Oral Anticoagulants
Mechanism of Action, Clinical Effectiveness, and Optimal Therapeutic Range

Jack Hirsh, M.D., F.C.C.P., Chairman;
James E. Dalen, M.D., F.C.C.P.;
Daniel Deykin, M.D.;
Leon Poller, M.D.

The optimal therapeutic range for oral anticoagulant therapy was reviewed by the Committee on Antithrombotic Therapy of the American College of Chest Physicians (ACCP) and the National Heart, Lung and Blood Institute (NHLBI) in 1986 and again in 1989. At that time, a recommendation was made that the intensity of warfarin treatment should be reduced for many indications. Since then, new clinical trials have been published which support these recommendations, and the optimal therapeutic range for many indications has been clarified. Nevertheless, the control of oral anticoagulant therapy remains a subject of confusion. The confusion persists for two related reasons. The first is the marked variation in the responsiveness of different commercial thromboplastin reagents to reductions by warfarin of vitamin K dependent clotting factors measured in the prothrombin time (PT) test; and the second is the reluctance of hematologists in North America to adopt the standardized international normalized ratio (INR) method of reporting which is now accepted internationally. In this update on oral anticoagulant therapy, we have made a number of changes. The first is to report our recommendations for therapeutic ranges of INR since recent reports indicate that the variations in responsiveness of commercial thromboplastins is so wide that the term typical North American thromboplastin is no longer valid. The second is to recommend an INR of 2.0 to 3.0 for all indications (including recurrent systemic embolism) except mechanical prosthetic heart valves for which an INR of 2.5 to 3.5 is recommended. The intensity of the therapeutic range has been lowered for mechanical prosthetic valves because of reports that a low intensity regimen is effective for this indication and because the risk of bleeding increases with increasing anticoagulant intensity. The third change is an expansion of this chapter to include mechanism of action of oral anticoagulants, their pharmacokinetics, practical dosing considerations, and the management of patients who require reversal or lowering of anticoagulant intensity.

Mechanism of Action, Pharmacokinetics and Pharmacodynamics of Warfarin

Oral anticoagulants produce their anticoagulant effect by interfering with the cyclic interconversion of vitamin K and its 2,3 epoxide (vitamin K epoxide). Vitamin K is a cofactor for the posttranslational carboxylation of glutamate residues to \( \gamma \)-carboxyglutamates (Gla) on the N-terminal regions of vitamin K-dependent proteins. The process of \( \gamma \)-carboxylation permits the coagulation proteins to undergo a conformational change in the presence of calcium ions; a necessary requirement for calcium-dependent complexing of vitamin K-dependent proteins to their cofactors on phospholipid surfaces and for their biologic activity. Carboxylation of vitamin K-dependent coagulation factors is catalyzed by a carboxylase which requires the reduced form of vitamin K (vitamin KH\(_2\)), molecular oxygen, and carbon dioxide. During this reaction, the vitamin KH\(_2\) is oxidized to vitamin K epoxide which is recycled to vitamin K by vitamin K epoxide reductase which in turn is reduced to vitamin KH\(_2\) by vitamin K reductase. The vitamin K antagonists exert their anticoagulant effect by inhibiting vitamin K epoxide reductase and possibly vitamin K reductase. This process leads to the depletion of vitamin KH\(_2\) and limits the \( \gamma \)-carboxylation of the vitamin K-dependent coagulant proteins (prothrombin, factor VII, factor IX and factor X). In addition, the vitamin K antagonists limit the carboxylation of the regulatory proteins (protein C and protein S), and as a result, impair the function of these anticoagulant proteins. By inhibiting the cyclic conversion of vitamin K oral anticoagulants result in the hepatic production and secretion of partially carboxylated and descarboxylated proteins. Reduction of the number of Gla residues on the prothrombin molecule from the normal complement of 10-13 to 9 Gla residues results in a 30 percent reduction in coagulant activity, while reduction to less than 6 residues results in a loss of more than 95 percent of coagulant activity.
PHARMACOKINETICS AND PHARMACODYNAMICS
OF WARFARIN

Warfarin (a 4-hydroxycoumarin compound) (Fig 1 and Table 1) is the most widely used oral anticoagulant in North America because its onset and duration of action are predictable and because it has excellent bioavailability. Warfarin is almost always administered by the oral route, although an injectable preparation is available. Warfarin is a racemic mixture of roughly equal amounts of two optical isomers, the R and S forms. Warfarin is rapidly absorbed from the gastrointestinal tract and reaches maximal blood concentrations in healthy volunteers in 90 min. Race-mic warfarin has a half-life of 36 to 42 hr, it circulates bound to plasma proteins and rapidly accumulates in the liver where the two isomers are metabolically transformed by different pathways. The dose-response relationship of warfarin differs between healthy subjects and can vary to a much greater extent among sick patients. Because of the variations in the dose response in individual patients during the course of anticoagulant therapy, their anticoagulant dosage must be monitored closely to prevent overdosing or underdosing.

The dose response to warfarin is influenced by both pharmacokinetic factors (due to differences in absorption or metabolic clearance of warfarin) and pharmacodynamic factors (due to differences in the hemostatic response to given concentrations of warfarin). Technical factors also contribute to the variability in dose response, including inaccuracies in laboratory testing and reporting, poor patient compliance, and poor communication between patient and physician. Occasionally, the cause of the variable dose-response within individual patients remains unexplained.

