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

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Abstract: Atrial Fibrillation, Aspirin, Anticoagulation; AMI = acute myocardial infarction; AF = atrial fibrillation; CABS = Coumadin Aspirin Reinfarction Study; CI = confidence interval; DVT = deep vein thrombosis; INR = international normalized ratio; IRP = international reference preparation; ISI = international sensitivity index; MI = myocardial infarction; PE = pulmonary embolism; PT = prothrombin time; SPAF = Stroke Prevention in Atrial Fibrillation; WHO = World Health Organization

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The optimal therapeutic range for oral anticoagulant therapy was reviewed by the Committee on Antithrombotic Therapy of the American College of Chest Physicians and the National Heart, Lung, and Blood Institute in 1986, 1989, 1992, 1995, and again in 1998. The validity of the recommendation made at the earlier conferences, that the intensity of warfarin treatment should be reduced for many indications, continues to be upheld. Thus, whenever a more intense international normalized ratio (INR) is compared directly in a randomized trial, with an INR of 2.0 to 3.0, the less intense INR is as effective and safer. The recommendations for the optimal therapeutic range for the various indications remains unchanged (Table 1).

A recommendation of an INR of 2.0 to 3.0 is made for most indications. The exceptions are some types of mechanical prosthetic heart valves (see chapter on Antithrombotic Therapy in Patients With Mechanical and Biological Prosthetic Heart Valves). In addition, certain patients with thrombosis and the antiphospholipid syndrome may require a higher targeted INR than 2.0 to 3.0. Results of studies in atrial fibrillation (AF) support the earlier findings that the effectiveness of warfarin is reduced when the INR falls to <2.0 and is essentially lost when the INR falls to <1.5.145,145a The Coumadin Aspirin Reinfarction Study (CARS)144 and recently reported CHAMP (combined hemotherapy and mortality prevention) study146 also showed that the addition of low-dose warfarin (mean INR 1.3 and 1.9, respectively) did not improve the efficacy of aspirin in the secondary prevention of acute myocardial infarction (AMI). In contrast, the Thrombosis Prevention Trial,119 a primary prevention study in men free of ischemic heart disease at entry, reported that warfarin is effective in reducing myocardial ischemic events (including fatal events) when used at a targeted INR of 1.3 to 1.8 (mean warfarin dose of 4.1 mg). The addition of low-dose aspirin to warfarin therapy resulted in a further small benefit but at a risk of increased bleeding.

In summary, the results of studies (1) do not support the use of fixed low-dose warfarin therapy for the treatment of patients with AMI or AF144,145, (2) indicate that the effectiveness of warfarin is reduced when the INR is <2.0144,145,145a, (3) indicate that adjusted-dose warfarin therapy produces some benefit at an INR of 1.3 to 2.0 when used for primary prevention, and that an INR of >1.5 confers some benefit in patients with AF, although the benefit is clearly less than that which occurs with an INR of >2.0145a, and (4) two studies evaluating the long-term treatment of deep vein thrombosis (DVT) reported that recurrences are prevented completely at an INR of 2.0 to 3.0147,148; the small number of events in the warfarin group occurred when the patients discontinued treatment. These findings suggest that it might be possible to lower the INR range to <2.0, a hypothesis that is being tested in a number of randomized trials.

Mechanism of Action of Coumarin Anticoagulant Drugs

Coumarins are vitamin K antagonists that 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 γ-carboxyglutamate on the N-terminal regions of vitamin K-dependent proteins (Fig 1).1–4 These coagulation factors (factors II, VII, IX, and X) require γ-carboxylation for their biological activity. Coumarins produce their anticoagulant effect by inhibiting the vitamin K conversion cycle, thereby causing hepatic production of partially carboxylated and decarboxylated proteins with reduced procoagulant activity.7,8 In addition to their anticoagulant effect, the vitamin K antagonists inhibit carboxylation of the regulatory anticoagulant proteins C and S and therefore have the potential to exert a procoagulant effect.

In the presence of calcium ions, carboxylation causes a conformational change in coagulation proteins9–11 that promotes binding to cofactors on phospholipid surfaces. The carboxylation reaction requires the reduced form of vitamin K (vitamin KH2), molecular oxygen, and carbon dioxide, and is linked to the oxidation of vitamin KH2 to vitamin K epoxide. Vitamin K epoxide is then recycled to vitamin KH2 through two reductase steps. The first, which is sensitive to vitamin K antagonists,1–3 reduces vitamin K epoxide to vitamin K1 (the natural food form of vitamin K1), while the second, which is relatively insensitive to vitamin K antagonists, reduces vitamin K1 to vitamin KH2. Treatment with vitamin K antagonists leads to the depletion of vitamin KH2, thereby limiting the γ-carboxylation of the vitamin K-dependent coagulant proteins. The effect of coumarins can be counteracted by vitamin K1 (either ingested in food or administered therapeutically) because the second reductase step is relatively insensitive to vitamin K antagonists (Fig 1). Patients treated with a large dose of vitamin K1 can also become warfarin resistant for...
up to a week because vitamin K₁ accumulates in the liver and is available to the coumarin-insensitive reductase.

Warfarin also interferes with the carboxylation of γ-carboxyglutamate proteins synthesized in bone. Although these effects contribute to fetal bone abnormalities in mothers treated with warfarin during pregnancy, there is no evidence that warfarin affects bone metabolism when administered to children or adults.

### Pharmacokinetics and Pharmacodynamics of Warfarin

Warfarin is a racemic mixture of two optically active isomers, the R and S forms in roughly equal proportion. It has high bioavailability, is rapidly absorbed from the GI tract, and reaches maximal blood concentrations in healthy volunteers in 90 min after oral administration. Racemic warfarin has a half-life of 36 to 42 h, circulates bound to plasma proteins (mainly albumin), and accumulates in the liver where the two isomers are metabolically transformed by different pathways. The dose-response relationship of warfarin is influenced by genetic and environmental factors, including a recently identified common mutation in the gene coding for one of the common cytochrome P450 enzymes (C59), the hepatic enzyme responsible for oxidative metabolism of the warfarin S-isomer. This mutation likely contributes to the variability in dose response to warfarin among healthy subjects. In addition to known and unknown genetic factors, various disease states, drugs, and dietary factors can interfere with the response to warfarin.

