AHA/ACC Scientific Statement

American Heart Association/American College of Cardiology Foundation Guide to Warfarin Therapy

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Pharmacology of Warfarin

Mechanism of Action of Coumarin Anticoagulant Drugs

Warfarin, a coumarin derivative, produces an 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 carboxylation of glutamate residues to γ-carboxyglutamates (Gla) on the N-terminal regions of vitamin K–dependent proteins (Figure 1) (1–6). These proteins, which include the coagulation factors II, VII, IX, and X, require γ-carboxylation by vitamin K for biological activity. By inhibiting the vitamin K conversion cycle, warfarin induces hepatic production of partially decarboxylated proteins with reduced coagulant activity (7,8).

Carboxylation promotes binding of the vitamin K–dependent coagulation factors to phospholipid surfaces, thereby accelerating blood coagulation (9–11). γ-Carboxylation requires the reduced form of vitamin K (vitamin KH_2). Coumarins block the formation of vitamin KH_2 by inhibiting the enzyme vitamin K epoxide reductase, thereby limiting the γ-carboxylation of the vitamin K–dependent coagulant proteins. In addition, the vitamin K antagonists inhibit carboxylation of the regulatory anticoagulant proteins C and S. The anticoagulant effect of coumarins can be overcome by low doses of vitamin K_1 (phytonadione) because vitamin K_1 bypasses vitamin K epoxide reductase (Figure 1). Patients treated with large doses of vitamin K_1 (usually >5 mg) can become resistant to warfarin for up to a week because vitamin K_1 accumulating in the liver is available to bypass vitamin K epoxide reductase.

Warfarin also interferes with the carboxylation of Gla proteins synthesized in bone (12–15). Although these effects contribute to fetal bone abnormalities when mothers are treated with warfarin during pregnancy (16,17), there is no evidence that warfarin directly affects bone metabolism when administered to children or adults.

Pharmacokinetics and Pharmacodynamics of Warfarin

Warfarin is a racemic mixture of 2 optically active isomers, the R and S forms, in roughly equal proportion. It is rapidly absorbed from the gastrointestinal tract, has high bioavailability (18,19), and reaches maximal blood concentrations in healthy volunteers 90 minutes after oral administration (18,20). Racemic warfarin has a half-life of 36 to 42 hours (21), circulates bound to plasma proteins (mainly albumin), and accumulates in the liver, where the 2 isomers are metabolically transformed by different pathways (21). The relationship between the dose of warfarin and the response is influenced by genetic and environmental factors, including common mutations in the gene coding for cytochrome P450, the hepatic enzyme responsible for oxidative metabolism of the warfarin S-isomer (18,19). Several genetic polymorphisms in this enzyme have been described that are associated with lower dose requirements and higher bleeding complication rates compared with the wild-type enzyme CYP2C9* (22–24).

In addition to known and unknown genetic factors, drugs, diet, and various disease states can interfere with the response to warfarin.

The anticoagulant response to warfarin is influenced both by pharmacokinetic factors, including drug interactions that affect its absorption or metabolic clearance, and by pharmacodynamic factors, which alter the hemostatic response to given concentrations of the drug. Variability in anticoagulant response also results from inaccuracies in laboratory testing, patient noncompliance, and miscommunication between the patient and physician. Other drugs may influence the pharmacokinetics of warfarin by reducing gastrointestinal absorption or disrupting 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 nonselective pathways (25,26). Stereoselective interactions may

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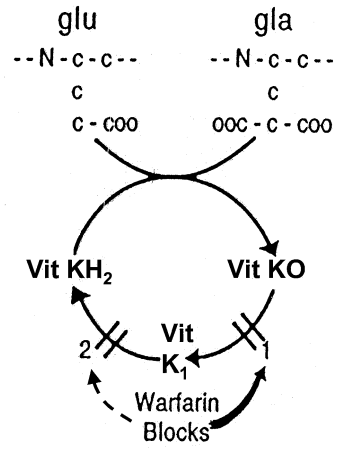

Figure 1. The vitamin K cycle and its link to carboxylation of glutamic acid residues on vitamin K–dependent coagulation proteins. Vitamin K_1 obtained from food sources is reduced to vitamin KH_2 by a warfarin-resistant vitamin K reductase. Vitamin KH_2 is then oxidized to vitamin K epoxide (Vit KO) in a reaction that is coupled to carboxylation of glutamic acid residues on coagulation factors. This carboxylation step renders the coagulation factors II, VII, IX, and X and the anticoagulant factors protein C and protein S functionally active. Vit KO is then reduced to Vit K_1 in a reaction catalyzed by vitamin KO reductase. By inhibiting vitamin KO reductase, warfarin blocks the formation of vitamin K_1 and vitamin KH_2, thereby removing the substrate (vitamin KH_2) for the carboxylation of glutamic acids. Vitamin K_1, either given therapeutically or derived from food sources, can overcome the effect of warfarin by bypassing the warfarin-sensitive vitamin KO reductase step in the formation of vitamin KH_2.

affect oxidative metabolism of either the S- or R-isomer of warfarin (25,26). Inhibition of S-warfarin metabolism is more important clinically because this isomer is 5 times more potent than the R-isomer as a vitamin K antagonist (25,26). Phenylbutazone (27), sulfinpyrazone (28), metronidazole (29), and trimethoprim-sulfamethoxazole (30) inhibit clearance of S-warfarin, and each potentiates the effect of warfarin on the prothrombin time (PT). In contrast, drugs such as cimetidine and omeprazole, which inhibit clearance of the R-isomer, potentiate the PT only modestly in patients treated with warfarin (26,29,31). Amiodarone inhibits the metabolic clearance of both the S- and R-isomers and potentiates warfarin anticoagulation (32). The anticoagulant effect is inhibited by drugs like barbiturates, rifampicin, and carbamazepine, which increase hepatic clearance (31). Chronic alcohol consumption has a similar potential to increase the clearance of warfarin, but ingestion of even relatively large amounts of wine has little influence on PT in subjects treated with warfarin (33). For a more thorough discussion of the effect of enzyme induction on warfarin therapy, the reader is referred to a recent critical review (34).

Warfarin pharmacodynamics are subject to genetic and environmental variability as well. Hereditary resistance to warfarin occurs in rats as well as in human beings (35–37). and patients with genetic warfarin resistance require doses 5- to 20-fold higher than average to achieve an anticoagulant effect. This disorder is attributed to reduced affinity of warfarin for its hepatic receptor.

A mutation in the factor IX propeptide that causes bleeding without excessive prolongation of PT also has been described (38). The mutation occurs in $<1.5\%$ of the population. Patients with this mutation experience a marked decrease in factor IX during treatment with coumarin drugs, and levels of other vitamin K–dependent coagulation factors decrease to 30% to 40%. The coagulopathy is not reflected in the PT, and therefore, patients with this mutation are at risk of bleeding during warfarin therapy (38–40). An exaggerated response to warfarin among the elderly may reflect its reduced clearance with age (41–43).

Subjects receiving long-term warfarin therapy are sensitive to fluctuating levels of dietary vitamin K (44,45), which is derived predominantly from phylloquinones in plant material (45). The phylloquinone content of a wide range of foodstuffs has been listed by Sadowski and associates (46). Phylloquinones counteract the anticoagulant effect of warfarin because they are reduced to vitamin KH_2 through the warfarin-insensitive pathway (47). Important fluctuations in vitamin K intake occur in both healthy and sick subjects (48). Increased intake of dietary vitamin K sufficient to reduce the anticoagulant response to warfarin (44) occurs in patients consuming green vegetables or vitamin K–containing supplements while following weight-reduction diets and in patients treated with intravenous vitamin K supplements. Reduced dietary vitamin K_1 intake potentiates the effect of warfarin in sick patients treated with antibiotics and intravenous 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 (49,50). 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. The anticoagulant effect of warfarin is augmented by the second- and third-generation cephalosporins, which inhibit the cyclic interconversion of vitamin K (51,52); by thyroxine, which increases the metabolism of coagulation factors (50); and by clofibrate, through an unknown mechanism (53). Doses of salicylates >1.5 g per day (54) and acetaminophen (55) also augment the anticoagulant effect of warfarin, possibly because these drugs have warfarin-like activity (56). Heparin potentiates the anticoagulant effect of warfarin but in therapeutic doses produces only slight prolongation of the PT.

Drugs such as aspirin (57), nonsteroidal antiinflammatory drugs (58), penicillins (in high doses) (59,60), and moxolactam (52) increase the risk of warfarin-associated bleeding by inhibiting platelet function. Of these, aspirin is the most important because of its widespread use and prolonged effect (61). Aspirin and nonsteroidal antiinflammatory drugs also can produce gastric erosions that increase the risk of upper gastrointestinal bleeding. The risk of clinically important bleeding is heightened when high doses of aspirin are taken

TABLE 1. Capillary Whole Blood (Point-of-Care) PT Instruments

Instrument	Clot Detection Methodology	Type of Sample	Home Use Approval
Protime Monitor 1000 Coumatrak* Ciba Corning 512 Coagulation Monitor* CoaguChek Plus* CoaguChek Pro* CoaguChek Pro/DM*	Clot initiation: Thromboplastin Clot detection: Cessation of blood flow through capillary channel	Capillary WB Venous WB	No
CoaguChek CoaguChek S Thrombolytic Assessment System Rapidpoint Coag	Clot initiation: Thromboplastin Clot detection: Cessation of movement of iron particles	Capillary WB Venous WB Plasma	Yes† (CoaguChek only)
ProTIME Monitor Hemochron Jr‡ GEM PCL‡	Clot initiation: Thromboplastin Clot detection: Cessation of blood flow through capillary channel	Capillary WB Venous WB	Yes
Avosure Pro+§ Avosure Pro§ Avosure PT§	Clot initiation: Thromboplastin Clot detection: Thrombin generations detected by fluorescent thrombin probe	Capillary WB Venous WB Plasma	Yes
Harmony	Clot initiation: Thromboplastin Clot detection: Cessation of blood flow through capillary channel	Capillary WB Venous WB	Yes
INRatio‖	Clot initiation: Thromboplastin Clot detection: Change in impedance in sample	Capillary WB Venous WB	Yes

WB indicates whole blood.