Drugs can influence the pharmacokinetics of warfarin by reducing its absorption from the intestine or by altering its metabolic clearance. The anticoagulant effect of warfarin is reduced by cholestyramine which impairs its absorption. It can be potentiated by drugs which inhibit the metabolic clearance of warfarin either through stereoselective or nonselective pathways. Stereoselective interactions can affect the oxidative metabolism of the S isomer or R isomer of warfarin. Inhibition of metabolism of S warfarin is more important clinically because this isomer is five times more potent as a vitamin K antagonist than the R form. Therefore, drugs which inhibit clearance of the S isomer prolong the prothrombin time to a much greater degree than drugs which inhibit the metabolic clearance of the R isomer. The clearance of S warfarin is inhibited by phenylbutazone, sulfinpyrazone, disulfiram, metronidazole, and trimethoprim-sulfamethoxazole, all of which have been documented to potentiate the effect of warfarin on the PT. In contrast, drugs such as cimetidine and omeprazole, which only inhibit the metabolic clearance of the R isomer, have only moderate potentiating effects on the prothrombin time in patients treated with oral anticoagulants. Amiodarone inhibits the metabolic clearance of both the S and R isomers and has an important potentiating effect on the anticoagulant.
The pharmacodynamics of warfarin are affected by many factors which can influence its anticoagulant effect.

Hereditary resistance to warfarin has been described in rats and humans. The affected humans require warfarin in doses which are 5- to 20-fold higher than average to achieve an anticoagulant effect. This disorder is thought to be caused by an altered affinity of the receptor for warfarin, since the plasma warfarin levels required to achieve an anticoagulant effect are much higher than average.

Subjects receiving long-term warfarin therapy are sensitive to fluctuating levels of dietary vitamin K which is obtained predominantly from phylloquinone in plant material. Important fluctuations in vitamin K intake occur in both apparently healthy and sick subjects. Increased intake of dietary vitamin K sufficient to reduce the anticoagulant response to warfarin occurs in patients on weight reduction diets (rich in green vegetables) and those treated with intravenous nutritional fluid supplements rich in vitamin K. The effects of warfarin can be potentiated in sick patients with poor vitamin K intake (particularly if they are treated with antibiotics and intravenous fluids without vitamin K supplementation) and in states of fat malabsorption. Hepatic dysfunction also potentiates the response to warfarin through impaired synthesis of coagulation factors. Hypermetabolic states produced by fever or hyperthyroidism increase responsiveness to warfarin probably by increasing the catabolism of vitamin K-dependent coagulation factors. Drugs can influence the pharmacodynamics of warfarin by inhibiting the synthesis of vitamin K-dependent coagulation factors, by increasing the metabolic clearance of vitamin K-dependent coagulation factors, and by interfering with other pathways of hemostasis (Table 1). The anticoagulant effect of vitamin K, which is obtained predominantly from phylloquinone in plant material, is augmented by thyroxine because this hormone increases the rate of metabolism of coagulation factors and by clofibrate through an unknown mechanism. Although heparin increases the anticoagulant effect of warfarin, it only causes a slight prolongation of the PT at therapeutic levels.

Drugs such as aspirin, other nonsteroidal anti-
inflammatory drugs, high doses of penicillins, and moxolactam can increase the risk of warfarin-associated bleeding by inhibiting platelet function. Aspirin is the most important because of its widespread use and prolonged effect on hemostasis. Aspirin can also produce gastric erosions which increase the risk of serious upper gastrointestinal bleeding.

The risk of clinically important bleeding is increased when high doses of aspirin are used in combination with high intensity warfarin therapy (INR 3.0 to 4.5). In contrast, a recent study reported that low doses of aspirin (100 mg/day) which retain their antithrombotic efficacy and have only minimal gastric side effects, increase the efficacy of warfarin without increasing significantly the risk of major bleeding.

Other drugs, including erythromycin and some anabolic steroids, potentiate the anticoagulant effect of warfarin through unknown mechanisms. Sulfonamides and many broad spectrum antibiotics have the potential to augment the anticoagulant effect of warfarin by eliminating bacterial flora, and thereby producing vitamin K deficiency, but these agents only potentiate the anticoagulant effect of warfarin in patients on a vitamin K-deficient diet.

Many other drugs either interact with oral anticoagulants or have been reported to alter the PT response to warfarin, but in most of these reports, convincing evidence of a causal association is lacking. Nevertheless, it would be prudent to take special care when treatment with any new drug is necessary in patients who are being treated with oral anticoagulants and to monitor the PT more frequently during the initial stages of combined drug therapy with dose adjustments made, when appropriate.

**Monitoring Oral Anticoagulant Therapy**

The PT test is the most common method used for monitoring oral anticoagulant therapy. The PT is responsive to depressions of three of the four vitamin K-dependent procoagulant clotting factors (factors II, VII, and X). These are reduced by warfarin at a rate proportionate to their respective half-lives. The PT is performed by adding calcium and thromboplastin to citrated plasma. The term "thromboplastin" refers to a phospholipid-protein extract of tissues, usually lung, brain, or placenta, that contains both the tissue factor and the phospholipid necessary to promote the activation of factor X by factor VII. During the first few days of warfarin therapy, the PT reflects primarily the depression of factor VII, which has a half-life of only approximately 6 h. Subsequently, the test is prolonged also by depression of factors II and X. The responsiveness of a given thromboplastin to warfarin-induced changes in clotting factors mirrors the strength of the activation of factor X by factor VII as the levels of both the clotting factors decrease. An "unresponsive" thromboplastin produces accelerated stimulation of factor X, resulting in a lesser prolongation of the prothrombin time for a given reduction in clotting factors than that caused by a less responsive thromboplastin.