The anticoagulant response to warfarin is influenced by pharmacokinetic factors, including drug interactions that affect the absorption or metabolic clearance of warfarin, and pharmacodynamic factors that alter the hemostatic response to given concentrations of the drug. Variability in anticoagulant response also occurs as a result of inaccuracies in laboratory testing, patient noncompliance, and miscommunication between patient and physician. Other drugs may influence the pharmacokinetics of warfarin by reducing GI absorption or by disrupting its metabolic clearance. For example, the anticoagulant effect of warfarin is reduced by cholestyramine, which impairs its absorption, and is potentiated by drugs that inhibit warfarin clearance through stereoselective or nonelective pathways.

### Table 1—Recommended Therapeutic Range for Oral Anticoagulant Therapy

<table>
<thead>
<tr>
<th>Indications</th>
<th>INR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prophylaxis of venous thrombosis (high-risk surgery)</td>
<td></td>
</tr>
<tr>
<td>Treatment of venous thrombosis</td>
<td></td>
</tr>
<tr>
<td>Treatment of PE</td>
<td></td>
</tr>
<tr>
<td>Prevention of systemic embolism</td>
<td></td>
</tr>
<tr>
<td>Tissue heart valves</td>
<td>2.0–3.0</td>
</tr>
<tr>
<td>AMI (to prevent systemic embolism)*</td>
<td></td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td></td>
</tr>
<tr>
<td>AF</td>
<td></td>
</tr>
<tr>
<td>Mechanical prosthetic valves (high risk)</td>
<td>2.5–3.5</td>
</tr>
<tr>
<td>Bileaflet mechanical valve in aortic position</td>
<td>2.0–3.0</td>
</tr>
</tbody>
</table>

*If oral anticoagulant therapy is elected to prevent recurrent MI, an INR of 2.5 to 3.5 is recommended, consistent with US Food and Drug Administration recommendations.
the anticoagulant response to warfarin occurs in patients on weight-reduction diets consuming green vegetables or receiving vitamin K-containing supplements, and in patients treated with IV supplements containing vitamin K. Reduced dietary vitamin K intake potentiates the effect of warfarin in sick patients treated with antibiotics and IV fluids without vitamin K supplementation and in states of fat malabsorption. Hepatic dysfunction potentiates the response to warfarin through impaired synthesis of coagulation factors. Hypermetabolic states produced by fever or hyperthyroidism increase warfarin responsiveness, probably by increasing the catabolism of vitamin K-dependent coagulation factors. Drugs may influence the pharmacodynamics of warfarin by inhibiting synthesis or increasing clearance of vitamin K-dependent coagulation factors or by interfering with other pathways of hemostasis (Table 3). The anticoagulant effect of warfarin is augmented by the second-generation and third-generation cephalosporins, which inhibit the cyclic interconversion of vitamin K, by thyroxine, which increases the metabolism of coagulation factors, and by clofibrate, through an unknown mechanism. Doses of salicylates > 1.5 g/d also augment the anticoagulant effect of warfarin, possibly because these drugs have warfarin-like activity. Acetaminophen has also been reported to augment the anticoagulant effect of warfarin, although this contention has been challenged (see below). Although heparin potentiates the anticoagulant effect of warfarin, in therapeutic doses, it produces only slight prolongation of the PT.

Drugs such as aspirin, nonsteroidal anti-inflammatory drugs, high doses of penicillins, and moxolactam increase the risk of warfarin-associated bleeding by inhibiting platelet function. Of these, aspirin is the anticoagulant-sensitive - warfarin sensitive
2. K - reductase - relatively warfarin resistant

Figure 1. Warfarin and the vitamin K cycle
most important because of its widespread use and prolonged effect.\textsuperscript{59} Aspirin and nonsteroidal anti-inflammatory drugs can also produce gastric erosions that increase the risk of upper-GI bleeding.\textsuperscript{58} The risk of clinically important bleeding is heightened when high doses of aspirin are taken in combination with high-intensity warfarin therapy (INR, 3.0 to 4.5).\textsuperscript{55,60} In two studies, one study\textsuperscript{61} in patients with prosthetic heart valves and the other study\textsuperscript{62} in asymptomatic individuals at high risk of coronary artery disease, low doses of aspirin (100 mg/d and 75 mg/d, respectively) were also associated with increased rates of minor bleeding when combined with moderate-intensity and low-intensity warfarin anticoagulation.

Table 2—Enzyme-Inducing Drug Interactions With Warfarin\textsuperscript{a}

<table>
<thead>
<tr>
<th>Inducing Agents</th>
<th>Isoenzyme Induced\textsuperscript{a}</th>
<th>Expected Onset, d</th>
<th>Anticipated Dosage Adjustments, %</th>
<th>Expected Offset, d</th>
<th>Predictive Confidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>CYP3A4</td>
<td>10–35</td>
<td>[100]</td>
<td>42</td>
<td>+++</td>
</tr>
<tr>
<td>Barbiturate\textsuperscript{b}</td>
<td>CYP3A</td>
<td>7–30</td>
<td>[12.5–25]</td>
<td>&gt; 42</td>
<td>++++</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Nonspecific</td>
<td>NA</td>
<td>[]</td>
<td>NA</td>
<td>+</td>
</tr>
<tr>
<td>Rifampin</td>
<td>CYP3A4</td>
<td>&lt; 7</td>
<td>[100–200]</td>
<td>21</td>
<td>++++</td>
</tr>
<tr>
<td>Griseofulvin\textsuperscript{c}</td>
<td>?</td>
<td>60</td>
<td>[40]</td>
<td>NA</td>
<td>+++</td>
</tr>
<tr>
<td>Nafcillin</td>
<td>NA</td>
<td>&lt; 7</td>
<td>[100–400]</td>
<td>7–28</td>
<td>+++</td>
</tr>
<tr>
<td>Dicloxacillin</td>
<td>NA</td>
<td>&lt; 7</td>
<td>[2–30]</td>
<td>NA</td>
<td>+++</td>
</tr>
<tr>
<td>Aminoglycosidem\textsuperscript{d}</td>
<td>CYP2B1</td>
<td>14</td>
<td>[50–75]</td>
<td>14</td>
<td>+++</td>
</tr>
<tr>
<td>Smoking</td>
<td>CYP1A1,1A2</td>
<td>NA</td>
<td>[']</td>
<td>NA</td>
<td>+++</td>
</tr>
<tr>
<td>Alcohol</td>
<td>CYP2E1</td>
<td>NA</td>
<td>[‘]</td>
<td>NA</td>
<td>+++</td>
</tr>
</tbody>
</table>