*All instruments in this category are based on the original Biotrack model (Protime Monitor 1000) and licensed under different names. The latest version available is the CoaguChek Pro and Pro/DM (as models evolved, they acquired added capabilities); earlier models are no longer available.

†CoaguChek not actively marketed for home use at the time of this writing. Thrombolytic Assessment System not available for home use.

‡Hemochron Jr and GEM PCL are simplified versions of the ProTIME Monitor.

§Avosure instruments removed from market when manufacturer (Avocet, Inc) ceased operations (2001). Technology has since been purchased by Beckman Coulter.

‖INRange system manufactured by Hemosense, Inc, is currently in development.

during high-intensity warfarin therapy (international normalized ratio [INR] 3.0 to 4.5) (57,62). In 2 studies, one involving patients with prosthetic heart valves (63) and the other involving asymptomatic individuals at high risk of coronary artery disease (64), low doses of aspirin (100 mg and 75 mg daily, combined with moderate- and low-intensity warfarin anticoagulation, respectively) also were associated with increased rates of minor bleeding.

The mechanisms by which erythromycin (65) and some anabolic steroids (66) potentiate the anticoagulant effect of warfarin are unknown. Sulfonamides and several broad-spectrum antibiotic compounds may augment the anticoagulant effect of warfarin in patients consuming diets deficient in vitamin K by eliminating bacterial flora and aggravating vitamin K deficiency (67).

Wells et al (68) critically analyzed reports of possible interactions between drugs or foods and warfarin. Interactions were categorized as highly probable, probable, possible, or doubtful. There was strong evidence of interaction in 39 of the 81 different drugs and foods appraised; 17 potentiate warfarin effect and 10 inhibit it, but 12 produce no effect. Many other drugs have been reported to either interact with oral anticoagulants or alter the PT response to warfarin (69,70). A recent review highlighted the importance of postmarketing surveillance with newer drugs, such as celecoxib, a drug that showed no interactions in Phase 2 studies but was subsequently suspected of potentiating the effect of warfarin in several case reports (71). This review also drew attention to potential interactions with less well-regulated herbal medicines. For these reasons, the INR should be measured more frequently when virtually any drug or herbal medicine is added or withdrawn from the regimen of a patient treated with warfarin.

The Antithrombotic Effect of Warfarin

The antithrombotic effect of warfarin conventionally has been attributed to its anticoagulant effect, which in turn is mediated by the reduction of 4 vitamin K–dependent coagulation factors. More recent evidence, however, suggests that the anticoagulant and antithrombotic effects can be dissociated and that reduction of prothrombin and possibly factor X are more important than reduction of factors VII and IX for the antithrombotic effect. This evidence is indirect and derived from the following observations: First, the experiments of Wessler and Gitel (72) more than 40 years ago, which used a stasis model of thrombosis in rabbits, showed

that the antithrombotic effect of warfarin requires 6 days of treatment, whereas an anticoagulant effect develops in 2. The antithrombotic effect of warfarin requires reduction of prothrombin (factor II), which has a relatively long half-life of ≈60 to 72 hours, compared with 6 to 24 hours for other K-dependent factors responsible for the more rapid anticoagulant effect. Second, in a rabbit model of tissue factor–induced intravascular coagulation, the protective effect of warfarin is mainly a result of lowering prothrombin levels (73). Third, Patel and associates (74) demonstrated that clots formed from umbilical cord plasma (containing about half the prothrombin concentration of adult control plasma) generated significantly less fibrinopeptide A, reflecting less thrombin activity, than clots formed from maternal plasma. The view that warfarin exerts its antithrombotic effect by reducing prothrombin levels is consistent with observations that clot-bound thrombin is an important mediator of clot growth (75) and that reduction in prothrombin levels decreases the amount of thrombin generated and bound to fibrin, reducing thrombogenicity (74).

The suggestion that the antithrombotic effect of warfarin is reflected in lower levels of prothrombin forms the basis for overlapping heparin with warfarin until the PT (INR) is prolonged into the therapeutic range during treatment of patients with thrombosis. Because the half-life of prothrombin is ≈60 to 72 hours, ≥4 days' overlap is necessary. Furthermore, the levels of native prothrombin antigen during warfarin therapy more closely reflect antithrombotic activity than the PT (76). These considerations support administering a maintenance dose of warfarin (≈5 mg daily) rather than a loading dose when initiating therapy. The rate of lowering prothrombin levels was similar with either a 5- or a 10-mg initial warfarin dose (77), but the anticoagulant protein C was reduced more rapidly and more patients were excessively anticoagulated (INR >3.0) with a 10-mg loading dose.

Management of Oral Anticoagulant Therapy

Monitoring Anticoagulation Intensity

The PT is the most common test used to monitor oral anticoagulant therapy (78). The PT responds to reduction of 3 of the 4 vitamin K–dependent procoagulant clotting factors (II, VII, and X) that are reduced by warfarin at a rate proportionate to their respective half-lives. Thus, during the first few days of warfarin therapy, the PT reflects mainly reduction of factor VII, the half-life of which is ≈6 hours. Subsequently, reduction of factors X and II contributes to prolongation of the PT. The PT assay is performed by adding calcium and thromboplastin to citrated plasma. The traditional term "thromboplastin" refers to a phospholipid-protein extract of tissue (usually lung, brain, or placenta) that contains both the tissue factor and phospholipid necessary to promote activation of factor X by factor VII. Thromboplastins vary in responsiveness to the anticoagulant effects of warfarin according to their source, phospholipid content, and preparation (79–81). 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 one. The responsiveness of a thromboplastin can be measured by assessing its International Sensitivity Index (ISI) (see below).

PT monitoring of warfarin treatment is very imprecise when expressed as a PT ratio (calculated as a simple ratio of the patient's plasma value over that of normal control plasma) because thromboplastins can vary markedly in their responsiveness to warfarin. Differences in thromboplastin responsiveness contributed to clinically important differences in oral anticoagulant dosing among countries (82) and were responsible for excessive and erratic anticoagulation in North America, where less responsive as well as responsive thromboplastins were in common use. Recognition of these shortcomings in PT monitoring stimulated the development of the INR standard for monitoring oral anticoagulant therapy, and the adoption of this standard improved the safety of oral anticoagulant therapy and its ease of monitoring.

The history of standardization of the PT has been reviewed by Poller (80) and by Kirkwood (83). In 1992, the ISI of thromboplastins used in the United States varied between 1.4 and 2.8 (84). Subsequently, more responsive thromboplastins with lower ISI values have come into clinical use in the United States and Canada. For example, the recombinant human preparations consisting of relipidated synthetic tissue factor have ISI values of 0.9 to 1.0 (85). The INR 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:

$$\text{INR} = (\text{patient PT/mean normal PT})^{\text{ISI}}$$

or

$$\log \text{INR} = \text{ISI} \ (\log \text{observed PT ratio}),$$

where ISI denotes the International Sensitivity Index of the thromboplastin used at the local laboratory to perform the PT measurement. The ISI reflects the responsiveness of a given thromboplastin to reduction of the vitamin K–dependent coagulation factors. The more responsive the reagent, the lower the ISI value (80,83,86).

Most commercial manufacturers provide ISI values for thromboplastin reagents, and the INR standard has been widely adopted by hospitals in North America. Thromboplastins with recombinant tissue factor have been introduced with ISI values close to 1.0, yielding 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 from 21% to 97% between 1991 and 1997 (82). As the INR standard of reporting was widely adopted, however, several problems surfaced. These are reviewed briefly below.

As noted above, the INR is based on ISI values derived from plasma of patients on stable anticoagulant doses for ≥6 weeks (87). 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 unconverted PT ratio (88) and is thus recommended during both initiation and maintenance of warfarin treatment. There is

also evidence that the INR is a reliable measure of impaired blood coagulation in patients with liver disease (89).

Theoretically, the INR could be made more precise by using reagents with low ISI values, but laboratory proficiency studies indicate that this produces only modest improvement (90–93), whereas reagents with higher ISI values result in higher coefficients of variation (94,95). Variability of ISI determination is reduced by calibrating the instrument with lyophilized plasma depleted of vitamin K–dependent clotting factors (95–97). Because the INR is based on a mathematical relationship using a manual method for clot detection, the accuracy of the INR measurement can be influenced by the automated clot detectors now used in most laboratories (98–103). In general, the College of American Pathologists has recommended that laboratories use responsive thromboplastin reagents (ISI <1.7) and reagent/instrument combinations for which the ISI has been established (104).

