Oral Anticoagulation: Improving the Risk-Benefit Ratio

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For four decades, warfarin has been used extensively to treat thromboembolic disorders. Major advances in monitoring have been achieved through recognition of thromboplastin variability and implementation of the international normalized ratio (INR). Recommended INR ranges have shifted to lower intensity, and new clinical information has led to the potential for increased use of warfarin to prevent venous thromboembolism, to treat patients with prosthetic heart valves, to prevent stroke in patients with atrial fibrillation, and to prevent death and recurrent events after myocardial infarction.

Optimal management of the patient who requires a drug that has a narrow therapeutic index, such as warfarin, remains challenging. Strategies to enhance patient outcomes with these drugs attempt to improve the risk-benefit ratio of such therapies, which requires optimizing the agent's effectiveness, improving its safety profile, or both.

Key words. Warfarin; anticoagulants; drug therapy; oral administration; narrow therapeutic index; risk-benefit ratio; risk assessment. (*J Fam Pract 1995; 41:261-269*)

Optimal management of the patient requiring a drug that has a narrow therapeutic index remains a challenge. A precise amount of drug, tailored to the individual patient's needs, is required to produce the desired pharmacological effect with minimal toxicity. A few examples of traditional drugs that have narrow therapeutic indices include aminoglycosides, digoxin, lithium, phenytoin, theophylline, and warfarin. These agents require careful monitoring and dosing for optimal management. If used properly, they can offer the patient a real clinical value. Strategies to enhance patient outcomes with such drugs attempt to improve the risk-benefit ratio, which requires optimizing the effectiveness of the agent or improving its safety profile, or both.

Since its introduction 40 years ago, warfarin, a racemic mixture of two stereoisomers, has been used extensively to treat thromboembolic disorders. The goal of warfarin therapy is to limit thrombus extension and prevent thromboemboli while minimizing bleeding complications. Warfarin possesses an indirect mechanism of action, results in a highly individualized patient response, can be the object of many drug interactions, and, like other preventive agents, may result in compliance problems because it does not make the patient subjectively "feel" better. Despite warfarin's inherent limitations, more than two million people in the United States require treatment with oral anticoagulants, as estimated by the National Center for Health Statistics.[1] Although no new agents have replaced warfarin as the standard oral anticoagulant, this article presents the significant evidence to support that its narrow therapeutic index is shifting as a result of less intense therapeutic ranges. Over the past 40 years, we have developed a better understanding of the agent and its actions, and we now use improved monitoring techniques and recommend less intense dosing regimens. These changes in warfarin-dosing regimens have led to reduced risks with its use, which, in turn, has led to its usefulness in a broader range of clinical settings. Clinicians must keep abreast of advances in oral anticoagulation reported in the literature and translate these advances into improved patient care. This article reviews warfarin's pharmacologic, safety, and efficacy profiles as a foundation to support contemporary guidelines for oral anticoagulation practice.

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Pharmacology

Since the discovery that bishydroxycoumarin (dicumarol) was the hemorrhagic agent responsible for "sweet clover disease" in cattle, numerous congeners of the compound have been synthesized.[2] Warfarin sodium is the most widely used coumarin derivative in the United States.

Mechanism of Action

Orally active coumarin derivatives indirectly decrease the relative concentration of the active vitamin-K–dependent clotting factors II, VII, IX, and X.[3] In the liver, warfarin competitively interferes with the cyclic interconversion of vitamin K and vitamin K epoxide. Inhibition of the enzyme vitamin K epoxide reductase results in the depletion of the active form of the cofactor (vitamin KH_2) and production of the hemostatically defective vitamin-K–dependent clotting factors. In the same manner but with less clinical relevance, warfarin alters two additional vitamin-K–dependent proteins that are relevant to the clotting system, proteins C and S.[3] These proteins function as circulating anticoagulants that inactivate factors V and VIII. Except in inherited deficiencies of protein C or S, the procoagulant effect is superseded by warfarin's anticoagulant effect.

