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*Chest* 2001;119;22S-38S
DOI 10.1378/chest.119.1_suppl.22S

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ISSN:0012-3692
Managing Oral Anticoagulant Therapy

Jack Ansell, MD; Jack Hirsh, MD, FCCP; James Dalen, MD, FCCP, Henry Bussey, PharmD; David Anderson, MD; Leon Poller, MD; Alan Jacobson, MD; Daniel Depkin, MD; and David Matchar, MD

Abbreviations: AMS = anticoagulation management service; CV = coefficient of variation; INR = international normalized ratio; IRP = international reference preparation; ISI = international sensitivity index; LMWH = low-molecular-weight heparin; NS = not significant; POC = point of care; PST = patient self-testing; PT = prothrombin time; SC = subcutaneous; TTR = time in therapeutic range; UC = usual care

(CHEST 2001; 119;22S–38S)

Several important developments in the last 2 decades have improved clinical outcomes with oral anticoagulation therapy and have led to an appropriate increase in the use of this therapy by improving its safety. These developments include defining the appropriate indications for oral anticoagulation through the results of large randomized trials, identifying the optimal therapeutic range and reporting format (ie, international normalized ratio [INR]) to maximize safety and effectiveness, and managing the dose of therapy to achieve the maximal time in therapeutic range (TTR). The intensity of therapy and the TTR are two of the most important determinants of therapeutic effectiveness and of reducing hemorrhagic risk. Ideally, the INR should be kept in the therapeutic range most of the time, but many factors influence the attainment of this goal. These include physiologic and pharmacologic factors, such as interacting drugs or illnesses that affect the pharmacokinetics or pharmacodynamics of warfarin, dietary or GI factors that affect the availability of vitamin K₁, or physiologic factors that affect the synthetic or metabolic fate of the vitamin K-dependent coagulation factors. Patient-specific factors such as adherence to a therapeutic plan are also important. Last, the physician’s ability to make appropriate dosing and follow-up decisions will have a profound impact, if such decisions are incorrect. The comprehensive management of these variables requires a knowledgeable provider, an organized system of follow-up, reliable prothrombin time (PT) monitoring, and good patient communication and education. This article focuses on dosing management and models of care, and it reviews the evidence that indicates that an organized approach to anticoagulant management leads to better outcomes.

PRACTICAL DOSING

Initiation and Maintenance Dosing

Following the administration of warfarin, an observable anticoagulant effect occurs within 2 to 7 days, depending on the dose administered. When a rapid effect is required, heparin should be given concurrently with warfarin for at least 4 days. The common practice of initiating warfarin therapy with a loading dose is unnecessary in most patients, and commencing with an average maintenance dose of 5 mg warfarin usually results in an INR of 2.0 in 4 or 5 days. Heparin treatment is usually discontinued when the INR has been in the therapeutic range on two measurements made at least 24 h apart. If treatment is not urgent (eg, chronic stable atrial fibrillation), treatment can be commenced out-of-hospital with an anticipated maintenance dose of 4 to 5 mg/d, which usually achieves a therapeutic anticoagulant effect in about 5 days, although a stable INR may take longer to achieve. The fear of creating a hypercoagulable state in patients with unrecognized protein C deficiency who are not simultaneously receiving heparin has not been substantiated. However, in patients with a known protein C deficiency or other thrombophilic state, it would be prudent to begin administering heparin before or at the same time as warfarin. There is room for flexibility in selecting a starting dose of warfarin. Some clinicians prefer to use a larger starting dose (eg, 7.5 to 10 mg) if there is urgency in obtaining a therapeutic INR. Additionally, starting doses <5 mg might be appropriate in the elderly, in patients with impaired nutrition or liver disease, and in patients at high risk for bleeding.

PT monitoring is usually performed daily until the therapeutic range has been achieved and maintained for at least 2 consecutive days, then it is monitored two or three times weekly for 1 to 2 weeks, then less often, depending on the stability of PT results. If the PT response remains stable, the frequency of testing can be reduced to intervals as long as every 4 weeks, although there is growing evidence to suggest that more frequent testing will lead to greater TTR (see below). If adjustments to the dose are required, then the cycle of more frequent monitoring is repeated until a stable dose response again is achieved.

Anticoagulation Therapy in the Elderly

The physician should be aware of the factors that influence the response to anticoagulation therapy in the elderly. The dose required to maintain a therapeutic range for patients >60 years of age has been shown to decrease with increasing age, possibly because the clearance of warfarin decreases with age. Older patients are also more likely to have a greater number of other factors that might influence INR stability or might influence the risk of bleeding, such as a greater number of other medical conditions or concurrent drug use. Consequently, it is advisable to monitor older patients more carefully in order to maximize their time in the therapeutic range.