ISI values provided by manufacturers of thromboplastin reagents are not invariably correct (105–107), and this adversely affects the reliability of measurements. Local calibrations can be performed by using plasma samples with certified PT values to determine the instrument-specific ISI. The mean normal plasma PT is determined from fresh plasma samples from $\geq$20 healthy individuals and is not interchangeable with a laboratory control PT (108). Because the distribution of PT values is not normal, log-transformation and calculation of a geometric mean are recommended. The mean normal PT should be determined with each new batch of thromboplastin with the same instrument used to assay the PT (108).

The concentration of citrate used to anticoagulate plasma affects the INR (109,110). In general, higher citrate concentrations ($\geq$3.8%) lead to higher INR values (109), and underfilling the blood collection tube spuriously prolongs the PT because excess citrate is present. Using collection tubes containing 3.2% citrate for blood coagulation studies can reduce this problem.

The lupus anticoagulants prolong the activated partial thromboplastin time but usually cause only slight prolongation of the PT, according to the reagents used (111,112). The prothrombin and proconvertin tests (113,114) and measurements of prothrombin activity or native prothrombin concentration have been proposed as alternatives (76,114–116), but the optimum method for monitoring anticoagulation in patients with lupus anticoagulants is uncertain.

Practical Warfarin Dosing and Monitoring

Warfarin dosing may be separated into initial and maintenance phases. After treatment is started, the INR response is monitored frequently until a stable dose-response relationship is obtained; thereafter, the frequency of INR testing is reduced.

An anticoagulant effect is observed within 2 to 7 days after beginning oral warfarin, according to the dose administered. When a rapid effect is required, heparin should be given concurrently with warfarin for $\geq$4 days. The common practice of administering a loading dose of warfarin is generally unnecessary, and there are theoretical reasons for beginning treatment with the average maintenance dose of $\approx$5 mg daily, which usually results in an INR of $\geq$2.0 after 4 or 5 days. Heparin usually can be stopped once the INR has been in the therapeutic range for 2 days. When anticoagulation is not urgent (eg, chronic atrial fibrillation), treatment can be commenced out of hospital with a dose of 4 to 5 mg/d, which usually produces a satisfactory anticoagulant effect within 6 days (77). Starting doses $<$4 to 5 mg/d should be used in patients sensitive to warfarin, including the elderly (40,117), and in those at increased risk of bleeding.

The INR is usually checked daily until the therapeutic range has been reached and sustained for 2 consecutive days, then 2 or 3 times weekly for 1 to 2 weeks, then less often, according to the stability of the results. Once the INR becomes stable, the frequency of testing can be reduced to intervals as long as 4 weeks. When dose adjustments are required, frequent monitoring is resumed. Some patients on long-term warfarin therapy experience unexpected fluctuations in dose-response due to changes in diet, concurrent medication changes, poor compliance, or alcohol consumption.

The safety and effectiveness of warfarin therapy depends critically on maintaining the INR within the therapeutic range. On-treatment analysis of the primary prevention trials in atrial fibrillation found that a disproportionate number of thromboembolic and bleeding events occurred when the PT ratio was outside the therapeutic range (118). Subgroup analyses of other cohort studies also have shown a sharp increase in the risk of bleeding when the INR is higher than the upper limit of the therapeutic range (116,119–122), and the risk of thromboembolism increased when the INR fell to $<$2.0 (123,124).

Point-of-Care Patient Self-Testing

Point-of-care (POC) PT measurements offer the potential for simplifying oral anticoagulation management in both the physician's office and the patient's home. POC monitors measure a thromboplastin-mediated clotting time that is converted to plasma PT equivalent by a microprocessor and expressed as either the PT or the INR. The original methodology was incorporated into the Biotrack instrument (Coumatrak; Biotrack, Inc) evaluated by Lucas et al (125) in 1987. These investigators reported a correlation coefficient (r) of 0.96 between reference plasma PT and capillary whole blood PT, findings that were confirmed in other studies (126).

By early 2000, the US Food and Drug Administration (FDA) had approved 3 monitors for patient self-testing at home (127), but each instrument has limitations. Instruments currently marketed for this purpose are listed in Table 1. In a study (128) in which a derivative of the Biotrack monitor (Biotrack 512; Ciba-Corning) was used, the POC instrument compared poorly with the Thrombotest, the former underestimating the INR by a mean of 0.76. Another Biotrack derivative (Coumatrak; DuPont) was accurate in an INR range of 2.0 to 3.0 but gave discrepant results at higher INR values (129). In another study, the Ciba-Corning monitor underestimated the results when the INR was $>$4.0, but the error was overcome by using a revised ISI value to calculate the INR (130). Several investigators (131–133) reported

TABLE 2. Studies of Patient Self-Testing and Self-Management of Anticoagulation

Study	Study Design	Study Groups	No. of Patients	Time in Range, % INR % Time	Major Hemorrhage, % per patient-year	Thromboembolism, % per patient-year	Indications
White[140] 1989	RCT						
		PST	23	93	0	0	Mixed
		AMS	23	75	0	0	Mixed
Anderson[139] 1993	Inception cohort						
		PST	40	74	0	0	Mixed
Beyth[141] 1997	RCT						
		PST	162	56	5.7	9	Mixed
		UC	163	33	12	13	Mixed
Ansell[145] 1995	Observational cohort						
		PSM	20	89	0	0	Mixed
		AMS	20	68	0	0	Mixed
Bernardo[146] 1996	Observational						
		PSM	216	83	NA	NA	Heart valves
Horstkotte[147] 1996	RCT						
		PSM	75	92	4.5*	0.9	Heart valves
		UC	75	59	10.9*	3.6	Heart valves
Hasenkam[142] 1997	Observational matched control						
		PSM	20	77	NA	NA	Heart valves
		UC	20	53	NA	NA	Heart valves
Sawicki[148] 1999	RCT						
		PSM	90	57/53†	2.2	2.2	Mixed
		UC	89	34/43†	2.2	4.5	Mixed
Kortke[149] 2001	RCT						
		PSM	305	78	1.7	1.2	Mixed
		UC	295	60	2.6	2.1	Mixed
Watzke[150] 2000	Prospective controlled						
		PSM	49	86	4‡	0	Mixed
		ACC	53	80	0	0	Mixed
Cromheecke[151] 2000	Randomized crossover						
		PSM	50	55	0	0	Mixed
		ACC	50	49	0	16	Mixed

RCT indicates randomized controlled trial; PST, patient self-testing; PSM, patient self-management; AMS, anticoagulation management service; UC, usual care; and Mixed, mixed indications.

*Major and minor bleeding.

†Time in target range at 3 and 6 mo.

‡Percentage of episodes in 49 patients.

excellent correlations with reference plasma PT values when a second category of monitor (CoaguChek; Roche Diagnostics, Inc) was used. The ISI calibration with this system, based on an international reference preparation, was extremely close to indices adopted by the manufacturer for both whole blood and plasma (134). Both classes of monitors (Biotrack and Coagu-Chek) compared favorably with traditionally obtained PT measurements at 4 laboratories and with

TABLE 3. Relationship Between Anticoagulation Intensity and Bleeding

Source	No. of Patients	Duration of Therapy	Target INR Range	Incidence of Bleeding, %	*P*
Hull et al 1982[167]—deep vein thrombosis	96	3 mo	3.0–4.5 vs 2.0–2.5	22.4 vs 4.3	0.015
Turpie et al 1988[168]—prosthetic heart valves (tissue)	210	3 mo	2.5–4.0 vs 2.0–2.5	13.9 vs 5.9	<0.002
Saour et al 1990[169]—mechanical prosthetic heart valves	247	3.47 y	7.4–10.8 vs 1.9–3.6	42.4 vs 21.3	<0.002
Altman et al 1991[170]—mechanical prosthetic heart valves*	99	11.2 mo	3.0–4.5 vs 2.0–2.9	24.0 vs 6.0	<0.02

*Patients also given aspirin 300 mg daily, and dipyridamole 75 mg BID.

the standard manual tilt-tube technique established by the World Health Organization using an international reference thromboplastin (135). Laboratories using a more sensitive thromboplastin showed close agreement with the standard, whereas agreement was poor when insensitive thromboplastins were used; INR determinations with the Coumatrak and CoaguChek monitors were only slightly less accurate than the conventional method used in the best clinical laboratories.

A third category of POC capillary whole blood PT instruments (ProTIME Monitor; International Technidyne Corporation) differs from the other 2 types of instruments in that it performs a PT in triplicate (3 capillary channels) and simultaneously performs level 1 and level 2 controls (2 additional capillary channels). In a multiinstitutional trial (136), the instrument INR correlated well with reference laboratory tests and those performed by a healthcare provider (venous sample, $r=0.93$; capillary sample, $r=0.93$; patient fingerstick, $r=0.91$). In a separate report involving 76 warfarin-treated children and 9 healthy control subjects, the coefficient of correlation between venous and capillary samples was 0.89. Compared with venous blood tested in a reference laboratory (ISI=1.0), correlation coefficients were 0.90 and 0.92, respectively (137). Published results with a fourth type of PT monitor (Avocet PT 1000) in 160 subjects demonstrate good correlation when compared with reference laboratory INR values with capillary blood, citrated venous whole blood, and citrated venous plasma ($r=0.97$, 0.97, and 0.96, respectively) (138).