Warfarin's complete anticoagulant effect may take a week to be expressed.[4] The initiation of warfarin therapy results in a decline in concentrations of functional factor VII and protein C (half-lives of approximately 5 hours) within the first 12 to 24 hours.[5] However, the full antithrombotic effects of warfarin are not seen until 3 to 4 days after initiation or dosage adjustment, when the levels of functional factors II, IX, and X are altered.[6]

Pharmacokinetics and Interactions

The absorption of oral warfarin is rapid and complete, with peak concentrations occurring within 90 minutes in healthy volunteers.[7–9] Warfarin has become the oral anticoagulant of choice because of its aqueous solubility and uniform absorption characteristics. The drug is highly plasma-protein bound (>97%),[10] and less than 3% of the drug exists in the free, unbound form, which is available to exert a pharmacologic effect on the liver. The drug crosses the placenta, and fetal concentrations approximate maternal plasma concentrations.[11] The drug can produce embryopathy, central nervous system abnormalities, or fetal bleeding. Warfarin, a racemic mixture, is metabolized by the hepatic microsomal enzymes to inactive metabolites. The S(−) optical isomer has a shorter half-life but is five times more potent than the R(+) isomer.[12,13] The half-life of the warfarin racemate is approximately 36 to 42 hours.[7,8]

The literature is replete with reports of pharmacokinetic drug interactions with warfarin, but only a limited number are clinically significant and well documented in controlled studies.[14] Drugs may interact with warfarin by altering its absorption or displacing it from albumin, although altering its hepatic microsomal metabolism appears to be the primary interaction. Examples of drugs that significantly reduce warfarin's anticoagulant effect include barbiturates[15] and rifampin.[16] Drugs that potentiate warfarin's anticoagulant effect include amiodarone,[17] androgens,[18] cimetidine,[19,20] clofibrate,[21] disulfiram,[22] metronidazole,[23] phenylbutazone,[24,25] sulfinpyrazone,[26] thyroxine,[27] and trimethoprim-sulfamethoxazole.[28] Some of these drugs are not used routinely today. In addition, today's less intense warfarin regimens reduce the likelihood of clinically significant interactions.

Pharmacodynamics and Interactions

The pharmacodynamics of warfarin can be affected by many factors, including hereditary resistance,[29,30] dietary vitamin K intake,[31] and the use of drugs such as aspirin,[32] which influence other hemostatic mechanisms.

Hereditary resistance, thought to be secondary to an altered affinity of warfarin receptors, may result in the requirement of 5 to 20 times the average dosage of warfarin.[29,30] Patients taking warfarin are sensitive to fluctuating amounts of dietary vitamin K.[33] Vitamin K is present in significant amounts (>500 μg per serving) in foods such as vegetables (eg, cauliflower, brussels sprouts), fats (eg, soybean oil), and green tea.[34] A case report describes a patient who required 30 mg to 35 mg warfarin per day to maintain therapeutic anticoagulation.[35] In this patient, warfarin resistance was attributed to a vegetable diet rich in vitamin K (1277 μg daily). Patients need to be aware of the vitamin K content of foods and instructed to maintain a relatively consistent daily intake.

Aspirin, an antiprostaglandin agent that is associated with gastric erosions, impairs hemostatic plug formation and can potentiate bleeding when used in high dosages and in combination with higher intensity warfarin therapy (international normalized ratio [INR] 3.0 to 4.5).[36,37] In contrast, low-dosage aspirin (100 mg daily) may increase the efficacy of warfarin without significantly increasing the risk of major bleeding.[38]

Technical Factors

Various factors, including preanalytic conditions, laboratory variation, and poor patient compliance, contribute to unexpected patient response to warfarin. For example, Palmer et al[39] reported that the length of time a blood sample is kept and the temperature at which it is stored before it is analyzed could result in a falsely short pro-

thrombin time (PT) and could potentially lead to serious clinical error. Less than obvious factors can include the source and preparation of the thromboplastin (TPL) reagent, the accuracy of the instrument used to perform the test, and the source of the plasma standard.[40,41]

Anticoagulation is a preventive measure that does not make the patient directly "feel better." Educating patients about the benefits of proper compliance is likely to be a critical factor in preventing this problem. Altered patient compliance should be considered routinely before any dosage adjustments are made.

