor II (prothrombin), which has a half-life of approximately 50 hours in patients with normal hepatic function.

The difference between the antithrombotic and anticoagulant effects of warfarin need to be understood and applied in clinical practice. Because antithrombotic effect depends on the clearance of prothrombin (which may take up to five days), loading doses of warfarin are of limited value.4,12 Because warfarin has a long half-life, increases in the INR may not be noted for 24 to 36 hours after administration of the first dose, and maximum anticoagulant effect may not be achieved for 72 to 96 hours.4

Loading doses of warfarin (i.e., 10 mg or more per day) may increase the patient’s risk of bleeding episodes early in therapy by eliminating or severely reducing the production of functional factor VII. The administration of loading doses is a possible source of prolonged hospitalization secondary to dramatic rises in INR that necessitate increased monitoring. Administration of loading doses has also been hypothesized to potentiate a hypercoagulable state because of severe depletion of protein C. The practice of using loading doses should be abandoned because it has no effect on the inhibition of thrombosis.4[corrected]

A potential paradoxic consequence of loading doses is the development of a hypercoagulable state because of a precipitous reduction in the concentration of protein C (approximate half-life of eight hours) during the first 36 hours of warfarin therapy.13 Thus, loading doses theoretically may cause clot formation and/or expansion by limiting the production of proteins C and S, which have shorter half-lives than prothrombin. Consequently, the concurrent use of heparin is extremely important.

The initial dose of warfarin should approximate the chronic maintenance dose that is anticipated. In most patients, the average maintenance dose is 4 to 6 mg per day. Dose
When initiating warfarin therapy, the physician should select a dose that represents the maintenance dose the patient is most likely to require.

Drug interactions (discussed in detail in another section) need to be considered when warfarin therapy is initiated. Other factors include the patient's nutritional status and gender. Patients who are malnourished should receive lower doses of warfarin because they probably have low vitamin K intake and decreased serum albumin concentrations. Women generally require lower doses than men.

Patients at highest risk for complications should probably be given a smaller initial dose (2 to 4 mg per day). This dose is then titrated to the lower end of a given therapeutic range, depending on the indication. For example, the goal may be an INR of 2 to 2.5 in a patient with a history of bleeding, chronic atrial fibrillation and no additional risk factors for thrombosis.

Current recommendations for the initiation of warfarin therapy differ based on the urgency for achieving an anticoagulant effect. While warfarin is being initiated, patients who require rapid anticoagulation should also be given unfractionated heparin or low-molecular-weight heparin intravenously or subcutaneously in doses appropriate for the given indication.

Heparin and warfarin therapies should overlap for approximately four to five days. The presence of a therapeutic INR does not confer protection from clot formation and expansion during the first few days of warfarin therapy because of the delay in the therapeutic inhibition of prothrombin.

Patients who rapidly achieve a therapeutic INR may metabolize warfarin slowly and thus may require lower maintenance doses. The opposite holds for patients who tend to respond slowly to warfarin.

A small decrease in the INR is expected to occur with the discontinuation of unfractionated heparin therapy. (A drop of 0.3 to 0.8 in the INR has been noted by the authors of this article.)

Patients who require nonurgent anticoagulation, such as those with stable chronic atrial fibrillation, can be started on warfarin as outpatients, without the concomitant administration of heparin.

