Complete Summary

GUIDELINE TITLE

American Heart Association/American College of Cardiology Foundation guide to warfarin therapy.

BIBLIOGRAPHIC SOURCE(S)

Hirsh J, Fuster V, Ansell J, Halperin JL. American Heart Association/American College of Cardiology Foundation guide to warfarin therapy. Circulation 2003 Apr 1;107(12):1692-711. [254 references] PubMed

COMPLETE SUMMARY CONTENT

SCOPE
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RECOMMENDATIONS
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INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES
IDENTIFYING INFORMATION AND AVAILABILITY

SCOPE

DISEASE/CONDITION(S)

Chronic atrial fibrillation; venous thromboembolism; deep venous thrombosis or pulmonary embolism; ischemic coronary events; acute myocardial infarction; and systemic embolism in patients with prosthetic heart valves

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Evaluation
Management
Prevention
Risk Assessment
Technology Assessment
Treatment

CLINICAL SPECIALTY

Cardiology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To provide a guide to warfarin therapy

TARGET POPULATION

Patients with cardiovascular disorders including chronic atrial fibrillation, deep venous thrombosis or pulmonary embolism, acute myocardial infarction, and prosthetic heart valves as well as patients requiring prophylaxis against venous thromboembolism and ischemic coronary events

INTERVENTIONS AND PRACTICES CONSIDERED

Evaluation/Management

1. Prothrombin time (PT)
2. Activated partial thromboplastin time (aPTT)
3. International normalized ratio (INR) testing
4. Point-of-care patient self-monitoring using Biotrack 512, Thrombotest, Coumatrack, CoaguChek, ProTIME monitor, and Avocet PT.
5. Use of computerized algorithms for warfarin dose adjustment

Treatment

1. Warfarin
2. Heparin and low-molecular-weight heparin (LMWH)
3. Aspirin
4. Vitamin K_1
5. Infusion of fresh plasma or prothrombin concentrate

MAJOR OUTCOMES CONSIDERED

- Morbidity and mortality
- Cardiovascular mortality
- Hemorrhage incidence
- Recurrence of thromboembolism
- Incidence of stroke
- Incidence of reinfarction

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Not stated

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Not stated

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Not stated

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

This statement was approved by the American Heart Association Science Advisory and Coordinating Committee in October 2002 and by the American College of Cardiology Board of Trustees in February 2003. It was published in Circulation 2003;107:1692-1711 and co-published in the May 7, 2003 issue of The Journal of the American College of Cardiology.

MAJOR RECOMMENDATIONS

Management of Oral Anticoagulant Therapy

Monitoring Anticoagulation Intensity

The prothrombin time (PT) is the most common test used to monitor oral anticoagulant therapy. 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 approximately 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. 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 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. In 1992, the ISI of thromboplastins used in the United States varied between 1.4 and 2.8. 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. The International Normalized Ratio (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:

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

or

log INR = ISI (log 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.

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. 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 $\geq$6 weeks. 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 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.

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, whereas reagents with higher ISI values result in higher coefficients of variation. Variability of ISI determination is reduced by calibrating the instrument with lyophilized plasma depleted of vitamin K–dependent clotting factors. 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. 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.

ISI values provided by manufacturers of thromboplastin reagents are not invariably correct, 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. 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.

The concentration of citrate used to anticoagulate plasma affects the INR. In general, higher citrate concentrations ($\geq$3.8%) lead to higher INR values, 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. The prothrombin and proconvertin tests and measurements of prothrombin activity or native prothrombin concentration have been proposed as alternatives, 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 approximately 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 (e.g., 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. Starting doses <4 to 5 mg/d should be used in patients sensitive to warfarin, including the elderly, 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. 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, and the risk of thromboembolism increased when the INR fell to <2.0.

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 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.

By early 2000, the United States Food and Drug Administration (FDA) had approved 3 monitors for patient self-testing at home, but each instrument has limitations. Instruments currently marketed for this purpose are listed in Table 1 of the original guideline document. In a study 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. 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. Several investigators reported 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. Both classes of monitors (Biotrack and Coagu-Chek) compared favorably with traditionally obtained PT measurements at 4 laboratories and with the standard manual tilt-tube technique established by the World Health Organization using an international reference thromboplastin.

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, 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. 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).

The feasibility and accuracy of patient self-testing at home initially was evaluated in 2 small studies with promising results. More recently, 325 newly treated elderly patients were randomized 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 of the original guideline document.