The feasibility and accuracy of patient self-testing at home initially was evaluated in 2 small studies with promising results (139,140). More recently, Beyth and Landefeld (141) randomized 325 newly treated elderly patients to either conventional treatment by personal physicians based on venous sampling or adjustment of dosage by a central investigator based on INR results from patient self-testing at home. Over a 6-month period, the rate of hemorrhage was 12% in the usual-care group compared with 5.7% in the self-testing group. These and other studies in which patient self-testing and self-management of anticoagulation have been evaluated are summarized in Table 2 (142).

Patient Self-Management

Coupled with self-testing, self-management with the use of POC instruments offers independence and freedom of travel to selected patients. The feasibility of initial patient self-management of oral anticoagulation was demonstrated in several studies (143–146). These descriptive studies were then followed by several randomized trials. In the first study, 75 patients with prosthetic heart valves who managed their own therapy were compared with a control group of the same size managed by their personal physicians (147). The self-managed patients tested themselves approximately every 4 days and achieved a 92% degree of satisfactory anticoagulation, as determined by the INR. The physician-managed patients were tested approximately every 19 days, but only 59% of INR values were in therapeutic range. Self-managed individuals experienced a 4.5% per year incidence of bleeding of any severity and a 0.9% per year rate of thromboembolism, compared with 10.9% and 3.6%, respectively, in the physician-managed group ($P<0.05$ between groups). Another comparison of self-management (n=90) with usual care (n=89) (148) found that the difference in the percentage of INR values within the therapeutic range at 3 months became statistically insignificant at 6 months. Results from the large, randomized Early Self-Controlled Anticoagulation Study in Germany (ESCAT) (149) showed that among 305 self-managed patients, INR values were more frequently in range (78%) compared with 61% in 295 patients assigned to usual care. The rate of major adverse events was significantly different between groups: 2.9% per patient-year of therapy in the self-managed group versus 4.7% in the usual-care group ($P=0.042$).

When patient self-management is compared with the outcomes of high-quality anticoagulation management delivered by an anticoagulation clinic, the differences between the 2 methods of management are less marked. Watzke et al (150) compared weekly INR patient self-management in 49 patients with management by an anticoagulation clinic in 53 patients. There was no significant difference for time in therapeutic range between groups, but the self-management group had a significantly smaller mean deviation from their target INR. Cromheecke et al (151) conducted a randomized crossover study with 50 patients managed by an anticoagulation clinic or by self-management. Although the differences did not achieve statistical significance, there was a trend toward greater time in therapeutic range in the self-management group (55% versus 49%).

Preliminary results from 2 recent studies further suggest that when compared with anticoagulation clinic management, patient self-testing or patient self-management offers limited advantages. Both Gadisseur et al (152) and Kaatz et al (153) found that time in therapeutic range was the same regardless of whether patients self-tested and self-managed or were managed by an anticoagulation clinic.

Computerized Algorithms for Warfarin Dose Adjustment

Several computer programs have been developed to guide warfarin dosing. They are based on various techniques: querying physicians (154), Bayesian forecasting (155), and a proprietary mathematical equation (156). In general, the latter involve fixed-effects log-linear Bayesian modeling, which accounts for factors unique to each measurement. The response variance not explained by previous warfarin dose and previous INR values is specific and constant over time for each patient but not entirely accounted for mathematically. In one randomized trial, the reliability of 3 established computerized dosage programs were compared with warfarin dosing by experienced medical staff in an outpatient clinic (157). Control was similar with the computer-guided and empirical dose adjustments in the INR range of 2.0 to 3.0, but the computer programs achieved significantly better control when more intensive therapy (INR 3.0 to 4.5) was required. In another randomized study of 101 chronically anticoagulated patients with prosthetic cardiac valves, computerized warfarin adjustments proved comparable to manual regulation in the percentage of INR values kept within the therapeutic range but required 50% fewer dose adjustments (158).

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A multicenter randomized study of 285 patients found computer-assisted dose regulation more effective than traditional dosing at maintaining therapeutic INR values. Taken together, these data suggest that computer-guided warfarin dose adjustment is superior to traditional dose regulation, particularly when personnel are inexperienced.

Management of Patients With High INR Values

There is a close relation between the INR and risk of bleeding (Table 1). The risk of bleeding increases when the INR exceeds 4, and the risk rises sharply with values >5. Three approaches can be taken to lower an elevated INR. The first step is to stop warfarin; the second is to administer vitamin K_1; and the third and most rapidly effective measure is to infuse fresh plasma or prothrombin concentrate. The choice of approach is based largely on clinical judgment because no randomized trials have compared these strategies with clinical end points. After warfarin is interrupted, the INR falls over several days (an INR between 2.0 and 3.0 falls to the normal range 4 to 5 days after warfarin is stopped) (159). In contrast, the INR declines substantially within 24 hours after treatment with vitamin K_1 (160).

Even when the INR is excessively prolonged, the absolute daily risk of bleeding is low, leading many physicians to manage patients with INR levels as high as 5 to 10 by stopping warfarin expectantly, unless the patient is at intrinsically high risk of bleeding or bleeding has already developed. Ideally, vitamin K_1 should be administered in a dose that will quickly lower the INR into a safe but not subtherapeutic range without causing resistance once warfarin is reinstated or exposing the patient to the risk of anaphylaxis. Though effective, high doses of vitamin K_1 (eg, 10 mg) may lower the INR more than necessary and lead to warfarin resistance for up to a week. Vitamin K_1 can be administered intravenously, subcutaneously, or orally. Intravenous injection produces a rapid response but may be associated with anaphylactic reactions, and there is no proof that this rare but serious complication can be avoided by using low doses. The response to subcutaneous vitamin K_1 is unpredictable and sometimes delayed (161,162). In contrast, oral administration is predictably effective and has the advantages of convenience and safety over parenteral routes. In patients with excessively prolonged INR values, vitamin K_1, 1 mg to 2.5 mg orally, more rapidly lowers the INR to <5 within 24 hours than simply withholding warfarin (163). In a prospective study of 62 warfarin-treated patients with INR values between 4 and 10, warfarin was omitted, and vitamin K_1, 1 mg, was administered orally (162,164). After 24 hours, the INR was lower in 95%, <4 in 85%, and <1.9 in 35%. None displayed resistance when warfarin was resumed. These observations indicate that oral vitamin K_1 in low doses effectively reduces the INR in patients treated with warfarin. Oral vitamin K_1, 1.0 to 2.5 mg, is sufficient when the INR is between 4 and 10, but larger doses (5 mg) are required when the INR is >10.

Oral vitamin K_1 is the treatment of choice unless very rapid reversal of anticoagulation is critical, when vitamin K_1 can be administered by slow intravenous infusion (5 to 10 mg over 30 minutes). In 2001, the American College of Chest Physicians published the following recommendations for managing patients on coumarin anticoagulants who need their INRs lowered because of either actual or potential bleeding (164):

(1) When the INR is above the therapeutic range but <5, the patient has not developed clinically significant bleeding, and rapid reversal is not required for surgical intervention, the dose of warfarin can be reduced or the next dose omitted and resumed (at a lower dose) when the INR approaches the desired range.
(2) If the INR is between 5 and 9 and the patient is not bleeding and has no risk factors that predispose to bleeding, the next 1 or 2 doses of warfarin can be omitted and warfarin reinstated at a lower dose when the INR falls into the therapeutic range. Alternatively, the next dose of warfarin may be omitted and vitamin K_1 (1 to 2.5 mg) given orally. This approach should be used if the patient is at increased risk of bleeding.
(3) When more rapid reversal is required to allow urgent surgery or dental extraction, vitamin K_1 can be given orally in a dose of 2 to 5 mg, anticipating reduction of the INR within 24 hours. An additional dose of 1 or 2 mg vitamin K can be given if the INR remains high after 24 hours.
(4) If the INR is >9 but clinically significant bleeding has not occurred, vitamin K_1, 3 to 5 mg, should be given orally, anticipating that the INR will fall within 24 to 48 hours. The INR should be monitored closely and vitamin K repeated as necessary.
(5) When rapid reversal of anticoagulation is required because of serious bleeding or major warfarin overdose (eg, INR >20), vitamin K_1 should be given by slow intravenous infusion in a dose of 10 mg, supplemented with transfusion of fresh plasma or prothrombin complex concentrate, according to the urgency of the situation. It may be necessary to give additional doses of vitamin K_1 every 12 hours.
(6) In cases of life-threatening bleeding or serious warfarin overdose, prothrombin complex concentrate replacement therapy is indicated, supplemented with 10 mg of vitamin K_1 by slow intravenous infusion; this can be repeated, according to the INR. If warfarin is to be resumed after administration of high doses of vitamin K, then heparin can be given until the effects of vitamin K have been reversed and the patient again becomes responsive to warfarin.

Bleeding During Oral Anticoagulant Therapy

The main complication of oral anticoagulant therapy is bleeding, and risk is related to the intensity of anticoagulation (Table 3) (165–170). Other contributing factors are the underlying clinical disorder (165,171) and concomitant administration of aspirin, nonsteroidal antiinflammatory drugs, or other drugs that impair platelet function, produce gastric erosions, and in very high doses impair synthesis of vitamin K–dependent clotting factors (57,60,62). The risk of major bleeding also is related to age >65 years, a history of stroke or gastrointestinal bleeding, and comorbid conditions such as renal insufficiency or anemia (164,165). These risk factors are additive; patients with 2 or 3 risk factors have a much higher incidence of warfarin-associated bleeding that those with none or one (172). The elderly are more prone to bleeding even after controlling for anticoagulation intensity

(118,167). Bleeding that occurs at an INR of <3.0 is frequently associated with trauma or an underlying lesion in the gastrointestinal or urinary tract (165).