Thromboplastins vary markedly in their responsiveness to the anticoagulant effects of warfarin, depending on their tissue of origin and method of preparation. Maintenance of the PT at a ratio of 2.0 requires a lower dose of warfarin using responsive United Kingdom thromboplastins than with the less responsive thromboplastins used in North America. Owing to the variable response of the thromboplastins and the different ways of reporting, PT results obtained from patients treated with oral anticoagulants have not been interchangeable between laboratories. The differences in responsiveness of various thromboplastins to the reduction of clotting factors II, VII, and X are mainly responsible for clinically important differences in the dosages of oral anticoagulants used in different countries as shown by Poller and Taberner. In our previous publication, we referred to the latter study which demonstrated a wide variation in the responsiveness of commonly used North American thromboplastins to reductions of vitamin K-dependent coagulation factors by warfarin. This problem has been addressed by a more recent study which has demonstrated that the variation in responsiveness of North American thromboplastins has widened even further over the last five years.

**Standardization of the Prothrombin Time**

The history of standardization of the PT has been reviewed by Poller and by Kirkwood. A standardized human brain thromboplastin reagent, the Manchester comparative reagent (MCR), was introduced in 1962 and used by nearly all hospitals in the United Kingdom. In 1977, the World Health Organization (WHO) designated a batch of human brain thromboplastin as the first international reference preparation (IRP) for thromboplastin. The first IRP was later replaced by a new primary and three secondary reference thromboplastins. A calibration system was developed, based on the assumption that a linear relationship would exist between the logarithm of the PT obtained with the reference and test thromboplastins. This calibration model adopted in 1982 is used to standardize the reporting of the PT by converting the PT ratio observed with the local thromboplastin into an INR, calculated as follows: INR = \( \frac{\text{Patient PT}^C}{\text{Control PT}} \)

where C is the power value which represents the international sensitivity index (ISI). A specially designed nomogram provides INR values from the prothrombin ratio value obtained with a thromboplastin.
reagent and its ISI without the need for calculations (Fig 2). The ISI is a measure of the responsiveness of a given thromboplastin to reduction of the vitamin K-dependent coagulation factor compared to the international reference preparation; the lower the ISI, the more responsive the reagent. The INR is the PT ratio which one would have obtained if the WHO reference thromboplastin had been used to perform the PT on the sample test. For practical purposes, it is sufficient to know that the first WHO primary human brain reference thromboplastin, which was very responsive to the anticoagulant effects of warfarin, had an ISI of 1.0. It has been recommended that manufacturers calibrate their thromboplastin reagent in terms of the first primary WHO reference standard and provide the user with an ISI value. When this is done, individual hospital laboratories can report their results in a standard way as INR. Although the variability of the PT test response to the vitamin K antagonists is also influenced by technical factors, the major source of variability in reporting is removed by relating the PT ratio obtained locally to the reference standard.

Many commercial manufacturers are now providing ISI values and corresponding INR with their reagents. In a study performed in 1987, Poller reported that the ISI values for the commercial rabbit brain thromboplastins widely used in North America vary between 2.0 and 2.6, while the single type of thromboplastin used in a majority of hospitals in the United Kingdom (originally human brain and now rabbit brain) and in many parts of Scandinavia and the Netherlands (bovine brain combined with plasma) are almost as responsive as the WHO human brain reference thromboplastin and have ISI values of 1.0 to 1.1. In a recent study, Bussey and associates reported that the ISI of most thromboplastins used in the United States vary from 1.8 to 2.8 and suggest that
the term "typical North American thromboplastin (ISI = 2.3)" used in our earlier publications is no longer valid. The report by Bussey and associates\(^6\) highlights the continuing unsatisfactory state of PT reporting in many centers in North America.

The more responsive reagents, particularly those with a low ISI (1.0 to 1.2), have the advantage of a wider therapeutic range in observed PT ratios and provide greater precision in the PT testing than less responsive reagents.\(^{14,75}\) A joint policy statement of the International Committee for Thrombosis and Hemostasis and the International Committee for Standardization in Hematology in 1985, recommended that editors and reviewers of scientific papers should no longer accept the expression of PT results unless the INR was also given.\(^73\) We strongly endorse this recommendation. The INR system of reporting has not yet been adopted by the vast majority of institutions in North America. Furthermore, editorial boards of medical journals continue to add to the confusion by publishing articles on oral anticoagulants which omit essential information from which the intensity of the anticoagulant effect achieved by treatment can be determined. The failure to standardize reporting of the PT ratio by the use of INR constitutes substandard medical care and makes accurate comparisons of the anticoagulant intensity used in studies evaluating the efficacy and safety of oral anticoagulant therapy impossible to achieve.\(^76\)

The conversion of the observed PT to the INR loses some reliability with some types of automated systems or, if the local thromboplastin is much less responsive to reduction of vitamin K-dependent clotting factors than the reference thromboplastin, and when the PT is performed on plasma from patients in the early stages of therapy.\(^2\) These imperfections are not the fault of the INR system, but reflect defects in PT reagents or technique used to perform the test. There appears to be general agreement, however, that the INR system of reporting should be adopted internationally. The study by Bussey and associates\(^6\) clearly indicates that the present state of PT reporting in North America is inappropriate and potentially dangerous, and that it should be replaced with the INR system.\(^76\)

**Optimal Therapeutic Range for the Control of Oral Anticoagulant Therapy**

Recently, much progress has been made in defining the optimal therapeutic range for laboratory control of oral anticoagulant therapy. Wright and associates\(^77,78\) recommended a therapeutic range of 2.0 to 2.5 prothrombin ratio. This recommendation was accepted and has been adhered to in North America for 30 years. In 1984, two separate reports, the British Society of Hematology and the Leuven Consensus Group, recommended a scale of therapeutic ranges for the PT which was linked to the indication for oral anticoagulant therapy.\(^3,70\) After carefully reviewing the evidence, the ACCP/NHLBI Committee modified