### Warfarin Dosing Adjustment Using One Tablet Strength (5 mg)

<table>
<thead>
<tr>
<th>Sunday</th>
<th>Monday</th>
<th>Tuesday</th>
<th>Wednesday</th>
<th>Thursday</th>
<th>Friday</th>
<th>Saturday</th>
<th>Total weekly dosage (mg)</th>
<th>Approximate adjustment (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 tablet</td>
<td>0.5 tablet</td>
<td>1 tablet</td>
<td>0.5 tablet</td>
<td>1 tablet</td>
<td>0.5 tablet</td>
<td>1 tablet</td>
<td>27.5 mg</td>
<td>20</td>
</tr>
<tr>
<td>1 tablet</td>
<td>0.5 tablet</td>
<td>1 tablet</td>
<td>1 tablet</td>
<td>1 tablet</td>
<td>0.5 tablet</td>
<td>1 tablet</td>
<td>30 mg</td>
<td>15</td>
</tr>
<tr>
<td>1 tablet</td>
<td>0.5 mg</td>
<td>1 tablet</td>
<td>1 tablet</td>
<td>1 tablet</td>
<td>1 tablet</td>
<td>32.5 mg</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>1 tablet</td>
<td>1 tablet</td>
<td>1 tablet</td>
<td>1 tablet</td>
<td>1 tablet</td>
<td>1 tablet</td>
<td>35 mg</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>1 tablet</td>
<td>1.5 tablets</td>
<td>1 tablet</td>
<td>1 tablet</td>
<td>1 tablet</td>
<td>1 tablet</td>
<td>37.5 mg</td>
<td>+5</td>
<td></td>
</tr>
<tr>
<td>1 tablet</td>
<td>1.5 tablets</td>
<td>1 tablet</td>
<td>1 tablet</td>
<td>1 tablet</td>
<td>1.5 tablets</td>
<td>1 tablet</td>
<td>40 mg</td>
<td>+15</td>
</tr>
<tr>
<td>1 tablet</td>
<td>1.5 tablets</td>
<td>1 tablet</td>
<td>1.5 tablets</td>
<td>1 tablet</td>
<td>1.5 tablets</td>
<td>1 tablet</td>
<td>42.5 mg</td>
<td>+20</td>
</tr>
</tbody>
</table>

FIGURE 1. Warfarin dosing adjustments based on the algorithms presented in Figures 2 and 3. Only one tablet strength (5 mg) is used. Fractions or multiples of the tablet can be used for different doses, or alternative doses can be given based on the day of the week. Dose adjustments should be made based on the total weekly dosage, with increases or decreases of 10 to 20 percent spread out over the week.

The goal of maintenance therapy is to achieve a regimen that is simple yet provides therapeutic anticoagulation. Currently, many physicians use drug regimens that appear simple but require differing tablet strengths. These regimens can be confusing to elderly patients who are taking several other medications concurrently and who may confuse...
Effective anticoagulation can be achieved using a single tablet strength and alternating fractions or multiples of that tablet on given days of the week rather than on odd or even days. As needed, doses can be easily changed by looking at the cumulative weekly dosage and adding or subtracting 10 to 20 percent evenly over the week (Figure 1). This approach is possible because of warfarin's long half-life. It is a safe and effective way to provide sufficient anticoagulation. Algorithms for establishing a percentage change in the weekly dosage to achieve an INR of 2 to 3 or 2.5 to 3.5 are presented in Figures 2 and 3, respectively.

Questions have recently been raised about the use of generic warfarin products. The cost savings of changing to generic products was investigated at Boston City Hospital during the late 1980s. The study found that patients who used Coumadin exclusively remained within the goal INR 68 percent of the time, whereas patients who used generic warfarin maintained goal INR only 39 percent of the time. Compared with the brand drug treated patients, the 15 patients who switched products had more dosage adjustments, one hospitalization for excessive anticoagulation and one emergency department visit for epistaxis. None of the patients maintained on the brand drug required hospitalization or emergency medical care.

Generic warfarin products and Coumadin have small pharmacokinetic differences in time to peak concentration, area under the curve, absorption rate constants, half-absorption time and tablet content uniformity. Therefore, increased monitoring may be prudent when a patient is switched from the brand drug to generic warfarin.

As noted in the Boston City Hospital study, the slight cost advantage of the generic product may be outweighed by increased monitoring costs, increased physician time and a possibly greater incidence of adverse events. If a generic warfarin product is started and then used exclusively in a patient, it is likely to be as safe as the brand drug.

### Altering Warfarin Dosage to Achieve INR of 2 to 3

<table>
<thead>
<tr>
<th>INR less than 2</th>
<th>INR of 3 to 3.5</th>
<th>INR of 3.5 to 4</th>
<th>INR greater than 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase weekly dose by 5 to 20 percent</td>
<td>Decrease weekly dose by 5 to 15 percent</td>
<td>Withheld no dose to one dose</td>
<td>Withheld no dose or one dose</td>
</tr>
<tr>
<td>Decrease weekly dose by 10 to 15 percent</td>
<td>Increase weekly dose by 10 to 20 percent</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**FIGURE 2.** Algorithm for establishing a percentage change in the weekly warfarin dosage to achieve an INR of 2 to 3. (INR=International Normalized Ratio)

### Monitoring

The prothrombin time (PT) is the primary assay used in monitoring warfarin therapy. The prolongation of PT depends on reductions in three of the vitamin K-dependent clotting factors (II, VII and IX). Changes in the PT noted in the first few days of warfarin therapy are primarily due to reductions in factors VII and IX, which have the shortest half-lives (six and 24 hours, respectively).