Begin Early with Less Drug

Hospitalized patients who have thromboembolic disorders are given a rapid-acting anticoagulant, eg, intravenous heparin, until they can be maintained on oral anticoagulant therapy. Several studies have documented that it is safe and effective to begin warfarin therapy on the first day of heparin therapy.[42–45] Achieving early therapeutic control with warfarin decreases the duration of heparin therapy, reduces the length of hospital stay, and decreases costs.[44,45] An overlap of heparin and warfarin for 4 to 5 days is required to maintain an anticoagulant effect while awaiting warfarin's full therapeutic effects.[46] Begin warfarin dosing with 7.5 mg to 10 mg daily until the INR is within the therapeutic range for at least 2 days, and then adjust dosing accordingly.[47] In patients who have chronic atrial fibrillation or a risk of bleeding, begin warfarin therapy more conservatively, with 5 mg daily. Further study is required to determine the optimal starting dosages of warfarin.

When the dosage of warfarin is changed, the full anticoagulant effect may not be seen for up to a week.[4] Therefore, warfarin dosage changes should be conservative and PTs monitored weekly until the therapeutic INR goal is reached. Once the patient's anticoagulation is controlled on warfarin, INRs can be monitored as infrequently as every 4 to 8 weeks.[47] The frequency of blood-clotting tests should not exceed an 8-week interval, because changes in other drugs, medical conditions, or dietary intake of vitamin-K–containing foods may cause long-term drug requirements to fluctuate.

Therapeutic INR Intensities Reduced: Shifting the Therapeutic Index

Although no new agents have replaced warfarin as the standard oral anticoagulant, its narrow therapeutic index is shifting through the use of less intense regimens. There have been two recent shifts in the recommended therapeutic INR intensities. First, in July 1987, the US Food and Drug Administration (FDA) approved the use of lower intensity anticoagulation with warfarin. Second, the October 1992 supplement issue of the journal *Chest* published the proceedings of the Third American College of Chest Physicians Consensus Conference on Antithrombotic Therapy,[48] which recommended further changes in the INR ranges.

Although these suggested reductions in anticoagulation intensity continue to provide effectiveness with a reduced risk of bleeding,[47] there remains a great deal of confusion about how best to monitor the degree of anticoagulation.

PT and INR

The one-stage PT has been used to monitor and regulate oral anticoagulant therapy for more than 40 years.[49] The PT is responsive to reductions in the concentrations of active clotting factors II, VII, and X.[47] The test is performed by adding calcium and tissue TPL to citrated plasma to activate the coagulation cascade.

Commercially available PT reagents (ie, TPLs) have tremendously variable responsiveness to warfarin-induced reduction in clotting factors.[47,50] PT results vary between laboratories using different TPLs. This problem of variability in responsiveness of TPLs has been addressed by the World Health Organization's introduction of the INR, a standardized system of reporting. The INR relates the prothrombin time ratio (PTR) to an arithmetic measure of the responsiveness of TPL and reductions in vitamin-K–dependent clotting factors, known as the international sensitivity index (ISI), as follows: $INR = PTR^{ISI}$. The INR uses a more sensitive TPL, from human brain, as the reference standard (ISI=1). Less sensitive TPLs, eg, from rabbit brain, have higher ISIs. This standardized reporting improves the clinician's capability to maintain a patient's anticoagulation therapy appropriately within a therapeutic range, despite variations in the TPL.