<table>
<thead>
<tr>
<th>Table 2—Recommended Therapeutic Range for Oral Anticoagulant Therapy*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indication</strong></td>
</tr>
<tr>
<td>Prophylaxis of venous thrombosis (high-risk surgery)</td>
</tr>
<tr>
<td>Treatment of venous thrombosis</td>
</tr>
<tr>
<td>Prevention of systemic embolism</td>
</tr>
<tr>
<td>Tissue heart valves</td>
</tr>
<tr>
<td>Mechanical prosthetic heart valves</td>
</tr>
<tr>
<td>Acute myocardial infarction (to prevent systemic embolism)</td>
</tr>
<tr>
<td>Valvular heart disease</td>
</tr>
<tr>
<td>Recurrent systemic embolism: Mechanical prosthetic valves (high risk)</td>
</tr>
</tbody>
</table>

*Because of difficulties in patient compliance, variations in vitamin K intake and absorption and other undefined factors, it is usually not possible to achieve this range during the complete course of therapy.

†Since the ISI values of commercial thromboplastins in North America vary from 1.8 to 2.8, it is not possible to include the PT ratio for a typical North American thromboplastin. The PT ratios for thromboplastins with ISI values of 1.8, 2.3 and 2.8 are as follows:

<table>
<thead>
<tr>
<th>PT RATIOS</th>
<th>INR</th>
<th>ISI 1.8</th>
<th>ISI 2.3</th>
<th>ISI 2.8</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.0-3.0</td>
<td>1.5-1.8</td>
<td>1.4-1.6</td>
<td>1.3-1.5</td>
<td></td>
</tr>
<tr>
<td>2.5-3.5</td>
<td>1.7-2.0</td>
<td>1.5-1.7</td>
<td>1.4-1.6</td>
<td></td>
</tr>
</tbody>
</table>
these recommendations. The ACCP/NHLBI recommendations are summarized in Table 2 which shows the ratios expressed as an INR. In this publication, we have omitted the corresponding PT ratios because the ISIs of North American thromboplastins have been shown to vary so widely (between 1.8 and 2.8) that such a conversion is no longer valid. In effect, we are recommending that all laboratories convert to the INR system of reporting because, as pointed out, the present system is potentially dangerous. The number of recommended ranges has been reduced to two levels; a less intense range corresponding to an INR of 2.0 to 3.0, and a more intense range corresponding to an INR of 2.5 to 3.5. The relationship between the PT ratio with thromboplastins (over an ISI range of 1.0 to 3.0), and the INR is shown in Figure 2.

WARFARIN DOSING: PRACTICAL CONSIDERATIONS

Following oral administration, there is rapid absorption of warfarin, but an observable anticoagulant effect is usually delayed for 24 to 36 h, representing the time required for the descarboxylated vitamin K-dependent clotting factors to replace the normal clotting factors as the latter are cleared from the circulation. The early anticoagulant effect is caused by replacement of normal factor VII which has a half-life of 6 to 7 h by descarboxylated species. Full anticoagulant activity is delayed for 72 to 96 h because the half-lives of the other three vitamin K-dependent clotting proteins (factors II, IX, and X) are considerably longer. Warfarin also suppresses the synthesis of carboxylated forms of the natural anticoagulants, protein C and protein S. Since protein C has a short half-life (similar to that of factor VII), there is the potential for the early anticoagulant effect to be counteracted by the prothrombotic effect of reduced protein C activity during the initial 24 to 48 h of oral anticoagulant therapy. In some cases, warfarin-induced skin necrosis has been attributed to this reduction in protein C (see Adverse Effects). Whether this presents a real problem is uncertain, but it is one of the reasons for overlapping warfarin with heparin for the first few days of anticoagulant therapy.

Warfarin therapy can be commenced with a maintenance dose or with a small loading dose which is approximately twice the average maintenance dose. The use of a large loading (eg, 20 to 40 mg) has no advantage over the smaller loading dose (10 mg) and is potentially dangerous, making stabilization more difficult. If the need for initiating antithrombotic therapy is not urgent (eg, chronic stable atrial fibrillation), treatment can be commenced with an average maintenance dose of 4 to 5 mg per day; this dosage achieves a steady state anticoagulant effect in five to seven days. If the need for an antithrombotic effect is more urgent, heparin should be given, and the daily dose of warfarin can be increased to 10 mg for the first two days. Heparin is then discontinued after four to five days when the PT is in the therapeutic range; a small reduction in the PT ratio should be anticipated when heparin is discontinued. The PT monitoring is usually performed daily for five days, then twice or three times weekly for one to two weeks, then once per week for one to two months, then once every two weeks. If the PT response remains stable, the frequency of testing can be reduced to progressively longer intervals, although it is important that these small not exceed eight weeks even in very stable patients, as changes in concomitant drug administration or intercurrent illness may alter the response to warfarin. If adjustments to the warfarin dose are required, then the cycle of more frequent monitoring is repeated until a stable dose-response is achieved. In most patients, a stable dose-response is achieved readily, but in a small percentage, the anticoagulant response is erratic, and frequent dosage adjustments are necessary. In this latter group, careful and detailed inquiry will sometimes uncover a history of fluctuating dietary intake of foods rich in vitamin K, the use of interacting drugs including alcohol or surreptitious ingestion of warfarin-like drugs as an underlying cause. Less commonly, no cause is found, and anticoagulant management is a difficult problem.

Acquired warfarin resistance is a rare and perplexing problem. This is when a patient's dosage requirements increase markedly after showing a normal response to average doses of warfarin. The mechanism of this phenomenon is unknown.