The early changes in PT vary based on the responsiveness of the particular thromboplastin that a laboratory uses to perform the PT test. The International Sensitivity Index is used to measure and compare the variability in thromboplastin responsiveness. Because of the variations in thromboplastin sensitivity and the different ways of reporting PT, information about patients treated with oral anticoagulants was not interchangeable among laboratories until 1982, when the World Health Organization Expert Committee on Biologic Standardization developed the INR.
TABLE 2
Risk Factors for Hemorrhagic Complications of Anticoagulation Therapy

- Age greater than 65 years
- Age greater than 75 years with concomitant atrial fibrillation (intracranial hemorrhage)
- History of gastrointestinal bleeding
- Comorbid disease states
  --Hypertension
  --Cerebrovascular disease
  --Serious heart disease
  --Renal insufficiency

Information from references 4, 20, and 23 through 27.

Hemorrhagic Complications

The most common complication of warfarin therapy is bleeding, which occurs in 6 to 39 percent of recipients annually. The incidence of bleeding is directly related to the intensity of anticoagulation. With the reductions in anticoagulation intensity that have evolved over the past 20 years, the incidence of hemorrhagic complications has decreased dramatically.

In patients receiving warfarin therapy, the median annual rate of major bleeding ranges from 0.9 to 2.7 percent, and the median annual rate of fatal bleeding ranges from 0.07 to 0.7 percent. The incidence of complications varies within the ranges, depending on the clinical indication and the intensity of anticoagulation. Intracranial hemorrhage accounts for approximately 2 percent of the reported hemorrhagic complications of warfarin therapy and is associated with a mortality rate of 10 to 68 percent.

Patient characteristics associated with a major risk of hemorrhage have been identified in a number of randomized studies (Table 2). Bleeding that occurs with an INR of less than 3 is often associated with an underlying occult gastrointestinal or renal lesion.

If bleeding occurs during warfarin therapy, the physician should immediately consider the severity of bleeding, the intensity of anticoagulation at the time of the bleeding episode and whether the patient has completed most of the prescribed course of therapy. Recommendations for the reversal of high INR values in patients with or without bleeding are summarized in Figure 4.

Warfarin resistance is common after the administration of large doses of vitamin K. If anticoagulation therapy must be continued, heparin therapy should be initiated until the effects of vitamin K have been reversed and the patient is again responsive to warfarin.
Anticoagulation Therapy in the Elderly

One of the physician's most difficult tasks is to decide whether the risk of anticoagulation outweighs the potential benefit of warfarin therapy in an elderly patient. One study found that the risk of intracranial hemorrhage among the elderly is highest in patients with poor control (large variations in INR), patients receiving high-intensity therapy (INR greater than 4) and patients older than 80 years. Data from the Stroke Prevention in Atrial Fibrillation (SPAF II) trial suggest that the safety of anticoagulation in the elderly can be maximized through careful monitoring and maintenance of an INR between 2 and 3.

Another recent study investigated the incidence of ischemic stroke in elderly patients with atrial fibrillation who were receiving anticoagulant therapy. This study found that subtherapeutic INRs (i.e., those below 2) have associated risks of thrombotic events. For example, the relative risk of ischemic stroke is 3.3 times higher (95 percent confidence interval 2.4 to 4.6) in a patient with an INR of 1.5 than in a patient with an INR of 2. The study findings suggest that tighter control of therapy at an INR range of 2 to 3 is superior to the use of lower levels of anticoagulation.