\textsuperscript{a}[ = an increase in warfarin dosage is anticipated with initiation of the inducing agent; \ = a decrease in warfarin dosage is anticipated with initiation of the inducing agent; ] = no change in warfarin dosage appears necessary based on available data; NA = not available.

\textsuperscript{b}Class effect, although time course and extent may vary with the individual barbiturate.

\textsuperscript{c}Interaction is more likely with the ultramicroncrystalline formulation of griseofulvin.

\textsuperscript{d}Dose-response relationship, so that 250 mg 4 times/day showed greater induction than 125 mg 4 times/day.

\textsuperscript{e}Warfarin clearance increased, but a corresponding change in PT was not reported. See text for further details.

\textsuperscript{f}Represents ingestion of 41–54 g of ethanol consumed either as a single dose or daily for 21 days.

\textsuperscript{g}Represents ingestion of large amounts of ethanol (250 g) consumed daily for more than 3 months.

most important because of its widespread use and prolonged effect.\textsuperscript{59} Aspirin and nonsteroidal anti-inflammatory drugs can also produce gastric erosions that increase the risk of upper-GI bleeding.\textsuperscript{58} The risk of clinically important bleeding is heightened when high doses of aspirin are taken in combination with high-intensity warfarin therapy (INR, 3.0 to 4.5).\textsuperscript{55,60} In two studies, one study\textsuperscript{61} in patients with prosthetic heart valves and the other study\textsuperscript{62} in asymptomatic individuals at high risk of coronary artery disease, low doses of aspirin (100 mg/d and 75 mg/d, respectively) were also associated with increased rates of minor bleeding when combined with moderate-intensity and low-intensity warfarin anticoagulation.

Table 3—Drug and Food Interactions With Warfarin and Direction of Interaction

<table>
<thead>
<tr>
<th>Type of Study</th>
<th>Potentiation</th>
<th>Inhibition</th>
<th>No Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized controlled trials</td>
<td>Alcohol (if concomitant liver disease) amiodarone, anabolic steroids, cimetidine,† clofibrate, cotrimoxazole, erythromycin, fluconazole, isoniazid (600 mg/d), metronidazole, micronazole, omeprazole, phenylbutazone, piroxicam, propafenone, propranolol, sulfipyrazole (biphasic with later inhibition)*</td>
<td>Barbiturates, carbamazepine, chlordiazepoxide, cholestyramine, griseofulvin, nafcillin, rifampin, sucralfate, high vitamin K content foods/enteral feeds, large amounts of avocado</td>
<td>Alcohol, antacids, atenolol, bumetanide, enoxacin, famotidine, fluoxetine, ketorolac, metoprolol, naproxen, nizatidine, pyyllium, ranitidine†</td>
</tr>
<tr>
<td>Randomized controlled trials</td>
<td>Acetaminophen, chloral hydrate, ciprofloxacin, dextropropoxyphene, disulfiram, itraconazole, quinidine, phenytoin (biphasic with later inhibition), tannoxifen, tetracycline, flu vaccine</td>
<td>Dicloxacillin</td>
<td>Ibuprofen, ketoconazole</td>
</tr>
<tr>
<td>Observational studies</td>
<td>Acetylsalicylic acid, disopyramide, fluorouracil, ifosfamide, ketoprofen, levocetabin, metotazalone, miconorinic, nalidixic acid, nortoxacin, ofloxacin, propoxyphene, sulindac, tolmetin, topical salicylates</td>
<td>Azathioprine, cyclosporine, etretinate, trazodone</td>
<td>Diltiazem, tobacco, vancomycin</td>
</tr>
<tr>
<td>Observational studies</td>
<td>Cefamandole, cefazolin, genfibrozil, heparin, indomethacin, sulfisoxazole</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{a}Has supporting level 1 evidence from both patients and volunteers.

\textsuperscript{†}In a small number of volunteer subjects, an inhibitory drug interaction occurred.

\textsuperscript{f}Randomized, controlled trial evidence of potentiation in patients.
The mechanisms by which erythromycin and some anabolic steroids potentiate the anticoagulant effect of warfarin are unknown. Sulfonamides and several broad-spectrum antibiotic compounds may augment the anticoagulant effect of warfarin by eliminating bacterial flora and aggravating vitamin K deficiency in patients whose diet is deficient of vitamin K.

Wells and associates performed a critical analysis of articles reporting possible interaction between drugs or foods and warfarin. Studies were assigned to one category if the interaction was considered highly probable, to a second category if interaction was probable, to a third level if judged possible, and to a fourth level if doubtful. Of 751 citations retrieved, pertinent results from 172 original articles are summarized in Table 3. Strong evidence of interaction was found for 39 of the 81 different drugs and foods appraised; 17 potentiate warfarin effect, 10 inhibit, and 12 produce no effect. Many other drugs have been reported to either interact with oral anticoagulants or alter the PT response to warfarin, but convincing evidence of a causal association is lacking. In a case-control study, low to moderate doses of acetaminophen (nine or more tablets per week) were reported to be associated with excessively prolonged INR values. The presence of a causal association between acetaminophen use and potentiation of a warfarin effect is uncertain. The article was supported by an editorial, but has been challenged by personal experiences (case series) cited in two letters and by the results of a prospective study in normal volunteers. However, until more information is presented, it would be prudent to monitor the INR more frequently when acetaminophen is used in this quantity by patients during warfarin therapy. Indeed, it would be reasonable to monitor the PT more frequently when any drug therapy is added or withdrawn from the regimen of a patient treated with an oral anticoagulant.