A simple protocol for predicting early dosage adjustments has been devised; warfarin is given in a dose of 10 mg on the first day of treatment, and subsequent daily adjustments are made on the basis of the PT ratio obtained approximately 16 h later. Computer-adjusted dosage schemes have also been devised for the control of short- and long-term therapy, but their efficacy and safety have not been evaluated in randomized trials. They offer possible advantages in anticoagulant record documentation and reporting which are benefits to large clinics.

CLINICAL RESULTS

The clinical effectiveness of the vitamin K antagonists has been established for a variety of indications based upon the results of well-designed clinical trials. Some of these trials have compared two levels of anticoagulant intensity and have shown that the less intense regimen (INR of 2.0 to 3.0) is as effective but produces significantly less bleeding than the more intense regimen (INR of 3.0 to 4.5) for each of the indications in which comparisons were performed (Table 3).

Oral anticoagulants have been shown to be effective...
in the primary and secondary prevention of venous thromboembolism; in the prevention of systemic embolism in patients with tissue and mechanical prosthetic heart valves or with atrial fibrillation; in the prevention of acute myocardial infarction in patients with peripheral arterial disease; and in the prevention of stroke, recurrent infarction, and death in patients with acute myocardial infarction. Oral anticoagulants are indicated in patients with valvular heart disease to prevent systemic embolism, although their effectiveness has never been demonstrated by a randomized clinical trial. For most indications, a moderate anticoagulant effect with a targeted INR of 2.0 to 3.0 (less intense regimen) is appropriate (Table 4). When the INR and ISI of the thromboplastin have not been reported in the relevant publication, we will provide our best estimate of the INR, which of necessity will be an approximation. For an INR of 2.0 to 3.0 and a thromboplastin with an ISI of 2.3 (which is roughly midway between the reported extreme ISI values), the corresponding PT ratio is approximately 1.35 to 1.6, while for an INR of 2.5 to 3.5, the corresponding PT ratio is approximately 1.5 to 1.7.

Prevention of Venous Thromboembolism

Oral anticoagulants are effective in preventing venous thrombosis after hip surgery and major gynecologic surgery when used at a targeted INR of 2.0 to 3.0. Benefit has been demonstrated when treatment is commenced a number of days before surgery, the evening before surgery, or on the first postoperative day. The risk of clinically important bleeding with the less intense regimen is small, but because warfarin prophylaxis is more complicated to use than fixed low dose heparin, warfarin is generally reserved for very high risk patients such as those with previous venous thrombosis or those having major orthopedic procedures. Very low fixed doses of warfarin (1 mg daily) have been reported to be effective in one small study in patients having gynecologic surgery and in a larger study in which 1 mg of warfarin per day was effective in preventing subclavian vein thrombosis in cancer patients with indwelling subclavian catheters. Surprisingly, the mechanism of action was associated with an increase in fibrinolysis in the gynecologic patients. One recent randomized study demonstrated that warfarin in a fixed dose of 1 mg is ineffective in preventing postoperative venographically proved venous thrombosis in patients having hip and knee surgery. The other studies in hip surgery, one uncontrolled and the second based on fibrinogen uptake studies, produced similar findings. Although attractive because of its safety and simplicity, it now clear that the 1 mg dose is ineffective in hip and knee replacements, and that this dose should not be used for these high risk conditions.

### Table 3: Relationship Between Bleeding and Intensity of Anticoagulant Therapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient Numbers</th>
<th>Anticoagulant Duration</th>
<th>Therapeutic Range, INR</th>
<th>Total % of Bleeding</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hull et al (1982)*</td>
<td>96</td>
<td>3 mo</td>
<td>3.0-4.5</td>
<td>22.4</td>
<td>0.015</td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td></td>
<td></td>
<td>vs</td>
<td>vs</td>
<td></td>
</tr>
<tr>
<td>Turpie et al (1988)**</td>
<td>210</td>
<td>3 mo</td>
<td>2.0-2.5</td>
<td>4.3</td>
<td></td>
</tr>
<tr>
<td>Prosthetic heart valves (tissue)</td>
<td></td>
<td></td>
<td>vs</td>
<td>vs</td>
<td></td>
</tr>
<tr>
<td>Saour et al (1990)**</td>
<td>247</td>
<td>3.47 yr</td>
<td>7.4-10.8</td>
<td>42.4</td>
<td>&lt;0.002</td>
</tr>
<tr>
<td>Prosthetic heart valves (mechanical)</td>
<td></td>
<td></td>
<td>vs</td>
<td>vs</td>
<td></td>
</tr>
<tr>
<td>Altman et al* (1991)**</td>
<td>99</td>
<td>11.2 mo</td>
<td>3.0-4.5</td>
<td>24.0</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>Prosthetic heart valves (mechanical)</td>
<td></td>
<td></td>
<td>vs</td>
<td>vs</td>
<td></td>
</tr>
</tbody>
</table>

*Patients also given aspirin 300 mg and dipyridamole, 75 mg BID.
validity of the evidence for the use of anticoagulants for this indication. Now, largely as a result of positive findings from two recent well-designed studies, the issue of anticoagulant therapy for long-term use in acute myocardial infarction has resurfaced.

The early evidence that oral anticoagulants are effective for the early treatment of acute myocardial infarction comes from studies performed in the 1960s and 1970s, which reported that a moderate intensity warfarin regimen (INR 1.5 to 2.5) was effective for preventing stroke and pulmonary embolism. Thus, three randomized trials (two level I and one level II) evaluated the effectiveness of oral anticoagulants in patients with acute myocardial infarction; of these two showed a significant reduction in stroke (Table 4), and the third reported a nonsignificant trend. There was also a reduction in the incidence of clinically diagnosed pulmonary embolism in all three studies. The intensity of the anticoagulant regimen in all three of these studies was below the targeted range of a PT ratio of 2.0 to 2.5 using a less responsive rabbit brain thromboplastin. In the British MRC study, the target therapeutic level was 15 percent Thrombotest (range 10 to 20 percent) equivalent to an INR of 1.6 to 2.5. In the other study showing a reduction in stroke, the precise INR of the human brain thromboplastin used is unknown, but the targeted range of 2.0 to 2.5 is likely to reflect a less intense anticoagulant effect.