The following case illustrates the difficulty that can result from extrapolating the results of PT tests from one laboratory to another without knowing the ISI. The PT for a patient taking warfarin at hospital A, whose laboratory uses a rabbit-brain TPL (ISI=2.64), is reported to be 18.1 seconds, with a control value of 12 seconds. Thus, the PT ratio is 1.51 (18.1/12). If the same sample were analyzed at hospital B, whose laboratory uses the more sensitive recombinant human TPL (ISI=1.0), the resultant PT would be 33 seconds, with a control value of 11 seconds, yielding a PTR of 3.0.

Hospital A	PT=18.1	ISI=2.64
	PT ratio=1.51	INR=3.0
Hospital B	PT=33.0	ISI=1.0
	PT ratio=3.0	INR=3.0

A dosage decrease would likely be made after hospital B's results were reported, unless the practitioner was aware of the differences in TPL reagents used by the two laboratories. Note that the INRs for both hospitals are the same, although the PTs and PTRs are considerably different.

Not only does the sensitivity vary between different sources of TPL, eg, rabbit vs human, but also there is significant variability in the sensitivities of TPLs from manufacturer to manufacturer and from lot to lot. A study by Bussey and colleagues[51] of 190 selected hospital laboratories revealed a large range in the sensitivities of the TPLs used (ISI range, 1.4 to 2.8), with less than 20% of ISI values reported between 2.2 and 2.6 (PTR guidelines are based on the expectation that the sensitivity of the North American TPL is between 2.2 and 2.6). What is the documented benefit of adopting the INR system? A study by Eckman et al[52] evaluated the effect of uncertainty about the sensitivity of TPLs on the benefits, risks, and cost-effectiveness of anticoagulation in patients who have prosthetic cardiac valves.[52] The study documented that when an INR range of 2.5 to 3.5 was not maintained, the benefit of anticoagulation was reduced because of uncertainty about reagent sensitivity. In fact, the calculated increase in life expectancy, adjusted for quality of life, was reduced by more than 50% in some situations, and the cost-effectiveness ratio was increased fivefold.

Even though the recent consensus statements on recommended guidelines for anticoagulation clearly support the adoption of the INR format, there remains misunderstanding and underutilization of this more reliable reporting system. A survey of hospitals in Massachusetts found fewer than 5% reporting the PT value as an INR.[53] Fifty-six different lots of TPL from six separate manufacturers were used, with ISIs ranging from 1.89 to 2.74. In a recent survey of 38 coagulation laboratories in Utah, fewer than one half used the INR reporting system.[54]

The INR system is not perfect.[55] A study by Le et al[56] suggested that converting to INRs failed to standardize PT results obtained with insensitive TPLs. Low-sensitivity TPLs (ISI≥2.3) gave erroneously high INRs in the upper therapeutic range (INR≥3.0). However, the recent introduction of recombinant human TPL (Dade Innovin, Baxter Diagnostics Inc, Deerfield, Ill) may simplify matters. It is a very sensitive reagent (ISI approaching 1.0) and, therefore, results in nearly equivalent PTR and INR (eg, $PTR^{(ISI=1.0)}$=INR; PTR=INR) results.[57] The benefit of using this new recombinant TPL must be evaluated in the context of its relatively higher cost compared with the cost of other TPLs.

Table 1. Bleeding and Intensity of Anticoagulation: Key Studies

Study	INR Ranges	Bleeding Total, %	*P* Value
Hull et al (1982)[62]	3.0–4.5	22.4	.015
Deep vein thrombosis (n=96; duration 3 mo)	2.0–2.5	4.3	
Turpie et al (1988)[63]	2.5–4.0	13.9	<.002
Prosthetic heart values (tissue; n=210; duration 3 mo)	2.0–2.5	5.9	
Saour et al (1990)[64]	7.4–10.8	42.4	<.002
Prosthetic heart valves (mechanical; n=247; duration 3.47 y)	1.9–3.6	21.3	
Altman et al* (1991)[65]	3.0–4.5	24.0	<.02
Prosthetic heart valves (mechanical; n=99; duration 11.2 mo)	2.0–2.9	6.0	

**Patients also given aspirin and dipyridamole.*
INR denotes international normalized ratio.
Adapted with permission from Hirsh J, Dalen JE, Deykin D, Poller L. Oral anticoagulants: mechanism of action, clinical effectiveness, and optimal therapeutic range. Chest 1992; 102(suppl):312S–326S. © American College of Chest Physicians, 1992.