The Antithrombotic Effect of Warfarin

The antithrombotic effect of warfarin is conventionally viewed as being a consequence of the reduction of all four vitamin K-dependent coagulation factors. However, there is evidence that the anticoagulant effect and the antithrombotic effect of warfarin is dissociated during the induction phase of treatment. Using a stasis model of thrombosis in rabbits, Wessler and Getell reported that the antithrombotic effect of warfarin requires 6 days of treatment, whereas an anticoagulant effect was observed after 2 days. This finding suggests that during the induction phase of warfarin treatment, the reduction of clotting factor(s) responsible for prolonging the PT in the first 2 days are less important for the antithrombotic effect of warfarin than those that are reduced after 4 days or 5 days. More recent evidence supports this notion and suggests that reduction of prothrombin (a zymogen with a relatively long half-life of about 96 h) is more important for the antithrombotic effect of warfarin than reduction of factors VII and IX zymogens with half-lives of 6 to 24 h, respectively. Thus, experiments in a rabbit model of tissue factor-induced intravascular coagulation demonstrated that the protective effect of warfarin was overcome with the infusion of factor II, and to a lesser extent factor X, while infusion of factors VII or IX had no effect. Support for the importance of reduction of prothrombin (factor II) for the antithrombotic effect of warfarin also comes from the studies of Patel and associates. Using fibrinopeptide A as an index of clot-associated thrombin activity, they demonstrated that clots formed from plasma with reduced prothrombin concentrations generated significantly less fibrinopeptide A than clots formed in the presence of normal concentrations of prothrombin, presumably because reduction in prothrombin levels decreases the amount of thrombin generated and bound to fibrin, thereby reducing the thrombogenicity of the clot. The concept that the antithrombotic effect of warfarin reflects its ability to lower prothrombin levels is important clinically. This is the basis for overlapping heparin with warfarin during treatment of patients with thrombosis, until the PT INR has been prolonged into the therapeutic range for at least 4 days. Further, the levels of native prothrombin antigen during warfarin therapy have been reported to more closely reflect antithrombotic activity than the PT. These considerations also support the use of a maintenance dose of warfarin (approximately 5 mg), rather than a loading dose, during initiation of therapy, since the rate of reduction of prothrombin levels is similar with either a 5-ng or a 10-ng initial warfarin dose. In contrast, the anticoagulant protein C is reduced more rapidly and more patients have excessive anticoagulation (INR > 3.0) with the 10-mg loading dose.

Monitoring Oral Anticoagulant Therapy

The PT test is the most common method for monitoring oral anticoagulant therapy. The PT responds to reduction of three of the four vitamin K-dependent procoagulant clotting factors (II, VII, and X). During the first few days of warfarin therapy, the prolongation of the PT reflects mainly a reduction of factor VII, while subsequently it also reflects a reduction of factors X and II. The PT assay is performed by adding calcium and thromboplastin to citrated plasma. The term thromboplastin traditionally refers to a phospholipid-protein extract of tissue, usually lung, brain, or placenta, containing both the tissue factor and phospholipid necessary to promote the activation of factor X by factor VII. Thromboplastins vary in their responsiveness to the anticoagulant effects of warfarin, depending on their source, phospholipid content, and preparation. The responsiveness of a given thromboplastin to warfarin-induced changes in clotting factors reflects the intensity of activation of factor X by the factor VIIa/tissue factor complex. An unresponsive thromboplastin produces less prolongation of the PT for a given reduction in vitamin K-dependent clotting factors than a responsive thromboplastin. The responsiveness of a thromboplastin can be measured by assessing its International Sensitivity Index (ISI; see below). Highly sensitive thromboplastins (ISI approximately 1.0) composed of human tissue factor and defined phospholipid preparations are now available.

In the past, PT monitoring of warfarin treatment was imprecise because the PT was expressed in seconds or as
a simple ratio of the patient over the normal control value. During the 1980s, most laboratories in the United States used insensitive thromboplastins with ISI values between 1.8 and 2.8, while many in Europe used more responsive reagents with ISI values of 1.0 to 1.4. Difference in thromboplastin responsiveness was the main reason for clinically important differences in oral anticoagulant dosing in different countries shown by Poller and Taberner.\textsuperscript{82} Recognition of the clinical importance of these differences led to the wide adoption of the INR standard for monitoring oral anticoagulant therapy.

The history of standardization of the PT has been reviewed by Poller\textsuperscript{80} and by Kirkwood.\textsuperscript{83} In 1992, the ISI of thromboplastins used in the United States varied between 1.4 and 2.8.\textsuperscript{84} Subsequently, more responsive thromboplastins with lower ISI values came into use in the United States and Canada. The recombinant human preparations consisting of repurposed synthetic tissue factor, for example, have ISI values of 0.9 to 1.0.\textsuperscript{85} The World Health Organization (WHO) designated a batch of human brain thromboplastin as the first International Reference Preparation (IRP) for thromboplastin in 1977.\textsuperscript{80,83} Subsequently, this first IRP was replaced with primary- and secondary-reference thromboplastins. Calibration was based on a linear relationship between the logarithm of the PT measured by the reference and test thromboplastin reagents.\textsuperscript{80,83,86} This calibration model, adopted in 1982, is now used to standardize reporting by converting the PT ratio measured with the local thromboplastin into an INR, calculated as follows:

\[ \text{INR} = \left( \frac{\text{patient PT}}{\text{mean normal PT}} \right)^{\text{ISI}} \]

or

\[ \log \text{INR} = \text{ISI} \times \log \text{-observed PT ratio} \]

where ISI denotes the ISI of the thromboplastin used to perform the PT measurement at the local laboratory. The ISI reflects the responsiveness of a given thromboplastin to reduction of the vitamin K-dependent coagulation factors compared to the primary WHO IRP, the more responsive the reagent, the lower the ISI value. Viewed another way, the INR is the PT ratio that would be obtained if the WHO IRP had been used to perform the PT test on the same sample with the manual PT technique.\textsuperscript{80,83}

An up-to-date classification of the current thromboplastin IRP and details of their application in ISI calibration have been described in the recent revision of the WHO guidelines.\textsuperscript{87} Recommended procedures for ISI calibration of reference and commercial batches of thromboplastin are provided.