The early evidence that oral anticoagulants are effective in the long-term management of acute myocardial infarction comes from analysis of pooled data from seven randomized trials published between 1964 and 1980 which showed that oral anticoagulant therapy during a one- to six-year treatment period reduced the combined endpoints of mortality and nonfatal reinfarction by approximately 20 percent. These observations did not lead to the use of anticoagulants in the long-term treatment of myocardial infarction in North America mainly because of the prevailing view that the potential benefits of anticoagulant therapy were outweighed by the risk of bleeding and the difficulty and inconvenience of laboratory monitoring. The results of two recent studies have reopened the question of the value of oral anticoagulants in the treatment of myocardial infarction. The first study was limited to patients over the age of 60 who had been treated with oral anticoagulants for at least six months. Although there was a significant reduction in reinfarction and in stroke in patients randomized to receive continuing anticoagulant therapy, because of its lack of generalizability as a "stopping trial" in a select age group, the findings were not sufficient to change the pattern of practice in most countries. The second study which had no age restrictions has attracted considerable attention since it showed a statistically significant and clinically impressive reduction in the incidence of recurrent infarction, in stroke and in mortality. Both contemporary studies used higher INR intensity regimens (INR of 2.7 to 4.5 and 2.8 to 4.8, respectively) and in both, surprisingly there was not an increase in bleeding. Indirect support for the efficacy of oral anticoagulants in patients with coronary artery disease comes from a randomized trial of patients with peripheral arterial disease; compared to an untreated control group, a relatively higher intensity oral anticoagulant regimen (INR 2.6 to 4.5) produced a significant reduction in mortality. Despite their effectiveness, oral anticoagulants are not used routinely for the long-term treatment of acute myocardial infarction because low dose aspirin (75 to 160 mg/day) is also effective, safe, and easy to administer. Therefore, aspirin is generally considered the antithrombotic treatment of choice for the long-term management of patients with acute myocardial infarction. Currently, the efficacy

<table>
<thead>
<tr>
<th>Condition</th>
<th>Minimum Effective INR</th>
<th>Recommended INR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevention of subclavian vein thrombosis</td>
<td>1.2</td>
<td>2.0-3.0</td>
</tr>
<tr>
<td>Prevention of DVT</td>
<td>1.5-2.5</td>
<td>2.0-3.0</td>
</tr>
<tr>
<td>Treatment of DVT</td>
<td>2.0-2.5</td>
<td>2.0-3.0</td>
</tr>
<tr>
<td>Acute MI</td>
<td>2.0</td>
<td>2.0-3.0</td>
</tr>
<tr>
<td>Prevention of stroke</td>
<td>2.7-4.5</td>
<td>3.0-4.5</td>
</tr>
<tr>
<td>Prevention of recurrent MI</td>
<td>2.7-4.5</td>
<td>3.0-4.5</td>
</tr>
<tr>
<td>Reduction of mortality</td>
<td>2.6-4.5</td>
<td></td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prevention of death</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prevention of systemic embolism</td>
<td>2.0-3.0</td>
<td>2.0-3.0</td>
</tr>
<tr>
<td>Cardiac valve replacement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mechanical valves</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 4—Minimum Effective INR* Based on Actual INR or Calculated From Reported ISI Values
and safety of the combination of low dose aspirin (75 mg/day) and very low intensity warfarin (INR 1.5) are being investigated in the primary prevention of cardiovascular morbidity and mortality. The results of this study are awaited with interest.

**Prosthetic Heart Valves**

There have been no clinical trials comparing patients receiving oral anticoagulants to an untreated control group of patients, all with prosthetic heart valves (for ethical reasons), but a recent clinical trial has confirmed the clinical impression that anticoagulants are effective in this group of patients. In this study, patients with mechanical prosthetic heart valves who were treated with warfarin for six months were randomized to receive warfarin (of uncertain intensity) or one of two aspirin-containing antiplatelet drug regimens. The incidence of thromboembolic complications in the group who continued to take warfarin was significantly less than in either of the two groups who received antiplatelet drugs (relative risk reduction 60 to 79 percent). The incidence of bleeding was highest in the warfarin group. The minimum effective intensity of anticoagulant therapy has been evaluated in three studies which compared the efficacy and safety of two levels of intensity of warfarin therapy. The first included only patients with tissue heart valves and showed that the less intense regimen (INR 2.0 to 2.25) was as effective but produced less bleeding than the more intense regimen (INR 2.5 to 4.0). The second study, which included patients with mechanical prosthetic heart valves, compared a very high intensity regimen prothrombin ratio (INR 7.4 to 10.8) with a lower intensity regimen (INR 1.9 to 3.6). There was no difference in effectiveness between the two regimens, but the higher intensity regimen produced significantly more bleeding. The third study, which included patients with mechanical prosthetic heart valves all of whom received aspirin and dipyridamole compared the efficacy and safety of a low intensity regimen (INR 2.0 to 3.0) with a high intensity regimen (INR 3.0 to 4.5). There was no difference in efficacy between the two regimens, but the high intensity regimen was associated with a statistically significant increase in bleeding. Thus, two studies have now demonstrated that moderate intensity warfarin treatment is as effective as a high dose regimen, although in one, all patients also received aspirin and dipyridamole. A recently completed randomized trials have shown that the addition of aspirin in a dose of 100 mg/day to warfarin (INR 3.0 to 4.5) results in a marked improvement in efficacy when compared with warfarin (INR 3.0-4.5) plus placebo. The combined low dose aspirin and high intensity warfarin regimen produced a significant and clinically impressive reduction in mortality, in cardiovascular mortality, and in stroke, without a significant increase in major bleeding or in cerebral hemorrhage.