PT Reagent Substitution and Bleeding

There has been much debate over the optimal PT therapeutic range for oral anticoagulant therapy. For 30 years in North America, the accepted PTR was 1.5 to 2.5.[58] This therapeutic range was established by a controversial British study that investigated the use of warfarin in the treatment of patients postmyocardial infarction.[59] Since then, the major source of the TPL used to perform the PT test in North America has changed from human brain to rabbit brain.[60,61] This has resulted in an increase in warfarin dosing of approximately 1 mg (or 20%). Rabbit-brain TPL is less sensitive to a reduction of vitamin K factors than is the human-brain TPL that is still used in the United Kingdom. Therefore, British studies documenting safety and efficacy with a PTR range of 2.0 to 2.5 (human reagent) are comparable to the North American PTR range of 1.3 to 1.4 (rabbit reagent).[61]

The results of properly designed, prospective, randomized studies have demonstrated that lower intensity anticoagulation results in statistically significantly fewer bleeding complications (50% to 80% less) than traditional regimens yet provides adequate protection against thromboembolism (Table 1).[62–65] The FDA approved the use of lower intensity warfarin anticoagulation in July 1987.

A recent survey of neurologists and neurology house

Table 2. Oral Anticoagulant Recommendations

Thromboembolic Disorder	INR*	Duration	Clinical Comments
Venous thromboembolism			
Prophylaxis (high-risk surgery)	2–3	≤3 months or until ambulatory	Alternatives include low-molecular-weight heparin or adjusted-dose heparin
Treatment: single episode (DVT or PE)	2–3	3–6 months	Recurrent DVT or PE requires indefinite anticoagulation
Prevention of systemic embolism			
Atrial fibrillation (AF)	2–3	Indefinite	Anticoagulation is not indicated in patients <65 years old with no associated CV disease If warfarin is contraindicated, consider aspirin (325 mg/d)
AF: Cardioversion	2–3	3 weeks prior; 4 weeks after sinus rhythm	Consider indefinite anticoagulation in patients who do not cardiovert
Postmyocardial infarction†	2.5–3.5	≥3 months	Especially consider high-risk patients for mural thrombosis and systemic embolism (SE)
Recurrent systemic embolism	2–3	Indefinite	Criteria for "recurrence": events, temporal and etiologic relationships
Tissue heart valves	2–3	3 months	Aspirin (325 mg/d) is second-line alternative
Valvular heart disease	2–3	Indefinite	Consider patients with history of SE, AF, or left atrium diameter >5.5 cm If recurrent embolism occurs, add aspirin (160–325 mg/d)±increase INR to 2.5–3.5
Mechanical prosthetic values	2.5–3.5	Indefinite	If recurrent embolism occurs, add aspirin (160–325 mg/d) or dipyridamole (400 mg/d) If high bleeding risk, INR 2–3 ± aspirin (160 mg/d)

*$INR = PTR^{ISI}$.

†*The FDA's Cardiovascular and Renal Drugs Advisory Committee recommended warfarin for approval for prevention of death, recurrent myocardial infarction, and thromboembolic events in patients postmyocardial infarction.[67] The FDA approved this product labeling change.*

INR denotes international normalized ratio; DVT, deep vein thrombosis; PE, pulmonary embolism; AF, atrial fibrillation; CV, cardiovascular; SE, systemic embolism; ISI, international sensitivity index.

Based on data from Hirsh et al[47] and F-D-C Reports.[67]

officers investigated whether anticoagulation practices changed from 1986 to 1992.[66] A significant reduction in the mean PTR, from 1.74 to 1.49, was shown in patients who had had strokes. Although it is likely that the reduction in PTR is secondary to adoption of less intense anticoagulation regimens, the study's validity is limited, because it did not provide comparable values (ie, INRs).