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. These descriptive studies were then followed by several randomized trials. In the first study, 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. 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 ($n=89$) 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) 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. One study 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. Another study 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 studies 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, Bayesian forecasting, and a proprietary mathematical equation. 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. 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. 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. 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). In contrast, the INR declines substantially within 24 hours after treatment with vitamin K_1.

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 sub-therapeutic 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 (e.g., 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. 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. 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. 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:

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 (i.e., 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 (See table 3 of the original guideline document). Other contributing factors are the underlying clinical disorder 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. 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. These risk factors are additive; patients with 2 or 3 risk factors have a much higher incidence of warfarin-associated bleeding than those with none or one. The elderly are more prone to bleeding even after controlling for anticoagulation intensity. Bleeding that occurs at an INR of <3.0 is frequently associated with trauma or an underlying lesion in the gastrointestinal or urinary tract.

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. Although this difference in anticoagulant intensity is associated with an average warfarin dose reduction of only approximately 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 approximately 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 (e.g., 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. In certain subgroups of patients with atrial fibrillation, aspirin may be an appropriate alternative to warfarin.

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. 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 approximately 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 5,000 U (or LMWH in prophylactic doses of 3,000 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 (1,300 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 (e.g., 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 (5,000 U) or LMWH administered subcutaneously every 12 hours, if necessary.
- Finally, for patients undergoing dental procedures, tranexamic acid or epsilon-aminocaproic acid mouthwash can be applied without interrupting anticoagulant therapy.

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. 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, 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 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 the section above titled "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, one study reported that LMWH produced safe and effective anticoagulation when given for an average of 14.1 days to 102 non-pregnant 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 medicolegal 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 approximately 40 weeks; or (3) heparin or LMWH in the first trimester of pregnancy, switching to warfarin in the second trimester, continuing it until approximately 38 weeks´ gestation, and then changing to heparin or LMWH at 38 weeks with planned labor induction at approximately 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.

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 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 and, less commonly, protein S deficiency 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 (e.g., 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.

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. 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. The trial was stopped at the first interim analysis of 1,316 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]), 2,206 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 in 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.

Please refer to the original guideline document for a full discussion on clinical trials in the areas below.

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 and major gynecologic surgery. The risk of clinically important bleeding at this

intensity is modest. 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 approximately 3% per year with an annual case fatality rate of approximately 0.6%. On the other hand, the case fatality rate from recurrent venous thromboembolism is approximately 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. 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.

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. 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 $\geq$3 months in patients with proximal deep vein thrombosis, for $\geq$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. 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. 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.

These recommendations are based on results of randomized trials 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, and that treatment for 2 years is more effective than treatment for 3 months.

Primary Prevention of Ischemic Coronary Events

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 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.

Acute Myocardial Infarction

From the results of clinical trials, conclusions can be drawn about long-term treatment of patients with acute myocardial ischemia: (1) High-intensity oral anticoagulation (INR approximately 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

Guidelines developed by the European Society of Cardiology 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 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 bi-leaflet 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. In contrast, a higher upper limit of the therapeutic range (INR 4.8 to 5.0) has been recommended by some European investigators.

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

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 (see figure 2 of the original guideline document).

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

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. Reduced left ventricular systolic function is associated with both stroke and mortality even in the absence of documented atrial fibrillation. Warfarin is used frequently in patients with dilated cardiomyopathy, although no randomized trials have confirmed the benefit of anticoagulation. 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 risk of recurrent stroke despite treatment with aspirin.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of evidence supporting each recommendation is not specifically stated.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate use of warfarin therapy

POTENTIAL HARMS

- Drugs such as aspirin, nonsteroidal anti-inflammatory drugs, penicillins (in high doses), and moxolactam increase the risk of warfarin-associated bleeding by inhibiting platelet function. Because of potential interaction, the international normalized ratio (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.
- There is a close relation between the INR and risk of bleeding. The risk of bleeding increases when the INR exceeds 4, and the risk rises sharply with values >5. See the "Major Recommendations" section of this summary and the original guideline document for further discussions of the risks associated with anticoagulant therapy.
- 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.

CONTRAINDICATIONS

CONTRAINDICATIONS

- 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.
- 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. 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.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

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Hirsh J, Fuster V, Ansell J, Halperin JL. American Heart Association/American College of Cardiology Foundation guide to warfarin therapy. Circulation 2003 Apr 1;107(12):1692-711. [254 references] PubMed

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

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AVAILABILITY OF COMPANION DOCUMENTS

None available

PATIENT RESOURCES

None available

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