**Atrial Fibrillation**

Four randomized studies have demonstrated that oral anticoagulant therapy reduces the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation. All included an untreated control group, and two also included an aspirin-treated group. In the first, a relatively high intensity anticoagulant regimen was used (INR 2.4 to 4.2). Oral anticoagulant therapy was significantly more effective than either aspirin or control. The risk reduction for systemic embolism was impressive, but there was a significant increase in bleeding. In a second study, a less intense warfarin regimen (stated to be 2.0 to 3.5 INR but as the thromboplastin reagents in this multicenter study were not standardized, this cannot be certain) was used. Both active treatments (warfarin and aspirin) were effective, but details of the contribution of warfarin alone were not reported. Thus, the incidence of stroke and systemic embolism was much less (81 percent risk reduction p<0.01) when warfarin and aspirin groups were combined and compared with the placebo group. In the third and most recent study, a less intense warfarin regimen was used (stated INR 1.5 to 2.7). To derive the INR, the ISI of the nonstandardized reagents at the different centers were assumed to be 2.3. Once again, there was an impressive reduction in the incidence of stroke (86 percent risk reduction; p<0.01) in the warfarin group without an increase in clinically important bleeding. In the fourth study, a nonsignificant risk reduction was observed with an INR of 2.0 to 3.0.

**Other Indications**

There are other important and well-accepted indications for oral anticoagulant therapy, but the use of oral anticoagulants for these indications has never been evaluated in properly designed clinical trials. Thus, oral anticoagulants have not been compared with an untreated control group or with another antithrombotic regimen in patients with native valvular heart disease (with or without atrial fibrillation) or in patients who have suffered one or more episodes of systemic embolism. Long-term oral anticoagulant therapy is indicated in patients with valvular heart disease with associated atrial fibrillation and in other selected patients with mitral valve disease. The optimal therapeutic range for this indication is uncertain, but on the basis of current evidence, it would be reasonable to use the less intense regimen of an INR of 2.0 to 3.0. Oral anticoagulants are indicated in patients who have suffered one or more episodes of systemic embolism. The optimal therapeutic range is uncertain. Although a high intensity regimen has been...
recommended (INR 3.0 to 4.5), it is possible that the safer less intense regimen (INR 2.0 to 3.0) would be equally effective. Anticoagulants are not indicated in patients with nonembolic cerebrovascular disease.114

In summary, therefore, there is good evidence that a less intense oral anticoagulant regimen with a targeted therapeutic range of an INR of 2.0 to 3.0 is effective in the prevention of venous thrombosis, in the treatment of venous thrombosis after an initial course of heparin, in the prevention of systemic embolism in patients with acute myocardial infarction, in patients with prosthetic tissue heart valves, and in patients with chronic atrial fibrillation. There is also suggestive evidence that this less intense regimen is effective in preventing systemic embolism in patients with atrial fibrillation who undergo direct current conversion. It is generally regarded that a more intense anticoagulant effect is required to provide protection in patients with mechanical prosthetic heart valves.112.113 This impression is based on a large amount of clinical experience (level V) and on the results of a retrospective survey (level IV).119 It has now been challenged by the results of the two randomized studies described above.112.113

ADVERSE EFFECTS

Bleeding is the main complication of oral anticoagulant therapy. The risk of bleeding is influenced by the intensity of anticoagulant therapy97,111-113,120,121 (Table 4), by the patient’s underlying clinical disorder,112,113 and by the concomitant use of high doses of aspirin which both impair platelet function and produce gastric erosions.96,97

Four randomized studies have demonstrated that the risk of clinically important bleeding is reduced by lowering the therapeutic range from 3.0 to 4.5 to 2.0 to 3.0. 97,111-112 Although this difference in anticoagulant intensity is associated with a reduction of the dose of warfarin of only approximately 1 mg, the effect on bleeding is profound.

The risk of major bleeding has been reported to be increased by the following: age over 65 years; a history of stroke or gastrointestinal bleeding; atrial fibrillation; and the presence of serious comorbid conditions such as renal insufficiency or anemia.114,115 Bleeding which occurs when the INR is less than 3.0 is frequently associated with an obvious underlying cause97 or an occult gastrointestinal or renal lesion.120

The most important nonhemorrhagic side effect of warfarin is skin necrosis. This uncommon complication is usually observed on the third to eighth day of therapy123,124 and is caused by extensive thrombosis of the venules and capillaries within the subcutaneous fat. An association has been reported between warfarin-induced skin necrosis and protein C deficiency,125-127 and less commonly, protein S deficiency,120 but this complication can also occur in nondeficient individuals. The pathogenesis of this striking complication is unknown. A role for protein C deficiency seems probable and is supported by the similarity of the lesions to those seen in neonatal purpura fulminans which complicates homozygous protein C deficiency. The reason for the unusual localization of the lesions remains a mystery. The treatment of patients with coumarin-induced skin necrosis who require lifelong anticoagulant therapy is problematic. Warfarin is considered to be contraindicated and long-term heparin therapy is inconvenient and associated with osteoporosis. A reasonable approach in such patients is to restart warfarin at a low dose, eg, 2 mg under the coverage of therapeutic doses of heparin, and to increase the warfarin gradually over several weeks. This approach should avoid an abrupt fall in protein C levels before there is a reduction in the levels of factors II, IX, and X and has been shown to be free of recurrence of skin necrosis in a number of recent case reports (level V).