Clinical Anticoagulation Guidelines

Indications, Intensities, and Duration

Contemporary recommendations were provided by the American College of Chest Physicians (ACCP) in 1992.[48] This consensus group established changes and reductions in the recommended INR ranges on the basis of its members' experience and opinions about the literature. These recommendations suggest that the only patients who should not receive the moderate-intensity anticoagulation regimen (INR 2 to 3) are those who have mechanical prosthetic cardiac valves. These patients should have INRs of 2.5 to 3.5.

Table 2 provides a summary of current clinical anticoagulation guidelines. In addition to significant reductions in INR intensities for recurrent thromboemboli from 3.0–4.5 to 2.0–3.0 and for mechanical prosthetic heart valves from 3.0–4.5 to 2.5–3.5, other changes in recommendations have extended the clinical utility of warfarin. It is now recognized that 45% of all embolic strokes are secondary to nonvalvular atrial fibrillation.[68] Long-term oral anticoagulation (INR 2.0 to 3.0) is recommended for all patients who have atrial fibrillation except for those younger than 60 years of age who have no associated cardiovascular disease (ie, lone atrial fibrillation).[47] The results recently published by the investigators of the Stroke Prevention in Atrial Fibrillation II (SPAF II) trial suggest a slightly more conservative approach in selecting candidates for warfarin therapy who have nonrheumatic atrial fibrillation.[69] These investigators recommend long-term oral anticoagulation (INR 2.0 to 3.0) for patients who have atrial fibrillation except for those younger than 75 years of age who have had no associated heart disease, history of hypertension, or previous stroke. In addition, this trial found no statistically significant difference in efficacy between treatment with 325 mg per day of aspirin and treatment with moderate-intensity warfarin. However, on-treatment analysis of the SPAF II data demonstrates a reduction in risk for ischemic stroke of approximately 50% for patients taking warfarin compared with that for those taking aspirin.[70] This rate of

Table 3. Vitamin K Recommendations

INR*	Vitamin K Dose†	Administration Route	Comments
>6–≤10	0.5–1.0 mg	PO, SC	Rule out excessive warfarin compliance prior to dosage reduction
>10–≤20	3.0–5.0 mg	PO, SC, IV‡	Check INR in 6–12 h; repeat vitamin K if necessary.
>20	5.0–10.0 mg§	SC, IV‡	Check INR in 6 h; repeat vitamin K if necessary.

**Without bleeding.*
†Withholding warfarin dose(s) in lieu of vitamin K use should be considered.
‡Intravenous route may produce anaphylactic reaction; subcutaneous preferred.
§May be difficult to achieve an anticoagulant effect of warfarin for up to 1 week.
INR denotes international normalized ratio; PO, oral; SC, subcutaneous, IV, intravenous.
Based on data from Hirsch and Fuster,[4] Hirsh et al,[47] and Hirsh and Poller.[55]

risk reduction is similar to that found in previously published reports.[71–74] The efficacy of aspirin for prevention of stroke is under further evaluation in SPAF III.[75] It is reasonable to consider warfarin treatment for those select patients who have atrial fibrillation, are younger than 65, and are poor candidates for oral antithrombotic therapy with 325 mg per day of aspirin.

Although the use of warfarin for the prevention and treatment of thromboembolic complications associated with cardiac valve replacements had been supported for years by the ACCP consensus group, the FDA expanded the approved labeling for warfarin to include this indication in March of 1994.