The revised WHO guidelines\textsuperscript{87} describe three levels of ISI calibration. The most accurate is the international multicentre calibration of thromboplastin IRP by at least 10 centers against the three species of WHO IRP (human, rabbit, and bovine). The ISI assigned is the mean of these, as the three different routes of calibration give different INRs. The second is the calibration of secondary standards against the relevant species of IRP by at least two laboratories. The third level, where the least precision is needed, is calibration of individual reagents and batch-to-batch testing by a manufacturer. For this step, pooled coumarin or artificially depleted plasmas are also allowed. With each successive step, there is a serial error so that the chain of calibrant reagents should be as short as possible.

Most commercial manufacturers now provide ISI values for thromboplastin reagents, and the INR standard has been widely adopted by hospitals in North America. Recently, thromboplastins with recombinant tissue factor have been introduced with ISI values close to 1.0 that yield PT ratios virtually equivalent to the INR. According to the College of American Pathologists Comprehensive Coagulation Survey, implementation of the INR standard in the United States increased between 1991 and 1997 from 21 to 97%.\textsuperscript{88} Although the adoption of the INR standard of reporting has markedly increased the reliability of warfarin monitoring, the system is not perfect. Problems identified with the INR system are listed in Table 4. They were discussed in detail in the last supplement, and the most clinically relevant are reviewed below.

The INR is based on ISI values derived from plasma of patients receiving stable doses of anticoagulant for at least 6 weeks.\textsuperscript{89} As a result, the INR is less reliable early in the course of warfarin therapy, particularly when results are obtained from different laboratories. Even under these conditions, however, the INR is more reliable than the uncorrected PT ratio\textsuperscript{89} and is thus recommended during both initiation and maintenance of warfarin treatment. Although its accuracy in patients with liver disease has been questioned, the reliability of the INR exceeds alternatives such as the PT ratio or the PT itself and is valid in this situation as well.\textsuperscript{91}

Although, from a theoretic viewpoint, the precision of the INR could be improved by using reagents with low ISI values, laboratory proficiency studies indicate that this produces only modest improvement in precision,\textsuperscript{88,92–94} but use of reagents with higher ISI values results in higher coefficients of interlaboratory variation for the INR measurement.\textsuperscript{95–96} The precision of INR measurement is also influenced by instrumentation. The INR is based on a mathematical relationship between the PT ratio obtained with test thromboplastin and the IRP using a manual method of clot detection. Thus the automated clot detectors now used in most laboratories introduces another variable that affects the accuracy of the INR.\textsuperscript{97–102} A

<table>
<thead>
<tr>
<th>Table 4—Potential Problems With the INR</th>
</tr>
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<tbody>
<tr>
<td>1. Lack of reliability of the INR system when used at the onset of warfarin therapy and for screening for a coagulopathy in patients with liver disease.</td>
</tr>
<tr>
<td>2. Relationship between precision of the INR determination and reagent ISI.</td>
</tr>
<tr>
<td>3. Effect of instrumentation in ISI values.</td>
</tr>
<tr>
<td>4. Lack of reliability of the ISI result provided by the manufacturer.</td>
</tr>
<tr>
<td>5. Incorrect calculation of the INR resulting from the use of inappropriate control plasma.</td>
</tr>
<tr>
<td>6. Problems with citrate concentration and interference with lupus anticoagulant with thromboplastins with low ISI values.</td>
</tr>
</tbody>
</table>
system ISI for an instrument/thromboplastin combination may reduce the error but is not dependable. Variability of ISI determination is reduced by calibrating the instrument with lyophilized plasma depleted of vitamin K-dependent clotting factors. Based on these observations, the College of American Pathologists has recommended that laboratories use reagent/instrument combinations for which the ISI has been established. For reliable INR, local ISI calibration is required. As conventional WHO-type ISI calibration is not usually feasible at local centers due to the requirement for parallel PT testing and the need for a thromboplastin IRP, a simpler method of ISI determination is required. The use of certified lyophilized plasmas with manual PT values with the thromboplastin IRP to derive ISI has been shown to give good correction for coagulometer effects in several recent national and international field studies. Some such procedure for verifying local INR is also desirable in clinical trials of anticoagulation to validate the stated values.

The mean normal plasma PT is not interchangeable with a laboratory control PT. The mean normal PT is determined with fresh plasma samples from at least 20 healthy individuals of both genders over a range of ages and should be checked with each new batch of thromboplastin with the same instrument used to assay the PT. Several investigators have noted incorrect ISI values provided by manufacturers of thromboplastin reagents. Although local calibrations can be performed with plasma samples with certified PT values to determine the instrument-specific ISI, the process is tedious and beyond the scope of many laboratories.

A simple ISI calibration procedure using lyophilized plasma calibrants with certified manual PT with reference IRP has been developed and one type recently has received US Food and Drug Administration approval as showing substantial equivalence to the WHO method. The ISI calculation has also been simplified by the use of a computer calibration disk available at token cost from the Health Technology Unit, WHO 1211, Geneva 27, Switzerland.

The lupus anticoagulants prolong the activated partial thromboplastin time, but usually cause only slight prolongation of the PT depending on the reagent. The optimum method for monitoring anticoagulation in patients with lupus anticoagulants is uncertain, but the prothrombin and proconvertin tests and measurements of prothrombin activity or native prothrombin concentration have been proposed.