<table>
<thead>
<tr>
<th>Warfarin-Treated Patient with Elevated INR</th>
</tr>
</thead>
</table>

### Bleeding?

<table>
<thead>
<tr>
<th>INR less than 10</th>
<th>INR greater than 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>Rapid reversal required?</td>
</tr>
</tbody>
</table>

#### Rapid reversal required?

<table>
<thead>
<tr>
<th>No</th>
<th>Yes</th>
</tr>
</thead>
</table>

**No**

- Withhold doses and resume when INR is within therapeutic range.
- Check INR at 6 hours.
- Repeat vitamin K if INR is not reduced at 6 hours.
- If INR is not reduced at 6 hours and INR is less than 2, give vitamin K 0.5 mg SC or IV.

**Yes**

- Give vitamin K 3 mg SC or IV infusion.
- Check INR at 6 hours.
- Vitamin K may be repeated if INR is not reduced at 6 hours or is not 2 to 3 at 24 hours.

1. Identify cause of bleeding (e.g., elevated INR).
2. Attempt to stop and treat the cause of bleeding.
3. Use clinical judgment in reversing elevated INR (e.g., withholding vitamin K).
4. Examine possibility of lower intensity INR goal if bleeding occurred at INR within goal range.

#### Not life-threatening bleeding or warfarin overdose

1. Give vitamin K 10 mg; if situation is urgent, supplement: give FFP, 15 mL per kg; PCC, 50 U per kg, may also be given depending on urgency.
2. Check INR at 6 hours.
3. If INR at 6 hours is not reduced from baseline, consider giving vitamin K.

#### Life-threatening bleeding or warfarin overdose

1. Give PCC, 50 U per kg.
2. If PCC does not contain factor VII, give vitamin K, 10 mg, by slow IV infusion.
3. Vitamin K may be repeated as necessary but may not be needed if PCC with factor VII is used for reversal.

### NOTE: Clinical judgment should be used when assessing the severity of bleeding. In addition, patients who are given doses of vitamin K that leave them refractory to warfarin should receive heparin until warfarin therapy is again therapeutic.

*--Rapid reversal of major warfarin overdose should be treated by following the steps for managing serious bleeding.
†--In patients with life-threatening bleeding or serious warfarin overdose, PCC should be given with IV vitamin K, 10 mg; if PCC contains factor VII, vitamin K administration is not usually necessary.
‡--Patients with an INR of less than 6 may not require vitamin K administration for reversal; if vitamin K is administered, a dose of 0.5 to 1 mg is sufficient.

**FIGURE 4.** Algorithm for the management of an elevated INR in adult patients with or without bleeding. (INR=International Normalized Ratio; SC=subcutaneous; IV=intravenous; FFP=fresh frozen plasma; PCC=prothrombin complex concentrate)
The SPAF III study compared the effects of combined fixed-dose warfarin and aspirin (goal INR of 1.2 to 1.5) with the effects of warfarin titrated to an INR of 2 to 3. The study was discontinued after a mean follow-up period of 1.1 years because of the occurrence of significantly fewer events in the adjusted-dose warfarin group (7.9 percent per year) compared with the warfarin and aspirin group (1.9 percent per year). This reduction in events was associated with similar major bleeding rates (2.1 percent for adjusted-dose warfarin and 2.4 percent for combination therapy). Interestingly, in the adjusted-dose group, the INR was greater than 3 in seven of the 12 major bleeding events.

Drug Interactions

In determining whether to treat a patient with warfarin, one of the major concerns is the risk of potential drug interactions. Drug interactions of varying severity have been identified with warfarin therapy. In most instances, the interacting drugs either inhibit or induce warfarin metabolism. These types of interactions are easily managed when the medications are for the treatment of chronic diseases. In such circumstances, close INR monitoring is required during the initiation or discontinuation of the medications.

Often, the interacting drugs that pose the greatest problem are those used for short-term indications. Antibiotics are a common example. When interactions occur, close monitoring or the use of alternative antimicrobial agents is appropriate.