Warfarin has been recently approved by the FDA for the prevention of death, recurrent myocardial infarction, and thromboembolic events in patients postmyocardial infarction, subsequent to a recommendation by the FDA's Cardiovascular and Renal Drugs Committee.[67] This recommendation was made on the basis of the results of the Warfarin Reinfarction Study,[76] which showed a 24% reduction in risk for mortality ($P<.05$), a 34% reduction in risk for recurrent myocardial infarction ($P=.001$), and a reduction in cerebrovascular events of 54% ($P=.002$). The FDA-recommended INR range in the product labeling is 2.5 to 3.5 for long-term administration.[67]

Uncertainty remains as to how little warfarin is enough to maintain the desired therapeutic outcome.[77] In addition, identification of the ideal antithrombotic combination remains elusive. Results from recent studies support the use of warfarin (INR 2.5 to 3.5 for a 3-month period) in combination with long-term therapy with aspirin (325 mg daily) and dipyridamole (225 mg daily) to reduce the restenosis rate of coronary artery stents.[78,79] A study by Hayashi et al[80] documented the effectiveness and safety of combined warfarin and antiplatelet therapy after prosthetic cardiac valve replacement.The Fourth ACCP Consensus Conference on Antithrombotic Therapy, held in March 1995, will likely provide recommendations on these and other novel uses and combinations of oral antithrombotic therapy.

Reversing Warfarin's Effect with Less Vitamin K

Bleeding is the most common and dangerous complication of warfarin therapy. High INRs may be secondary to overcompliance, a drug interaction, or a change in diet or medical condition. When it is necessary to reduce or reverse the anticoagulant effects of warfarin, consider stopping treatment, administering a modest dose of vitamin K, or replacing the vitamin-K–dependent clotting factors with plasma or factor concentrates (Table 3).[47]

Withholding warfarin dosing must be considered first. Stopping treatment with warfarin will result in a reduced INR after a period of several days, after warfarin concentrations fall and the newly synthesized functional vitamin-K–dependent clotting factors replace the dysfunctional ones.

If a more rapid effect is desired, consider the moderate use of vitamin K. The INR is generally reduced within 6 hours after a 5- to 10-mg oral, subcutaneous, or intravenous dose of vitamin K; however, patients often remain resistant to subsequent warfarin for 7 to 10 days.[81] The problem of warfarin resistance can be overcome by using much lower doses of vitamin K. Vitamin K, in an intravenous dose of 0.5 mg to 1.0 mg, reduced INR levels of 10–20 to 3.0–7.5 in 8 hours, and to 1.5–5.0 in 24 hours, without interfering with subsequent warfarin therapy.[82] The intravenous form of vitamin K should be administered very slowly (1 mg per minute) to limit the potential for an anaphylactic reaction[4]; intravenous use should be limited to acute emergencies.[83] Intramuscular administration of vitamin K is not recommended because of the risk of hematoma formation at the injection site. Because only 5-mg oral tablets of vitamin K are available, the intravenous formulation can be considered for oral administration. An immediate reversal of anticoagulant effect occurs by replacing the vitamin-K–dependent clot-

ting factors with fresh frozen plasma or factor concentrates.

Patient Education and Documentation

Informed patients play a critical role in the management of their anticoagulant therapy. Standards of the Joint Commission on the Accreditation of Healthcare Organizations now require chart documentation of patient education.[84] Clinicians should emphasize to patients the importance of complying with the prescribed regimen, and patients should understand why a "blood thinner" has been prescribed and should be informed about the duration of therapy, ie, short-term or indefinite. Patients should be counseled to avoid starting or discontinuing any other medication without consulting with a health care professional. The clinician should ensure that the patient is able to recognize signs of minor hemorrhaging, eg, gingival bleeding or nosebleeds, as well as the signs of more severe bleeding, eg, bruising, red or dark brown urine, and red or tarry black stools. Wearing a medical bracelet identifying the patient as a warfarin user also should be encouraged to alert medical personnel in the event of a medical emergency (eg, major hemorrhage).

Future Issues

What are the ideal INR intensities? How long should a patient be treated with warfarin? What are the appropriate indications for oral anticoagulation? Should aspirin be combined with warfarin? How much vitamin K is just enough? What is the role of the newer antiplatelet agents? We hope that the Fourth ACCP Consensus Conference on Antithrombotic Therapy will provide more insight into better anticoagulation and patient-care methods.

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