Four randomized studies have demonstrated that lowering the INR target range from 3.0 to 4.5 to 2.0 to 3.0 reduces the risk of clinically significant bleeding (167–169). Although this difference in anticoagulant intensity is associated with an average warfarin dose reduction of only ≈1 mg/d, the effect on bleeding risk is impressive. It is prudent to initiate warfarin at lower doses in the elderly, as patients >75 years of age require ≈1 mg/d less than younger individuals to maintain comparable prolongation of the INR.

Long-term management is challenging for patients who have experienced bleeding during warfarin anticoagulation yet require thromboembolic prophylaxis (eg, those with mechanical heart valves or high-risk patients with atrial fibrillation). If bleeding occurred when the INR was above the therapeutic range, warfarin can be resumed once bleeding has stopped and its cause corrected. For patients with mechanical prosthetic heart valves and persistent risk of bleeding during anticoagulation in the therapeutic range, a target INR of 2.0 to 2.5 seems sensible. For those in this situation with atrial fibrillation, anticoagulant intensity can be reduced to an INR of 1.5 to 2.0, anticipating that efficacy will be diminished but not abolished (123). In certain subgroups of patients with atrial fibrillation, aspirin may be an appropriate alternative to warfarin (173).

Management of Anticoagulated Patients Who Require Surgery

The management of patients treated with warfarin who require interruption of anticoagulation for surgery or other invasive procedures can be problematic. Several approaches can be taken, according to the risk of thromboembolism (174). In most patients, warfarin is stopped 4 to 5 days preoperatively, thereby allowing the INR to return to normal (<1.2) at the time of the procedure. Such patients remain unprotected for ≈2 to 3 days preoperatively. The period off warfarin can be reduced to 2 days by giving vitamin K_1, 2.5 mg orally, 2 days before the procedure with the expectation that the patient will remain unprotected for <2 days and that the INR will return to normal at the time of the procedure. Heparin can be given preoperatively to limit the period of time that the patient remains unprotected, and anticoagulant therapy can be recommenced postoperatively once it is deemed to be safe to restart treatment. Low-molecular-weight heparin (LMWH) can be used instead of heparin, but information on its efficacy in patients with prosthetic heart valves who require intercurrent surgery is lacking.

Moreover, the FDA and Aventis strengthened the "Warning" and "Precautions" sections of the Lovenox prescribing information to inform health professionals that the use of Lovenox injection is not recommended for thromboprophylaxis in patients with prosthetic heart valves.

- For patients at moderate risk of thromboembolism, preoperative heparin in prophylactic doses of 5000 U (or LMWH in prophylactic doses of 3000 U) can be given subcutaneously every 12 hours. Heparin (or LMWH) in these prophylactic doses can be restarted 12 hours postoperatively along with warfarin and the combination continued for 4 to 5 days until the INR returns to the desired range. If patients are considered to be at high risk of postoperative bleeding, heparin or LMWH can be delayed for 24 hours or longer.
- For patients at high risk of thromboembolism, low doses of heparin or LMWH might not provide adequate protection after warfarin is discontinued preoperatively, and these high-risk patients should be treated with therapeutic doses of heparin (15 000 U every 12 hours by subcutaneous injection) or LMWH (100 U/kg every 12 hours by subcutaneous injection). These anticoagulants can be administered on an ambulatory basis or in hospital and discontinued 24 hours before surgery with the expectation that their effect will last until 12 hours before surgery. If maintaining preoperative anticoagulation is considered to be critical, the patient can be admitted to hospital, and heparin can be administered in full doses (1300 U/h) by continuous intravenous infusion and stopped 5 hours before surgery, allowing the activated partial thromboplastin time to return to baseline at the time of the procedure. Heparin or LMWH can then be restarted in prophylactic doses 12 hours postoperatively along with warfarin and continued until the INR reaches the desired range.
- For patients at low risk of thromboembolism (eg, atrial fibrillation), the dose of warfarin can be reduced 4 to 5 days in advance of surgery to allow the INR to fall to normal or near normal (1.3 to 1.5) at the time of surgery. The maintenance dose of warfarin is resumed postoperatively and supplemented with low-dose heparin (5000 U) or LMWH administered subcutaneously every 12 hours, if necessary.
- Finally, for patients undergoing dental procedures, tranexamic acid or ϵ-aminocaproic acid mouthwash can be applied without interrupting anticoagulant therapy (175,176).

Anticoagulation During Pregnancy

Oral anticoagulants cross the placenta and can produce a characteristic embryopathy with first-trimester exposure and, less commonly, central nervous system abnormalities and fetal bleeding with exposure after the first trimester (17). For this reason, it has been recommended that warfarin therapy be avoided during the first trimester of pregnancy and, except in special circumstances, avoided entirely throughout pregnancy. Because heparin does not cross the placenta, it is the preferred anticoagulant in pregnant women. Several reports of heparin failure resulting in serious maternal consequences involving patients with mechanical heart valves, however (170,177,178), have caused some authorities to recommend that warfarin be used preferentially in women with mechanical prosthetic valves during the second and third trimesters of pregnancy. It even has been suggested that the inadequacy of heparin for prevention of maternal thromboembolism might outweigh the risk of warfarin embryopathy during the first trimester. Although reports of heparin failures in pregnant women with mechanical prosthetic valves could reflect inadequate dosing, it also is possible that heparin is a less

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effective antithrombotic agent than warfarin in patients with prosthetic heart valves. This notion is supported by recent experience with LMWH in pregnant women with prosthetic heart valves. Thus, as described above (see Management of Anticoagulated Patients Who Require Surgery), the FDA and Aventis have issued an advisory warning against the use of Lovenox in pregnant women with mechanical prosthetic heart valves. This warning was based on a randomized trial comparing enoxaparin to warfarin in pregnant patients with prosthetic heart valves. In contrast to the reported problems of using heparin or LMWH in pregnant patients with mechanical prosthetic valves, Montalescot and associates (179) reported that LMWH produced safe and effective anticoagulation when given for an average of 14.1 days to 102 nonpregnant patients with mechanical prosthetic heart valves. Nevertheless, it should be emphasized that LMWH is not approved by the FDA for use in any patients with mechanical prosthetic heart valves.

Given the potential medico-legal implications in the United States of using warfarin during pregnancy, the FDA warning related to the use of Lovenox, and the reported lack of efficacy of heparin in pregnant patients with mechanical prosthetic valves, physicians managing these patients are faced with a real dilemma. Three options are available. These are to use: (1) heparin or LMWH throughout pregnancy; (2) warfarin throughout pregnancy, changing to heparin or LMWH at 38 weeks' gestation with planned labor induction at ≈40 weeks; or (3) heparin or LMWH in the first trimester of pregnancy, switching to warfarin in the second trimester, continuing it until ≈38 weeks' gestation, and then changing to heparin or LMWH at 38 weeks with planned labor induction at ≈40 weeks. If heparin or LMWH is used in pregnant women with mechanical prosthetic valves, they should be administered in adequate doses and monitored carefully. Heparin should be given subcutaneously twice daily, starting at a total daily dose of 35 000 U. Monitoring should be performed at least twice weekly with either activated partial thromboplastin time or heparin assays, and higher heparin requirements should be anticipated in the third trimester because of an increase in heparin-binding proteins. LMWH should be given subcutaneously in a dose of 100 anti-Xa U/kg twice daily and the dose adjusted to maintain the anti-Xa level between 0.5 and 1.0 U/mL 4 to 6 hours after injection. Heparin or LMWH should be discontinued 12 hours before planned induction of labor. Heparin or LMWH should be started postpartum and overlapped with warfarin for 4 to 5 days. There is convincing evidence that, when administered to a nursing mother, warfarin does not induce an anticoagulant effect in the breast-fed infant (180,181).

Nonhemorrhagic Adverse Effects of Warfarin

Other than hemorrhage, the most important side effect of warfarin is skin necrosis. This uncommon complication usually is observed on the third to eighth day of therapy (182,183) and is caused by extensive thrombosis of venules and capillaries within subcutaneous fat. The pathogenesis of this striking complication is uncertain. An association between warfarin-induced skin necrosis and protein C deficiency (184–186) and, less commonly, protein S deficiency (187) has been reported, but warfarin-induced skin necrosis also occurs in patients without these deficiencies. A pathogenic role for protein C deficiency is supported by the similarity of the necrotic lesions to those of neonatal purpura fulminans, which complicates homozygous protein C deficiency. Patients with coumarin-induced skin necrosis who require further anticoagulant therapy are problematic. Warfarin is considered contraindicated, and long-term treatment with heparin is inconvenient and associated with osteoporosis. A reasonable approach is to restart warfarin at a low dose (eg, 2 mg daily), while therapeutic doses of heparin are administered concurrently, and gradually increase warfarin over several weeks. This approach should avoid an abrupt fall in protein C levels before reduction in levels of factors II, IX, and X occurs, and several case reports have suggested that warfarin can be resumed in this way without recurrence of skin necrosis (184,185).