PREGNANCY

Oral anticoagulants cross the placenta and can produce a characteristic embryopathy, central nervous system abnormalities, or fetal bleeding.129 Warfarin should not be used in the first trimester of pregnancy, and if possible, it should also be avoided throughout the entire pregnancy. In some cases, however, eg, a mechanical heart valve treated with warfarin, where there is a high risk of embolism, and full dose heparin cannot be used, or where a temporary loss of therapeutic control would be life-threatening, a decision to continue warfarin throughout pregnancy could be justified. Heparin is preferred when anticoagulants are indicated in pregnancy. There is convincing evidence that warfarin does not induce an anticoagulant effect in the breast-fed infant when the drug is administered to a nursing mother.130,131

REVERSING THE ANTICOAGULANT EFFECT OF WARFARIN

Reduction or reversal of the anticoagulant effect of warfarin can be achieved by stopping treatment, by administering vitamin K, or by replacing the vitamin K-dependent coagulation factors with plasma or factor concentrates. When treatment with warfarin is stopped, there is a delay for two or more days before an effect on the INR is seen because warfarin has a half-life clearance of 36 to 42 h, and there is a delay before the newly synthesized functional (carboxylated) coagulation factors replace the dysfunctional coagulation factors. The administration of vitamin K lowers the INR much more rapidly depending on the dose of vitamin K used and the severity of the anticoagulant effect. With high doses of vitamin K, eg, 10 to 15 mg
by intravenously. reversal is rapid and clearly seen at 6 h, but patients often remain resistant to warfarin for up to a week, making continued treatment problematic. The problem of temporary warfarin resistance can be overcome by using much lower doses. Thus, a recent study of 31 subjects with a prolonged INR (level IV) reported that intravenous doses of vitamin K of 0.5 to 1 mg lowered INR levels of between 10.0 to 20.0 to ranges of 3.0 to 7.5 in 8 h and 1.5 to 5.0 in 24 h without interfering with continuing warfarin therapy. The vitamin K was given by slow intravenous injection.

Replacement of vitamin K-dependent coagulation factors with plasma or factor concentrates produces an immediate effect, although rapid replacement of coagulation factors by plasma is limited by the volume necessary.

**RECOMMENDATIONS**

1. If the INR is above the therapeutic range but below 6.0, the patient is not bleeding, and rapid reversal is not indicated for reasons of surgical intervention, then the next few doses can be omitted and warfarin commenced at a lower dose when the patient is in the therapeutic range.

2. If the INR is above 6.0 but below 10.0 and the patient is not bleeding, or more rapid reversal is required because the patient requires elective surgery, then vitamin K, intravenously in a dose of 0.5 to 1 mg can be given with the expectation that a demonstrable reduction of the INR will occur at 8 h, and many patients will be in the therapeutic range of 2.0 to 3.0 in 24 h. If the INR is still too high at 24 h, the dose of 0.5 mg can be repeated. Warfarin treatment can then be resumed at a lower dose.

3. If the INR is above 10.0 but below 20.0 and the patient is not bleeding, a higher dose of vitamin K of 3 to 5 mg intravenously should be given with the expectation that INR will be reduced substantially at 6 h. The INR should be checked every 6 to 12 h, and vitamin K can then be repeated if necessary.

4. If a rapid reversal of an anticoagulant effect is required because of serious bleeding or major warfarin overdose (eg, INR>20.0), vitamin K in a dose of 10 mg should be given by intravenous injection and the INR checked every 6 h. Vitamin K may have to be repeated every 12 h and supplemented with plasma transfusion or factor concentrate depending on the urgency of the situation.

5. In case of life-threatening bleeding or serious warfarin overdose, replacement with factor concentrates is indicated supplemented with intravenously given vitamin K, 10 mg, to be repeated as necessary depending on the INR.

6. If continued warfarin therapy is indicated after high doses of vitamin K administration, then heparin can be given until the effects of vitamin K have been reversed, and the patient becomes responsive to warfarin.

**REFERENCES**


O'Reilly RA, Trager WF. Stereoselective interaction of phenylbutazone with \( ^{14}C/^{14}C \) labelled racemates of warfarin in man [abstract]. Fed Proc 1978; 37:545


O'Reilly RA. Interaction of chronic daily warfarin therapy and rifampin. Ann Intern Med 1975; 83:506-08

Denbow CE, Fraser HS. Clinically significant hemorrhage due to warfarin-carbamazepine interaction. South Med J 1990; 83:981-85


Richards RK. Influence of fever upon the action of 3,3-methylene bis-(4-hydroxyanisal). Science 1943; 97:313-16


Weitkamp M, Aber R. Prolonged bleeding times and bleeding diathesis associated with moxaclactam administration. JAMA 1983; 249:69-71


Udall JA. Human sources and absorption of vitamin K in relation to anticoagulation. JAMA 1965; 149:125-29


69 Quick AJ. The prothrombin time in haemophilia and in obstructive jaundice. J Biol Chem 1935; 109:73-4
71 Hirsh J. Is the dose of warfarin prescribed by American physicians unnecessarily high? Arch Intern Med 1987; 147:769-71
72 Poller L. A simple nomogram for the derivation of international normalised ratios for the standardisation of prothrombin time. Thromb Haemost 1988; 60:18-20
77 Wright IS, Beck DF, Marple CD. Myocardial infarction and its treatment with anticoagulants: summary of findings in 1,031 cases. Lancet 1954; 1:92-5
121 Landefeld CS, Goldman L. Major bleeding in outpatients treated with warfarin: incidence and prediction by factors known at the start of outpatient therapy. Am J Med 1989; 87:144-52