**Clinical Applications of Oral Anticoagulant Therapy**

The clinical effectiveness of oral anticoagulants has been established in a variety of conditions, based on well-designed clinical trials. Oral anticoagulants are effective for primary and secondary prevention of venous thromboembolism, for prevention of systemic embolism in patients with tissue or mechanical prosthetic heart valves or AF, for prevention of AMI in patients with peripheral arterial disease, for prevention of stroke, recurrent infarction, or death in patients with AMI, and for prevention of myocardial infarction (MI) in men at high risk. Although effectiveness has not been proven by a randomized trial, oral anticoagulants are indicated for prevention of systemic embolism in high-risk patients with mitral stenosis. For most indications, a moderate anticoagulant effect (INR, 2.0 to 3.0) is appropriate (Table 5).

Although anticoagulants are sometimes used for secondary prevention of cerebral ischemia of presumed arterial origin when antiplatelet agents have failed, this practice has never been shown to be effective and the Stroke Prevention in Reversible Ischemia Trial found high-intensity oral anticoagulation (INR, 3.0 to 4.5) dangerous in such cases. Patients in that study who had experienced transient ischemic attack or minor ischemic stroke were randomly assigned to treatment with oral anticoagulation (INR, 3.0 to 4.5) or aspirin, 30 mg/d. The primary measure of outcome was the constellation of death from vascular causes, stroke, MI, or major bleeding. The trial was stopped at the first interim analysis of 1,316 patients with a mean follow-up of 14 months because of excess primary outcome events in the anticoagulated group (hazard ratio, 2.3; 95% confidence interval [CI], 1.6 to 3.5).

### Table 5—Relationship Between Bleeding and Intensity of Anticoagulant Therapy

<table>
<thead>
<tr>
<th>Source, yr</th>
<th>Patients, No.</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 (DVT)</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>Turpie et al, 1988 (Prosthetic Heart Valves [Tissue])</td>
<td>210</td>
<td>3 mo</td>
<td>2.0–2.5</td>
<td>4.3</td>
<td>vs</td>
</tr>
<tr>
<td>Saour et al, 1990 (Prosthetic Heart Valves [Mechanical])</td>
<td>247</td>
<td>3.47 yr</td>
<td>2.0–2.5</td>
<td>5.9</td>
<td>vs</td>
</tr>
<tr>
<td>Altman et al, 1991* (Prosthetic Heart Valves [Mechanical])</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>
</tbody>
</table>

*Patients also given aspirin, 300 mg, and dipyridamole, 75 mg bid.
There were 53 major bleeding complications (27 intracranial, 17 fatal) during anticoagulant therapy vs 6 during aspirin therapy (3 intracranial, 1 fatal).

**Prevention of Venous Thromboembolism**

Oral anticoagulants are effective for prevention of venous thrombosis after hip surgery, and major gynecologic surgery when given at a dose sufficient to maintain INR between 2.0 and 3.0. The risk of clinically important bleeding at this intensity is small. A very low fixed dose of warfarin (1 mg/d) was effective in a study in which subclavian vein thrombosis was prevented in patients with malignancy and indwelling catheters. In contrast, four randomized trials found this dose of warfarin ineffective for preventing postoperative venous thrombosis in patients undergoing major orthopedic surgery. Levine and associates reported that warfarin, 1 mg/d for 6 weeks, followed by adjustment to a targeted INR of 1.5, prevented thrombosis in patients with stage IV breast cancer receiving chemotherapy.

**Treatment of DVT**

The optimum duration of oral anticoagulant therapy is influenced by whether thrombosis is unprovoked (idiopathic), associated with ongoing risk factors (such as malignancy), or is secondary to a reversible cause; a longer course of therapy should be given for idiopathic thrombosis and when there is an ongoing risk factor. Treatment should also be longer in patients with proximal vein thrombosis than in those with distal thrombosis and in patients with recurrent thrombosis vs those with a single episode. Laboratory evidence of thrombophilia may warrant a longer duration of anticoagulant therapy. Oral anticoagulant therapy is indicated for at least 3 months in patients with proximal DVT, or in patients with acute pulmonary embolism (PE) for at least 6 months in those with idiopathic proximal vein thrombosis or recurrent venous thrombosis, and for 6 to 12 weeks in patients with symptomatic calf vein thrombosis. Indefinite anticoagulant therapy is indicated in patients with more than one episode of idiopathic proximal vein thrombosis or PE, thrombosis complicating malignancy, or idiopathic venous thrombosis associated with homozygous factor V Leiden genotype, the antiphospholipid antibody syndrome, or deficiencies of antithrombin, protein C, or protein S. Prospective cohort studies indicate that in patients with idiopathic venous thrombosis, neither heterozygous factor V Leiden nor the G20210A prothrombin gene mutation increases the risk of recurrence. Moderate-intensity anticoagulation (INR, 2.0 to 3.0) is as effective as a more intense regimen (INR, 3.0 to 4.5) but associated with less bleeding (Table 5). Randomized trials evaluating short vs long courses of warfarin therapy have demonstrated that oral anticoagulants effectively prevent recurrent venous thrombosis (risk reduction > 90%), that treatment for 6 months is more effective than for 6 weeks, and that treatment for 2 years is more effective than for 3 months.

**Primary Prevention of Ischemic Coronary Events**

The Thrombosis Prevention Trial evaluated warfarin (target INR, 1.3 to 1.8), aspirin (75 mg/d), both, or neither in 5,499 men aged 45 to 69 years at risk of a first MI. The primary outcome consisted of acute ischemic coronary events defined as coronary death or nonfatal MI. Although the anticoagulant intensity was low, the mean warfarin dose was 4.1 mg/d. The annual incidence of coronary events was 1.4%/yr in the placebo group. The combination of warfarin and aspirin reduced the relative risk by 34% (p = 0.006); however, when administered separately, neither warfarin nor aspirin produced a significant reduction in acute ischemic events (although they both showed a similar trend), and the efficacy of these treatments was similar to one another (relative risk reductions of 22% and 23%, respectively). The combined treatment, though most effective, was associated with a small but significant increase in hemorrhagic stroke. The importance of these results is that in the primary prevention setting, they show that targeting an INR of 1.3 to 1.8 is about as effective as aspirin for prevention of acute ischemic events, and that the combination of low-intensity warfarin plus aspirin is more effective than either agent alone at the price of a small increase in bleeding.