Clinical Applications of Oral Anticoagulant Therapy

The clinical effectiveness of oral anticoagulants has been established by well-designed clinical trials in a variety of disease conditions. Oral anticoagulants are effective for primary and secondary prevention of venous thromboembolism, for prevention of systemic embolism in patients with prosthetic heart valves or atrial fibrillation, for prevention of acute myocardial infarction (AMI) in patients with peripheral arterial disease and in men otherwise at high risk, and for prevention of stroke, recurrent infarction, or death in patients with AMI (64). Although effectiveness has not been proved by a randomized trial, oral anticoagulants also are indicated for prevention of systemic embolism in high-risk patients with mitral stenosis and in patients with presumed systemic embolism, either cryptogenic or in association with a patent foramen ovale. For most of these indications, a moderate anticoagulant intensity (INR 2.0 to 3.0) is appropriate.

Although anticoagulants are sometimes used for secondary prevention of cerebral ischemia of presumed arterial origin when antiplatelet agents have failed, the Stroke Prevention in Reversible Ischemia Trial (SPIRIT) study found high-intensity oral anticoagulation (INR 3.0 to 4.5) dangerous in such cases (121). The trial was stopped at the first interim analysis of 1316 patients with a mean follow-up of 14 months because there were 53 major bleeding complications during anticoagulant therapy (27 intracranial, 17 fatal) versus 6 on aspirin (3 intracranial, 1 fatal). The authors concluded that oral anticoagulants are not safe when adjusted to a targeted INR range of 3.0 to 4.5 in patients who have experienced cerebral ischemia of presumed arterial origin. In a second study (the Warfarin Aspirin Recurrent Stroke Study [WARSS]) (187a), 2206 patients with noncardioembolic ischemic stroke were randomly assigned to receive either low-intensity warfarin (INR 1.4 to 2.8) or aspirin (325 mg/d). The primary end point of death or recurrent ischemic stroke occurred 17.8 patients assigned to warfarin and 16.0 assigned to aspirin ($P=0.25$). The rates of major bleeding were 2.2% and 1.5% in the warfarin and aspirin groups, respectively (not significant). Thus, low-intensity warfarin and aspirin exhibit

similar efficacy and safety in patients with noncardioembolic ischemic stroke.

Prevention of Venous Thromboembolism

Oral anticoagulants when given at a dose sufficient to maintain an INR between 2.0 and 3.0 are effective for prevention of venous thrombosis after hip surgery (188–190) and major gynecologic surgery (191,192). The risk of clinically important bleeding at this intensity is modest. A very low fixed dose of warfarin (1 mg daily) prevented subclavian vein thrombosis in patients with malignancy who had indwelling catheters (193). In contrast, 4 randomized trials found this dose of warfarin ineffective for preventing postoperative venous thrombosis in patients undergoing major orthopedic surgery (194–197). Levine and associates (198) reported that warfarin, 1 mg daily for 6 weeks followed by adjustment to a targeted INR of 1.5, prevented thrombosis in patients with stage 4 breast cancer receiving chemotherapy. In general, when warfarin is used to prevent venous thromboembolism, the targeted INR should be 2.0 to 3.0.

Treatment of Deep Venous Thrombosis or Pulmonary Embolism

The optimum duration of oral anticoagulant therapy is influenced by the competing risks of bleeding and recurrent venous thromboembolism. The risk of major bleeding during oral anticoagulant therapy is ≈3% per year with an annual case fatality rate of ≈0.6%. On the other hand, the case fatality rate from recurrent venous thromboembolism is ≈5% to 7%, with the rate being higher in patients with pulmonary embolism. Therefore, at an annual recurrence rate of 12%, the risk of death from recurrent thromboembolism is balanced by the risk of death from anticoagulant-related bleeding. The risk of recurrent thromboembolism when anticoagulant therapy is discontinued depends on whether thrombosis is unprovoked (idiopathic) or is secondary to a reversible cause; a longer course of therapy is warranted when thrombosis is idiopathic or associated with a continuing risk factor (199). The reported risk of recurrence in patients with idiopathic proximal vein thrombosis has been reported to be between 10% and 27% when anticoagulants are discontinued after 3 months. Extending therapy beyond 6 months seems to reduce the risk of recurrence to 7% during the year after treatment is discontinued (200).

Patients should be treated with anticoagulants for a minimum of 3 months. Moderate-intensity anticoagulation (INR 2.0 to 3.0) is as effective as a more intense regimen (INR 3.0 to 4.5) but is associated with less bleeding (166). Treatment should be longer in patients with proximal vein thrombosis than in those with distal thrombosis and in patients with recurrent thrombosis versus those with an isolated episode. Laboratory evidence of thrombophilia also may warrant a longer duration of anticoagulant therapy, according to the nature of the defect. Oral anticoagulant therapy is indicated for ≥3 months in patients with proximal deep vein thrombosis (201,202), for ≥6 months in those with proximal vein thrombosis in whom a reversible cause cannot be identified and eliminated or in patients with recurrent venous thrombosis, and for 6 to 12 weeks in patients with symptomatic calf vein thrombosis (203–205). Indefinite anticoagulant therapy should be considered in patients with >1 episode of idiopathic proximal vein thrombosis, thrombosis complicating malignancy, or idiopathic venous thrombosis and homozygous factor V Leiden genotype, the antiphospholipid antibody syndrome, or deficiencies of antithrombin III, protein C, or protein S (206–208). Prospective cohort studies indicate that heterozygous factor V Leiden or the G20210A prothrombin gene mutation in patients with idiopathic venous thrombosis does not increase the risk of recurrence (207,209).

These recommendations are based on results of randomized trials (207) that demonstrated that oral anticoagulants effectively prevent recurrent venous thrombosis (risk reduction >90%), that treatment for 6 months is more effective than treatment for 6 weeks (206), and that treatment for 2 years is more effective than treatment for 3 months (208).

Primary Prevention of Ischemic Coronary Events

The Thrombosis Prevention Trial (64) evaluated warfarin (target INR 1.3 to 1.8), aspirin (75 mg/d), both, or neither in 5499 men aged 45 to 69 years at risk of a first myocardial infarction (MI). The primary outcome was acute myocardial ischemia, 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% per year in the placebo group, whereas the combination of warfarin and aspirin reduced the relative risk by 34% ($P=0.006$). Given separately, neither warfarin nor aspirin produced a significant reduction in acute ischemic events, and the efficacy of the 2 drugs was similar (relative risk reductions 22% and 23% with warfarin and aspirin, respectively). The combined treatment, though most effective, was associated with a small but significant increase in hemorrhagic stroke. These results suggest that, in the primary prevention setting, low-intensity warfarin anticoagulation targeting an INR of 1.3 to 1.8 is effective for prevention of acute ischemic events (particularly fatal 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.

Despite its effectiveness, low-intensity warfarin is not preferred over aspirin for primary prophylaxis in high-risk patients because warfarin requires INR monitoring and is associated with greater potential for bleeding.

The effectiveness of the combination of low-intensity warfarin plus aspirin in the Thrombosis Prevention Trial (64) contrasts with the results of the Coumadin Aspirin Reinfarction Study (CARS) (210), Stroke Prevention in Atrial Fibrillation (SPAF) III trial (124), and Post Coronary Artery Bypass Graft (Post-CABG) (211) study, in which this type of combination therapy was ineffective. In the Thrombosis Prevention Trial, the dose of warfarin was adjusted between 0.5 and 12.5 mg/d (INR of 1.3 to 1.8), whereas in the CARS and SPAF III studies, warfarin was given in fixed doses. The reason for the contrasting effectiveness of low-intensity warfarin in these primary and secondary prevention situations is not clear.

Acute Myocardial Infarction

Initial evidence supporting use of oral anticoagulants in patients with AMI dates to the 1960s and 1970s, when

TABLE 4. Randomized Trials in MI Comparing ASA, the Combination of ASA and Moderate- or Low-Intensity Warfarin, and High-Dose Warfarin: Efficacy

Study (No. of patients; follow-up period)	Acute Coronary Syndromes Patients	Efficacy Outcome	ASA Efficacy Outcome, % (Dose)	OA [INR] Plus ASA Efficacy Outcome, % (Dose)	OA [INR]
ASPECT II[119] (n=993; 26 mo)	MI	Death, MI, stroke	9.0% (80 mg)	5.0% [2.0–2.5] (80 mg)	5.0% [3.0–4.0]
WARIS II[222] (n=3630; 48 mo)	MI	Death, MI, stroke	20% (160 mg)	16.7% [2.0–2.5] (75 mg)	15.0% [2.8–4.2]
APRICOT 2[221] (n=308; 3 mo)	MI (All received thrombolytic therapy)	Reocclusion at 3 mo	30% (80 mg,160 mg)	18% [2.0–3.0] (80 mg,160 mg)	...
CARS[210] (n=8803; 14 mo)	MI	Death, MI, stroke	8.6% (160 mg)	8.4% [warfarin 3 mg] (80 mg)	...
CHAMP[223] (n=5059; 31 mo)	MI	Death, MI, stroke	33.9% (162 mg)	34% [1.5–2.5] (81 mg)	...

OA indicates oral anticoagulation.

warfarin given in moderate intensity (estimated INR of 1.5 to 2.5) was found effective for prevention of stroke and pulmonary embolism (212–216). Of 3 randomized trials in which the effectiveness of oral anticoagulants was evaluated in patients with AMI (213–215), 2 (213,215) showed a significant reduction in stroke but no significant impact on mortality, whereas there was a reduction in mortality in the third (214). In all 3 studies, the incidence of clinically diagnosed pulmonary embolism was reduced. Effectiveness of oral anticoagulants in the long-term management of patients with AMI was supported by the results of a meta-analysis of data pooled from 7 randomized trials published between 1964 and 1980, which showed that oral anticoagulants reduced the combined end points of mortality and nonfatal reinfarction by ≈20% during treatment periods of between 1 and 6 years (215–217).