Patient Education

Warfarin is more likely to be used safely by a patient who is aware of the potential for drug interactions, understands the rationale for monitoring and can identify the symptoms of warfarin toxicity early. Patient instruction booklets in English and other languages are available from several sources. Du Pont Pharma (1-800-COUMADIN) provides literature for patients, and Barr Laboratories, Inc. (1-888-WARFARIN) has prepared information booklets for both patients and physicians. Most local pharmacies supply similar information to patients.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Severity</th>
<th>Onset</th>
<th>Evidence</th>
<th>Mechanism</th>
<th>Management of interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen (Tylenol)</td>
<td>Minor</td>
<td>Delayed</td>
<td>Poor</td>
<td>• Inhibits warfarin metabolism</td>
<td>• Advise patient to limit total acetaminophen dosage to less than 2 g per day; if higher dosages are used, increased monitoring may be necessary.</td>
</tr>
<tr>
<td>Allopurinol (Zyloprim)</td>
<td>Moderate</td>
<td>Delayed</td>
<td>Poor</td>
<td>• Unknown</td>
<td>• Monitor INR when allopurinol is added or withdrawn.</td>
</tr>
<tr>
<td>Amiodarone (Cordarone)</td>
<td>Moderate</td>
<td>Delayed</td>
<td>Excellent</td>
<td>• Decreases warfarin metabolism within a week of coadministration; effect may persist for 1 to 3 months after discontinuation of amiodarone</td>
<td>• A 25 percent reduction in the warfarin dosage is recommended when amiodarone is initiated.</td>
</tr>
<tr>
<td>Antifungal agents</td>
<td>Major</td>
<td>Delayed</td>
<td>Good</td>
<td>• Fluconazole (Diflucan), ketoconazole (Nizoral) and miconazole (Monistat) decrease warfarin metabolism</td>
<td>• Monitor INR when azole antifungals are added or withdrawn.</td>
</tr>
<tr>
<td>Antithyroid drugs</td>
<td>Moderate</td>
<td>Delayed</td>
<td>Fair</td>
<td>• Hyperthyroidism results in metabolism of vitamin K clotting factors and</td>
<td>• Monitor INR when antithyroid medications are added or withdrawn.</td>
</tr>
<tr>
<td>Drug</td>
<td>Type</td>
<td>Interaction</td>
<td>Metabolism Effect</td>
<td>Monitoring</td>
<td></td>
</tr>
<tr>
<td>-------------------------------</td>
<td>--------</td>
<td>-------------</td>
<td>-------------------</td>
<td>------------</td>
<td></td>
</tr>
<tr>
<td>Barbiturates</td>
<td>Major</td>
<td>Delayed</td>
<td>Excellent</td>
<td>Monitor INR when barbiturates are added or withdrawn; the addition of warfarin in patients stabilized on a chronic barbiturate regimen is of less significance.</td>
<td></td>
</tr>
<tr>
<td>Binding resins</td>
<td>Moderate</td>
<td>Delayed</td>
<td>Good</td>
<td>Use colestipol (Colestid), which has a lower potential for interaction, instead of cholestyramine (Questran) in patients who need a bile sequestrant.</td>
<td></td>
</tr>
<tr>
<td>Carbamazepine (Tegretol)</td>
<td>Moderate</td>
<td>Delayed</td>
<td>Fair</td>
<td>Increase warfarin doses when carbamazepine is added, and reduce doses when carbamazepine is discontinued (stabilization occurs after 4 to 6 weeks).</td>
<td></td>
</tr>
<tr>
<td>Cephalosporins</td>
<td>Moderate</td>
<td>Delayed</td>
<td>Poor</td>
<td>Avoid concomitant use of warfarin and cefoperazone, cefamandole, cefotetan or cefmetazole.</td>
<td></td>
</tr>
<tr>
<td>Cimetidine (Tagamet)</td>
<td>Moderate</td>
<td>Delayed</td>
<td>Excellent</td>
<td>Use alternative agents in patients receiving warfarin. Monitor INR when concomitant use of warfarin and cimetidine is necessary.</td>
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</tr>
<tr>
<td>Contraceptives, oral</td>
<td>Minor</td>
<td>Delayed</td>
<td>Poor</td>
<td>If possible, avoid oral contraceptives because of increased risk of thromboembolism. Monitor INR frequently when oral contraceptives are used concurrently with warfarin.</td>
<td></td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Moderate</td>
<td>Delayed</td>
<td>Poor</td>
<td>Monitor for gastric toxicity.</td>
<td></td>
</tr>
<tr>
<td>Danazol (Danocrine)</td>
<td>Major</td>
<td>Delayed</td>
<td>Good</td>
<td>Monitor prothrombin time and INR for 2 days to 3 weeks after danazol is added.</td>
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<tr>