The effectiveness of the combination of low-intensity warfarin plus aspirin in the Thrombosis Prevention Trial contrasts with the results of the CARS and Stroke Prevention in Atrial Fibrillation (SPAF)-III studies, in which this type of combination therapy (for different indications) was ineffective. In the Thrombosis Prevention Trial, the dose of warfarin was adjusted between 0.5 mg/d and 12.5 mg/d, whereas in the CARS and SPAF-III studies, warfarin was given in fixed doses. Thus, if low-intensity warfarin is to be evaluated further for any indication, the marked dose-response variability mandates that dose be adjusted to the required INR (1.5).

**AMI**

The role of coumarins in AMI has been the subject of intense controversy almost from the time that they were introduced into clinical practice. Coumarins have been evaluated in AMI using different levels of intensity and either used alone or in combination with aspirin. The results have been summarized in a recent meta-analysis that stratified the studies by intensity of anticoagulation and use of aspirin to yield five categories (Tables 6, 7): (1) high-intensity INR (approximately 2.8 to 4.8) vs control treatment; (2) moderate-intensity INR (approximately 2.0 to 3.0) vs control treatment; (3) moderate-intensity INR plus aspirin vs aspirin; (4) moderate- to high-intensity INR vs aspirin; and (5) low-intensity (low fixed dose) plus aspirin vs aspirin.

There were a total of 44 trials on 24,115 patients identified. The largest number of patients (n = 10,056) were enrolled in studies comparing high-intensity oral anticoagulants with control treatment. Substantial numbers (n = 5,435) were also enrolled in studies of low-fixed-dose warfarin plus aspirin vs aspirin and in studies of moderate- to high-intensity oral anticoagulants vs aspirin.
Conclusions from these trials are as follows: (1) high-intensity oral anticoagulants are more effective than control treatment, but at a substantially increased risk of major bleeding; (2) low-fixed-dose unmonitored warfarin plus aspirin is no more effective than aspirin, but produces a small increase in major bleeding; and (3) treatment with moderate- to high-intensity oral anticoagulants is only moderately (not significantly) more effective than aspirin but causes more bleeding. Although the number of patients studied is small (n = 480), moderate-intensity warfarin plus aspirin appears to be substantially better than aspirin alone, with only a marginal (nonsignificant) increase in major bleeding. These promising results with the combination of moderate-intensity warfarin and aspirin should be confirmed in a much larger sample of patients with AMI.

PROSTHETIC HEART VALVES

The most convincing evidence that oral anticoagulants are effective in patients with prosthetic heart valves comes from a study of patients treated with warfarin for 6 months who were randomized to receive warfarin of uncertain intensity vs either of two aspirin-containing platelet-inhibitor drug regimens.147 The incidence of thromboembolic complications in the group who continued warfarin therapy was significantly lower than in the groups that received either of the two antiplatelet drug regimens (relative risk reduction, 60 to 79%). The incidence of bleeding was significantly lower than in the groups that received either of the two antiplatelet drug regimens (relative risk reduction, 60 to 79%).

Table 6—Risk Benefit per Thousand Patients With AMI Treated With Oral Anticoagulants*

<table>
<thead>
<tr>
<th>Intensity of INR</th>
<th>Trials, No. (No. of Patients)</th>
<th>Events Prevented,† No.</th>
<th>p Value</th>
<th>Major Bleeds Caused, No.</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>High vs control</td>
<td>16 (10,056)</td>
<td>98</td>
<td>0</td>
<td>39</td>
<td>0</td>
</tr>
<tr>
<td>Moderate vs control</td>
<td>4 (1,365)</td>
<td>24</td>
<td>&gt;0.10</td>
<td>35</td>
<td>0</td>
</tr>
<tr>
<td>Moderate to high vs aspirin</td>
<td>7 (3,457)</td>
<td>13</td>
<td>&gt;0.10</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Moderate + aspirin vs aspirin</td>
<td>3 (480)</td>
<td>54</td>
<td>0.01</td>
<td>16</td>
<td>&gt;0.01</td>
</tr>
<tr>
<td>Low + aspirin vs aspirin</td>
<td>3 (8,435)</td>
<td>7</td>
<td>&lt;0.01</td>
<td>5</td>
<td>0.05</td>
</tr>
</tbody>
</table>

*Forty-four trials on 24,115 patients. Adapted from Anand and Yusuf.146
†Combination of death, MI, or stroke.

which included patients with mechanical prosthetic heart valves, compared a very high-intensity regimen (estimated INR, 7.4 to 10.8) with a lower-intensity regimen (estimated INR, 1.9 to 3.6) and found no difference in effectiveness but significantly more bleeding with the higher-intensity regimen. A third study150 of patients with mechanical prosthetic valves treated with aspirin and dipyridamole compared moderate-intensity (INR, 2.0 to 3.0) and high-intensity (INR, 3.0 to 4.5) warfarin regimens and found no difference in efficacy but significantly more bleeding with the high-intensity regimen. A more recent randomized trial61 showed that addition of aspirin, 100 mg/d, to warfarin (INR, 3.0 to 4.5) improved efficacy compared to warfarin (INR, 3.0 to 4.5) plus placebo. This combination of low-dose aspirin and high-intensity warfarin therapy was associated with a statistically and clinically significant reduction in all-cause mortality, cardiovascular mortality, and stroke. This benefit occurred at the expense of increased minor bleeding and a nonsignificant trend for an increase in major bleeding.

In a retrospective study of 16,081 patients with mechanical heart valves attending four regional anticoagulation clinics in The Netherlands with a target range of 3.6 to 4.8, Cannegieter and associates151 reported that the incidence of embolic events rose sharply when INR fell to < 2.5, while bleeding increased when INR rose to > 5.0.