Subsequently, a higher INR was evaluated in several European studies. The Sixty-Plus Re-infarction Study included patients >60 years of age who had been treated with oral anticoagulants for ≥6 months; lower rates of reinfarction and stroke were observed in patients randomized to continue anticoagulant therapy than in those from whom anticoagulation was withdrawn (218). As a treatment-interruption trial in a select age group, the findings were of limited generalizability. In another study with no age restriction (the WArfarin Re-Infarction Study [WARIS]), Smith and associates (219) reported a 50% reduction in the combined outcomes of recurrent infarction, stroke, and mortality. Similarly, the Anticoagulants in the Secondary Prevention of Events in Coronary Thrombosis (ASPECT) trial (119), which also had no age restriction, reported ≥50% reduction in reinfarction and a 40% reduction in stroke among survivors of MI. Each of these studies (119,218,219) used high-intensity warfarin regimens (INR 2.7 to 4.5 in the Sixty-Plus Study and 2.8 to 4.8 in the WARIS and ASPECT studies); each found the incidence of bleeding was increased with anticoagulants.

More recently, several studies have evaluated different intensities of anticoagulation, either alone or in combination with aspirin (Tables 4 and 5). The ASPECT II study compared warfarin alone (goal INR 3.0 to 4.0) with aspirin (80 mg daily) and with the combination of aspirin (80 mg daily) plus warfarin (INR 2.0 to 2.5) in 993 patients after an acute coronary syndrome. The sponsor halted the study because of slow recruitment when the composite end point of death, MI, and stroke occurred in 9.0% of patients on aspirin alone, 5.0% of those on warfarin alone, and 5.0% of those on the combined regimen. There was an excess of minor bleeding in those on the combination of warfarin (INR 2.0 to 2.5) and aspirin (220) In the Antithrombotics in the Prevention of Reocclusion In COronary Thrombolysis (APRICOT) II study (221) of 308 patients with TIMI grade 3 coronary flow after thrombolysis for ST segment–elevation MI, aspirin (160 mg initially followed by 80 mg daily) was compared with aspirin in the same dosage combined with warfarin (INR 2.0 to 3.0) to assess the 3-month rate of angiographic reocclusion. Reocclusion occurred in 30% of the group given aspirin alone compared with 18% in those given aspirin plus warfarin (relative risk 0.60; 95% CI 0.39 to 0.93). There was an increase in minor but not major bleeding in the combination group (221). The WARIS II trial (222) compared warfarin or aspirin or both in 3630 patients <75 years of age with AMI randomized at the time of hospital discharge and followed up for 2 years for the first occurrence of the composite of all-cause death, nonfatal reinfarction, or thromboembolic stroke. This composite end point occurred in 20% of the patients on aspirin alone (160 mg/d), 16.7% of those on

TABLE 5. Randomized Trials in MI Comparing ASA, the Combination of ASA and Moderate- or Low-Intensity Warfarin, and High-Dose Warfarin: Bleeding

Study (No. of patients; follow-up period)	Acute Coronary Syndromes Patients	Bleeding	ASA	OA Plus ASA	OA (High Intensity)
ASPECT II[119] (n=993; 26 mo)	MI	Major	0.9%	2.1%	0.9%
WARIS II[222] (n=3630; 48 mo)	MI	Major	0.15% per y	0.58% per y	0.52% per y
APRICOT 2[221] (n=308; 3 mo)	MI All received thrombolytic therapy	Total	3%	5%	
CARS[210] (n=8803; 14 mo)	MI	Spontaneous	0.74%	1.4%	

OA indicates oral anticoagulation.

TABLE 6. Risk-Benefit Assessment of Oral Anticoagulant Therapy in Patients With Coronary Artery Disease: Meta-Analysis of 44 Trials Involving 24 115 Patients*

Anticoagulation Intensity	No. of Trials (No. of Patients)	Ischemic Events Odds Ratio (95% CI)	*P*	Major Bleeding Odds Ratio	*P*
High vs control	16 (n=10 056)	0.57 (0.51–0.63)	0.0001	39	0.00001
Moderate vs control	4 (n=1365)	0.85 (0.80–1.34)	>0.10	35	0.00001
Moderate to high vs ASA	7 (n=3457)	0.88 (0.63–1.24)	>0.10	14	0.00001
Moderate + ASA vs ASA	3 (n=480)	0.44 (0.23–0.83)	0.01	16	>0.01
Low + ASA vs ASA	3 (n=8435)	0.91 (0.79–1.06)	>0.01	5	0.05

*Constellation of death, myocardial infarction, or stroke events per 1000 patients.
Adapted from Anand and Yusuf, 1999.[225]

warfarin alone (mean INR 2.8), and 15% of those on the combination of both drugs (mean INR 2.2; aspirin 75 mg/d). Odds ratios for the combined end point were 0.71 for the combination of warfarin plus aspirin versus aspirin alone (95% CI 0.58 to 0.86; $P=0.0005$), 0.81 for warfarin alone versus aspirin alone (95% CI 0.67 to 0.98; $P=0.028$), and 0.88 for the combination versus warfarin alone (95% CI 0.72 to 1.07; $P=0.20$). The superiority of the combination over aspirin was highly significant at $P=0.0005$, but there was no significant difference between the 2 warfarin groups. Major bleeding occurred at a rate of 0.15% per year in the aspirin-alone group, 0.58% per year in the warfarin-alone group, and 0.52% per year in the combination group (222).

Two studies, CARS (210) and the Combined Hemotherapy And Mortality Prevention Study (CHAMP) (223), compared aspirin alone with the combination of aspirin and low-intensity warfarin (lower limit of targeted INR <2.0). The CARS study in 8803 patients with AMI showed that low fixed-dose warfarin (1 or 3 mg/d) plus aspirin (80 mg) was no more effective than aspirin alone (160 mg) for the long-term treatment of survivors of MI (209). Thus, after a mean of 14 months of follow-up, the incidence of death, recurrent MI, or stroke was 8.6 in the aspirin group and 8.4 in the combination of aspirin and warfarin (3 mg/d) group. Despite the lack of increased efficacy, the combined aspirin and warfarin (3 mg/d) group showed an increase in major bleeding. The CHAMP study (223) was an open-label trial that evaluated the relative efficacy and safety of aspirin alone (162 mg/d) and the combination of warfarin (INR 1.5 to 2.5) and aspirin (81 mg/d) in 5059 patients with AMI. There was no difference in total mortality (17.3% versus 17.3%), in nonfatal MI (13.1% versus 13.3%), or in nonfatal stroke (4.7% versus 4.2%). Despite lack of increased efficacy, major bleeding was more common in the combined treatment group.

Indirect support for the efficacy of oral anticoagulants in patients with coronary artery disease also comes from a randomized trial of patients with peripheral arterial disease (224). A relatively high-intensity oral anticoagulant regimen (INR 2.6 to 4.5) produced a significant 51% reduction in mortality (from 6.8% to 3.3% per year) compared with an untreated control group ($P<0.023$).

A meta-analysis of 31 randomized trials of oral anticoagulant therapy published between 1960 and 1999 involving patients with coronary artery disease treated for ≥3 months, stratified by the intensities of anticoagulation and aspirin therapy, is shown in Table 6. High-intensity (INR 2.8 to 4.8) and moderate-intensity (INR 2 to 3) oral anticoagulation regimens reduced the rates of MI and stroke but increased the risk of bleeding 6.0- to 7.7-fold. When combined with aspirin, low-intensity anticoagulation (INR <2.0) was not superior to aspirin alone, whereas moderate- to high-intensity oral anticoagulation and aspirin versus aspirin alone seemed promising. There was a modest increase in the bleeding risk associated with the combination (225).

Because a rebound increase in ischemic events has been documented after discontinuation of heparin (226) and LMWH (227,228), the use of oral anticoagulants to prevent reinfarction has been evaluated in several studies. The ischemic event rate was reduced by 65% after 6 months in one study of 102 patients ($P<0.05$) (229). In the Antithrombotic Therapy in Acute Coronary Syndromes (ATACS) trial (230), the combined rate of death, MI, and recurrent ischemia decreased from 27.5% to 10.5% after 2 weeks with an INR of 2.0 to 2.5 in 214 patients ($P=0.004$), but most of the benefit accrued during the earlier phase of heparin therapy. The Organization to Assess Strategies for Ischemic Syndromes (OASIS) (231) pilot study of hirudin versus heparin found a dose-adjusted warfarin regimen (INR 2 to 2.5) superior to a fixed dose (3 mg daily) over 6 months in 506 patients, all of whom were given aspirin concurrently. The 58% difference in the rate of death, MI, or refractory angina was marginally significant, but fewer patients were hospitalized for unstable angina ($P=0.03$).