<td>Diflunisal (Dolobid)</td>
<td>Moderate</td>
<td>Delayed</td>
<td>Fair</td>
<td>If possible, avoid concomitant use of warfarin and diflunisal. Monitor INR if concomitant use is necessary.</td>
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<tr>
<td>Disulfiram (Antabuse)</td>
<td>Moderate</td>
<td>Delayed</td>
<td>Fair</td>
<td>If possible, avoid concomitant use of warfarin and disulfiram. Monitor INR if</td>
<td></td>
</tr>
<tr>
<td>Drug</td>
<td>Interaction Type</td>
<td>Metabolism Effect</td>
<td>Notes</td>
<td></td>
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</table>
| Ethanol                       | Moderate Delayed Excellent | • Acute ethanol use may inhibit anticoagulant metabolism.  
• Chronic ethanol use induces liver enzymes.  
• Cirrhosis is associated with reduced warfarin metabolism.  
• Caution patients to drink in moderation and to avoid binge drinking.  
• Because liver damage results in greater sensitivity to warfarin, use lower starting doses. |
| Fluvoxamine (Luvox)           | Moderate Delayed Fair | • Probably inhibits warfarin metabolism  
• Monitor INR more closely for 1 to 2 weeks after fluvoxamine is started. |
| Heparin                       | Moderate Rapid   Good | • Has additive anticoagulant effects  
• Heparin may prolong INR, and warfarin may prolong partial thrombin time.  
• Be aware of small risk of bleeding events. |
| HMG CoA reductase inhibitors  | Moderate Delayed Poor | • May inhibit warfarin metabolism  
• Note that lovastatin (Mevacor) is more commonly associated with hypoproteinemina. |
| Isoniazid (Laniazid)          | Moderate Delayed Poor | • May inhibit warfarin metabolism  
• Monitor INR when isoniazid is added or withdrawn. |
| Metronidazole (Flagyl)        | Moderate Delayed Fair | • Inhibits metabolism of S enantiomer of warfarin  
• Avoid concomitant use of warfarin and metronidazole.  
• Monitor INR if concomitant use is necessary. |
| Nalidixic acid (NegGram)      | Moderate Delayed Poor | • Displaces warfarin from protein-binding sites  
• Inhibits warfarin metabolism  
• Avoid concomitant administration of warfarin and nalidixic acid.  
• Monitor INR if concomitant use is necessary.  
• Advise patients to avoid NSAIDs or to use them only intermittently.  
• Instruct patients to take NSAIDs with food or antacids.  
• Consider having patients take misoprostol (Cytotec) to reduce risk of gastric erosions. |
| NSAIDs                        | Moderate Delayed Fair | • Inhibit platelet aggregation  
• Cause gastric erosions  
• Monitor INR frequently when paroxetine is added. |
| Paroxetine (Paxil)            | Moderate Delayed Poor | • Probably inhibits warfarin metabolism  
• Monitor INR frequently when paroxetine is added.  
• Monitor INR: dicloxacillin and nafcillin decrease INR, and penicillin increases INR. |
| Penicillins                   | Moderate Delayed Fair | • Dicloxacillin (Pathocil) and nafcillin (Unipen) may enhance warfarin metabolism.  
• Penicillin may reduce gastrointestinal flora synthesis of vitamin K.  
• Monitor INR: dicloxacillin and nafcillin decrease INR, and penicillin increases INR. |
| Phenytoin (Dilantin)          | Major Delayed Fair | • Induces warfarin metabolism  
• Displaces warfarin from protein-binding sites  
• Enhances metabolism of clotting factors  
• Monitor INR frequently for 1 month or more after phenytoin is added. |
| Propafenone (Rythmol)         | Moderate Delayed Fair | • Probably inhibits warfarin metabolism  
• Monitor INR frequently when propafenone is added. |
<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Interaction</th>
<th>Anticoagulant Impact</th>
<th>Monitor INR</th>
<th>Additional Instructions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quinolones</td>
<td>Moderate</td>
<td>Delayed Poor</td>
<td>Monitor INR</td>
<td>Possibly inhibit warfarin metabolism</td>
</tr>
<tr>
<td>Rifampin (Rifadin) and rifabutin (Mycobutin)</td>
<td>Moderate</td>
<td>Delayed Poor</td>
<td>Monitor INR closely for 1 to 2 weeks after rifampin or rifabutin is added. If possible, avoid concurrent use of warfarin and salicylates. If aspirin is needed, advise patients to use a small dosage (325 mg or less per day). Consider having patients take misoprostol to reduce the risk of NSAID-induced ulceration.</td>