Guidelines developed by the European Society of Cardiology152 called for anticoagulant intensity in proportion to the thromboembolic risk associated with specific types of prosthetic heart valves. For first-generation valves, an INR of 3.0 to 4.5 was recommended, an INR of 3.0 to 3.5 was considered sensible for second-generation valves in the mitral position, and an INR of 2.5 to 3.0 was deemed sufficient for second-generation valves in the aortic posi-

Table 7—Efficacy and Safety of Oral Anticoagulants in AMI*

<table>
<thead>
<tr>
<th>Intensity of INR</th>
<th>Trials, No. (No. of Patients)</th>
<th>Death, MI, or Stroke Odds Ratio (95% CI)</th>
<th>p Value</th>
<th>Bleeding Fold Increase (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>High vs control</td>
<td>16 (10,056)</td>
<td>0.57 (0.51–0.63)</td>
<td>0</td>
<td>6.0 (4.4–8.2)</td>
<td>0</td>
</tr>
<tr>
<td>Moderate vs control</td>
<td>4 (1,365)</td>
<td>0.85 (0.90–1.34)</td>
<td>&gt;0.10</td>
<td>7.7 (3.3–18)</td>
<td>0</td>
</tr>
<tr>
<td>Moderate to high vs aspirin</td>
<td>7 (3,457)</td>
<td>0.88 (0.63–1.24)</td>
<td>&gt;0.10</td>
<td>2.4 (1.6–3.6)</td>
<td>0</td>
</tr>
<tr>
<td>Moderate + aspirin vs aspirin</td>
<td>3 (480)</td>
<td>0.44 (0.23–0.83)</td>
<td>0.01</td>
<td>1.9 (0.6–6.0)</td>
<td>&gt;0.10</td>
</tr>
<tr>
<td>Low + aspirin vs aspirin</td>
<td>3 (8,435)</td>
<td>0.91 (0.79–1.06)</td>
<td>&gt;0.10</td>
<td>1.3 (0.96–1.75)</td>
<td>0.09</td>
</tr>
</tbody>
</table>

*Forty-four trials on 24,115 patients. Adapted from Anand and Yusuf.146

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tion. The American College of Chest Physicians 1998 guidelines recommended an INR of 2.5 to 3.5 for most patients with mechanical prosthetic valves, and 2.0 to 3.0 for those with bioprosthetic valves and low-risk patients with bileaflet mechanical valves (such as the St. Jude Medical device) in the aortic position.

**Atrial Fibrillation**

Five trials with relatively similar study designs have addressed anticoagulant therapy for primary prevention of ischemic stroke in patients with nonvalvular (nonhemorrhagic) AF. The SPAF study, 153 the Boston Area Anticoagulation Trial for Atrial Fibrillation, 154 and the Stroke Prevention in Nonhemorrhagic Atrial Fibrillation Trial 155 were carried out in the United States; the Atrial Fibrillation, Aspirin, Anticoagulation (AFASAK) study was carried out in Denmark 156; the Canadian Atrial Fibrillation Anticoagulation study 157 was stopped before completion because of convincing results in three of the other trials. 158 In the AFASAK and SPAF trials, patients were also randomized to aspirin therapy. Eligibility required that patients be acceptable candidates for anticoagulant therapy. The results of all five studies were similar; pooled analysis on an intention-to-treat basis showed a 69% risk reduction and > 80% risk reduction in patients who remained on treatment with warfarin (efficacy analysis). 159 There was little difference between rates of major or intracranial hemorrhage in the warfarin and control groups, but minor bleeding was approximately 3%/yr more frequent in the warfarin-assigned groups. 160 Pooled results from two studies were consistent with a smaller benefit from aspirin. In the AFASAK study, 75 mg/d did not significantly reduce thromboembolism, while in the SPAF trial, 325 mg/d was associated with a 44% stroke risk reduction in younger patients.

A secondary prevention trial in Europe 161 compared anticoagulant therapy, aspirin, and placebo in patients with AF who had sustained nondisabling stroke or transient ischemic attack within 3 months. Compared to placebo, there was a 68% reduction in stroke with warfarin and an insignificant 16% stroke risk reduction with aspirin. None of the patients in the anticoagulant group suffered intracranial hemorrhage.

The SPAF-II 162 trial compared the efficacy and safety of warfarin with aspirin in patients with AF. Warfarin was more effective than aspirin for preventing ischemic stroke, but this difference was almost entirely offset by a higher rate of intracranial hemorrhage with warfarin, particularly among patients > 75 years old, in whom the rate of intracranial hemorrhage was 1.8%/yr. The intensity of anticoagulation was greater in the SPAF trials than in most of the other primary prevention studies; in addition, the majority of intracranial hemorrhages during these trials occurred when estimated INR was > 3.0. In the SPAF III study, 145 warfarin (INR, 2.0 to 3.0) was much more effective than a fixed-dose combination of warfarin (1 to 3 mg/d; INR, 1.2 to 1.5) plus aspirin (325 mg/d) in high-risk patients with AF, while aspirin alone was sufficient for patients at low intrinsic risk of thromboembolism.

**OTHER INDICATIONS FOR ORAL ANTICOAGULANT THERAPY**

There are other widely accepted indications for oral anticoagulant therapy that have not been evaluated in properly designed clinical trials. These indications include patients with valvular heart disease associated with AF and certain patients with mitral stenosis, and patients who have sustained one or more episodes of systemic thromboembolism of unknown etiology. For both of these indications, a moderate-dose regimen (INR, 2.0 to 3.0) is recommended. Anticoagulants are not presently indicated in patients with ischemic cerebrovascular disease, but this issue is presently under investigation. 163

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144a The Veterans Administration Cooperative Study Program Trial. Combination, hemotherapy and mortality prevention (CHAMP) rates of major hemorrhage. Poster presented at: 39th Annual Scientific Session of the American College of Cardiology. Anaheim, CA, March 12–17, 2000


155 Deleted in proof.