From the results of these clinical trials, conclusions can be drawn about long-term treatment of patients with acute myocardial ischemia: (1) High-intensity oral anticoagulation (INR ≈3.0 to 4.0) is more effective than aspirin but is associated with more bleeding; (2) the combination of aspirin and moderate-intensity warfarin (INR 2.0 to 3) is more effective than aspirin but is associated with a greater risk of bleeding; (3) the combination of aspirin and moderate-intensity warfarin (INR 2.0 to 3.0) is as effective as high-intensity warfarin and is associated with a similar risk of bleeding; (4) the contemporary trials have not addressed the effectiveness of moderate-intensity warfarin (INR 2.0 to 3.0), and in the absence of direct evidence, it cannot be assumed that moderate-intensity warfarin is any more effective than aspirin in preventing death or reinfarction; and (5) there is no evidence that the combination of aspirin and low-intensity

warfarin (INR <2.0) is more effective than aspirin alone, despite the fact that the combination produces more bleeding.

Therefore, the choice for long-term management involves aspirin alone, aspirin plus moderate-intensity warfarin (INR 2.0 to 3.0), or high-intensity warfarin (INR 3.0 to 4.0). The latter 2 regimens are more effective than aspirin but are associated with more bleeding and are much less convenient to administer. Furthermore, in the absence of tight INR control, the high-intensity regimen has the potential to cause unacceptable bleeding. An alternative approach to long-term antithrombotic management of patients with acute myocardial ischemia is to use a combination of aspirin plus clopidogrel. Recommendations of the choice among these competing approaches is beyond the scope of this review on oral anticoagulants but should be addressed in future recommendations for the management of patients with acute myocardial ischemia.

Prosthetic Heart Valves

The most convincing evidence that oral anticoagulants are effective in patients with prosthetic heart valves comes from a study of patients randomized to receive warfarin in uncertain intensity versus either of 2 aspirin-containing platelet-inhibitor drug regimens for 6 months (232). The incidence of thromboembolic complications in the group that continued warfarin was significantly lower than that of the groups that received antiplatelet drugs (relative risk reduction 60% to 79%). The incidence of bleeding was highest in the warfarin group. Three studies addressed the minimum effective intensity of anticoagulant therapy. One study of patients with bioprosthetic heart valves found a moderate dose regimen (INR 2.0 to 2.25) as effective as a more intense regimen (INR 2.5 to 4.0) but associated with less bleeding (167). A second study (168), involving patients with mechanical prosthetic heart valves, found no difference in effectiveness between a very high-intensity regimen (INR 7.4 to 10.8) and a lower-intensity regimen (INR 1.9 to 3.6), but the higher-intensity regimen produced more bleeding. Another study (169) of patients with mechanical prosthetic valves treated with aspirin and dipyridamole found no difference in efficacy between moderate-intensity (INR 2.0 to 3.0) and high-intensity (INR 3.0 to 4.5) warfarin regimens, but more bleeding occurred with the high-intensity regimen. A more recent randomized trial showed that addition of aspirin (100 mg/d) to warfarin (INR 3.0 to 4.5) improved efficacy compared with warfarin alone (63). This combination of low-dose aspirin and high-intensity warfarin was associated with a reduction in all-cause mortality, cardiovascular mortality, and stroke at the expense of increased minor bleeding; the difference in major bleeding, including cerebral hemorrhage, did not reach statistical significance. A retrospective study of 16 081 patients with mechanical heart valves in the Netherlands attending 4 regional anticoagulation clinics (target INR 3.6 to 4.8) found a sharp rise in the incidence of embolic events when the INR fell to <2.5, whereas bleeding increased when the INR rose to >5.0 (120).

Guidelines developed by the European Society of Cardiology (233) 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, whereas an INR of 2.5 to 3.0 was deemed sufficient for second-generation valves in the aortic position. The American College of Chest Physicians guidelines (234) of 2001 recommended an INR of 2.5 to 3.5 for most patients with mechanical prosthetic valves and of 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. Similar guidelines have been promulgated conjointly by the American College of Cardiology and the American Heart Association (235). In contrast, a higher upper limit of the therapeutic range (INR 4.8 to 5.0) has been recommended by some European investigators (118,236).

Management of women with prosthetic heart valves during pregnancy and the potential shortcomings of heparin and LMWH in such patients have been discussed in the section on pregnancy.

Atrial Fibrillation

Five trials with relatively similar study designs have addressed anticoagulant therapy for primary prevention of ischemic stroke in patients with nonvalvular (nonrheumatic) atrial fibrillation. The SPAF study (237), the Boston Area Anticoagulation Trial for Atrial Fibrillation (BAATAF) (238), and the Stroke Prevention In Nonvalvular Atrial Fibrillation (SPINAF) trial were carried out in the United States (239); the Atrial Fibrillation, Aspirin, Anticoagulation study (AFASAK) was carried out in Denmark (240); and the Canadian Atrial Fibrillation Anticoagulation (CAFA) study (241) was stopped before completion because of convincing results in 3 of the other trials (242). In the AFASAK and SPAF trials, patients also were randomized to aspirin therapy (238,241). The results of all 5 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) (243). There was little difference between rates of major or intracranial hemorrhage in the warfarin and control groups, but minor bleeding was ≈3% per year more frequent in the warfarin-assigned groups (244). Pooled results from 2 studies were consistent with a smaller benefit from aspirin. In the AFASAK study, 75 mg daily did not significantly reduce thromboembolism, whereas in the SPAF trial, 325 mg per day was associated with a 44% stroke risk reduction in younger patients.

A secondary prevention trial in Europe (the European Atrial Fibrillation Trial [EAFT]) (245) compared anticoagulant therapy, aspirin, and placebo in patients with atrial fibrillation who had sustained nondisabling stroke or transient ischemic attack within 3 months. Compared with 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 (246) trial compared the efficacy and safety of warfarin with aspirin in patients with atrial fibrillation. Warfarin was more effective than aspirin for preventing

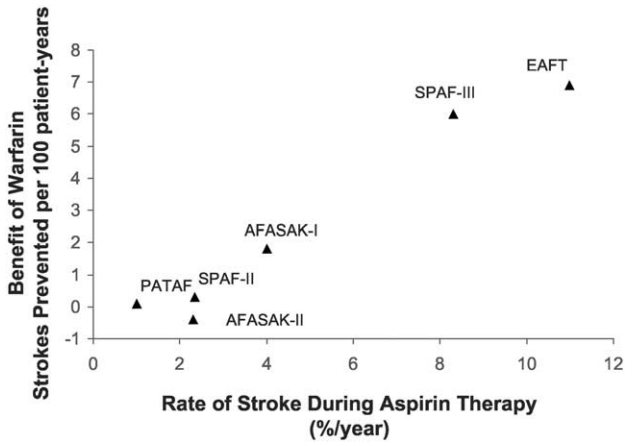

Figure 2. Advantage of anticoagulation over aspirin for patients with atrial fibrillation in 6 randomized trials: PATAF (249), SPAF II (247), AFASAK II (254), AFASAK I (241), SPAF III (124), and EAFT (246).

ischemic stroke, but this difference was almost entirely offset by a higher rate of intracranial hemorrhage with warfarin, particularly among patients >75 years of age, in whom the rate of intracranial hemorrhage was 1.8% per year. The intensity of anticoagulation was greater in the SPAF trials than in several of the other primary prevention studies; in addition, the majority of intracranial hemorrhages during these trials occurred when the estimated INR was >3.0. In the SPAF III study (124), 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 atrial fibrillation, whereas aspirin alone was sufficient for patients at low intrinsic risk of thromboembolism. Whether treatment targeted to the lower end of the therapeutic INR range (near 2) provides much, if not all, the benefit achieved remains to be evaluated in a prospective trial (123). In a Dutch general practice population without established indications for warfarin, neither low- nor standard-intensity anticoagulation was better than aspirin in preventing ischemic events (247).

In summary, the evidence indicates that both warfarin and aspirin are effective for prevention of systemic embolism in patients with nonvalvular atrial fibrillation. Warfarin is more effective than aspirin but is associated with a higher rate of bleeding. As might be expected, randomized trials involving high-risk atrial fibrillation patients (stroke rates >6% per year) show larger absolute risk reductions by adjusted-dose warfarin relative to aspirin, whereas the absolute risk reductions are consistently smaller in trials of atrial fibrillation patients with lower stroke rates. Warfarin, adjusted to achieve an INR of 2 to 3, is therefore most advantageous (from the perspective of benefit versus risk) for patients at greatest intrinsic risk. Subgroup analysis of the atrial fibrillation studies identified the following high-risk features: prior stroke or thromboembolism, age >65 years, hypertension, diabetes mellitus, coronary arterial disease, and moderate to severe left ventricular dysfunction by echocardiography (Figure 2) (173).

American College of Cardiology/American Heart Association/European Society of Cardiology guidelines for the management of patients with atrial fibrillation were published in 2001 (248).

Other Indications for Oral Anticoagulant Therapy

Other widely accepted indications for oral anticoagulant therapy have not been evaluated in properly designed clinical trials. Among these are atrial fibrillation associated with valvular heart disease, and mitral stenosis in the presence of sinus rhythm. Long-term anticoagulation (INR 2.0 to 3.0) also is indicated in patients who have sustained one or more episodes of systemic thromboembolism. Anticoagulants are not presently indicated in patients with ischemic cerebrovascular disease (249,250). Reduced left ventricular systolic function is associated with both stroke and mortality even in the absence of documented atrial fibrillation (251). Warfarin is used frequently in patients with dilated cardiomyopathy, although no randomized trials have confirmed the benefit of anticoagulation (252). Long-term anticoagulant therapy also is indicated in patients with ischemic stroke of unknown origin who have a combination of a patent foramen ovale and atrial septal aneurysm because these patients have an increased the risk of recurrent stroke despite treatment with aspirin (253).

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