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<tr>
<td>Salicylates</td>
<td>Major</td>
<td>Delayed Excellent</td>
<td>Monitor INR closely for 1 to 2 weeks after rifampin or rifabutin is added. If possible, avoid concurrent use of warfarin and salicylates. If aspirin is needed, advise patients to use a small dosage (325 mg or less per day). Consider having patients take misoprostol to reduce the risk of NSAID-induced ulceration.</td>
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<tr>
<td>Sulfapyrazone (Anturane)</td>
<td>Moderate</td>
<td>Delayed Poor</td>
<td>Monitor INR closely for 1 to 2 weeks after rifampin or rifabutin is added. If possible, avoid concurrent use of warfarin and salicylates. If aspirin is needed, advise patients to use a small dosage (325 mg or less per day). Consider having patients take misoprostol to reduce the risk of NSAID-induced ulceration.</td>
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<tr>
<td>Thyroid hormones</td>
<td>Moderate</td>
<td>Delayed Poor</td>
<td>Monitor INR closely for 1 to 2 weeks after rifampin or rifabutin is added. If possible, avoid concurrent use of warfarin and salicylates. If aspirin is needed, advise patients to use a small dosage (325 mg or less per day). Consider having patients take misoprostol to reduce the risk of NSAID-induced ulceration.</td>
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<tr>
<td>Ticlopidine (Ticlid)</td>
<td>Moderate</td>
<td>Delayed Poor</td>
<td>Monitor INR closely for 1 to 2 weeks after rifampin or rifabutin is added. If possible, avoid concurrent use of warfarin and salicylates. If aspirin is needed, advise patients to use a small dosage (325 mg or less per day). Consider having patients take misoprostol to reduce the risk of NSAID-induced ulceration.</td>
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</tr>
<tr>
<td>Trimethoprim-sulfamethoxazole (Bactrim)</td>
<td>Major</td>
<td>Delayed Excellent</td>
<td>Monitor INR closely for 1 to 2 weeks after rifampin or rifabutin is added. If possible, avoid concurrent use of warfarin and salicylates. If aspirin is needed, advise patients to use a small dosage (325 mg or less per day). Consider having patients take misoprostol to reduce the risk of NSAID-induced ulceration.</td>
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<tr>
<td>Vitamin E</td>
<td>Moderate</td>
<td>Delayed Poor</td>
<td>Monitor INR closely for 1 to 2 weeks after rifampin or rifabutin is added. If possible, avoid concurrent use of warfarin and salicylates. If aspirin is needed, advise patients to use a small dosage (325 mg or less per day). Consider having patients take misoprostol to reduce the risk of NSAID-induced ulceration.</td>
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</tr>
<tr>
<td>Vitamin K</td>
<td>Moderate</td>
<td>Delayed Excellent</td>
<td>Monitor INR closely for 1 to 2 weeks after rifampin or rifabutin is added. If possible, avoid concurrent use of warfarin and salicylates. If aspirin is needed, advise patients to use a small dosage (325 mg or less per day). Consider having patients take misoprostol to reduce the risk of NSAID-induced ulceration.</td>
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INR=International normalized ratio; HMG-CoA=3-hydroxy-3-methylglutaryl coenzyme A; NSAIDs=nonsteroidal anti-inflammatory drugs.


Final Comment

When used appropriately, warfarin is a highly effective and safe medication. To maximize the safety of warfarin therapy, the physician should do the following:

1. Identify the therapeutic goal.
2. Estimate the chronic maintenance dosage based on the presence of factors associated with hyperresponsiveness or hyporesponsiveness, such as concomitant drug use, liver disease and poor nutrition.
3. Initiate therapy at the patient's anticipated maintenance dosage. Loading doses are not necessary.
4. Make any necessary adjustments by looking at the cumulative weekly dosage and adding or subtracting 10 to 20 percent evenly over the week.

5. Remain alert to potential warfarin-drug interactions.


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Correction 2006

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REFERENCES