Management of Nontherapeutic INRs

Some patients receiving long-term warfarin therapy are difficult to manage because they have unexpected fluctuations in dose response. These unexpected fluctuations could be due to a number of variables, including inaccuracy in PT testing, changes in vitamin K₁ intake (ie, increased or decreased vitamin K₁ in the diet), changes in

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vitamin K$_1$ or warfarin absorption (eg, GI factors or drug effects), changes in warfarin metabolism (eg, liver disease or drug effects), changes in vitamin K$_1$-dependent coagulation factor synthesis or metabolism (eg, liver disease, drug effects, or other medical conditions), other effects of undisclosed concomitant drug use, or patient compliance issues (eg, surreptitious self-medication, missed doses, miscommunication about dose adjustment, etc).

Three approaches can be taken to reduce an elevated INR. The first is to stop warfarin therapy; the second is to administer vitamin K$_1$; the third, and most rapidly effective, is to infuse fresh frozen plasma or prothrombin concentrate, although the latter may be difficult to obtain and may carry the risk of virus transmission. The choice of approach is based largely on clinical judgment, since to our knowledge, there have been no randomized trials using clinical end points to compare these strategies. When warfarin therapy is interrupted, White and associates$^{20}$ found that it takes about 4 to 5 days for the INR to return to the normal range in patients whose INRs are between 2.0 and 3.0. After treatment with oral vitamin K$_1$, the INR declined substantially within 24 h. Since the absolute daily risk of bleeding is low even when the INR is excessively prolonged, many physicians manage patients with INR values of 4.0 to 10.0 by stopping warfarin therapy and monitoring more frequently.$^{20}$ unless the patient is at an 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 therapy is reinstated$^{31}$ or without exposing the patient to the risk of anaphylaxis. High doses of vitamin K$_1$, though effective, may lower the INR more than is necessary and may lead to warfarin resistance for up to a week. Vitamin K$_1$ can be administered by IV, subcutaneous, or oral routes. IV injection may be associated with anaphylactic reactions,$^{32}$ and there is no definitive evidence that this serious, but rare, complication can be avoided by using low doses. The response to subcutaneous vitamin K$_1$ may be unpredictable and sometimes delayed.$^{33,34}$ Recent studies confirm earlier reports that oral administration is predictably effective and has the advantages of safety and convenience over parenteral routes.

In 1993, Pengo and associates$^{35}$ confirmed earlier observations$^{36,37}$ of the effectiveness of oral vitamin K$_1$ by a randomized trial demonstrating that 2.5 mg oral vitamin K$_1$ was more effective than withholding warfarin for correcting the INR to $<5.0$ at 24 h. Weibert and associates,$^{38}$ in a retrospective cohort study, evaluated the effectiveness of a 2.5-mg dose of oral vitamin K$_1$ for reversing an excessive warfarin effect in 81 patients with an INR of $>5.0$. Ninety percent of the patients achieved an INR of $<5.0$, and only 17% developed an INR of $<2.0$. An INR of $<5.0$ was achieved in 48 h in all patients whose initial INRs were $<9.0$. However, a dose of 2.5 mg oral vitamin K$_1$ failed to lower the INR to $<5.0$ in five of eight patients (63%) whose initial INRs were $>9.0$. In patients with excessively prolonged INR values, oral vitamin K$_1$, 5 mg, more reliably lowered the INR to $<5.0$ within 24 h than simply withholding warfarin therapy. Crowther and associates$^{39}$ carried out a prospective cohort study of 62 patients treated with warfarin who had INR values between 4.0 and 10.0. The next dose of warfarin was omitted, and vitamin K$_1$, 1 mg, was administered orally. After 24 h, the INR was lowered in 59 patients (95%), fell to $<4.0$ in 53 patients (85%), and to $<1.9$ in 22 patients (35%). No patients developed resistance when warfarin therapy was resumed. These observations indicate that oral vitamin K$_1$ is effective in low doses for reducing the INR in patients treated with warfarin. A dose range of 1.0 to 2.5 mg is effective when the INR is between 5.0 and 9.0, but larger doses (5 mg) are required to correct INRs $>9.0$.

Oral vitamin K$_1$ is the treatment of choice, but vitamin K$_1$ can be administered by slow IV infusion when there is a greater urgency to reverse anticoagulation. The 1998 American College of Chest Physicians recommendations for managing patients receiving coumarin anticoagulants who need their INRs lowered because of actual or potential bleeding are listed at the end of this chapter. These recommendations have not changed in the last 2 years and are all grade 2C.

**Management of Oral Anticoagulation During Invasive Procedures**

Clinicians often are required to assess the risk of bleeding from a procedure if anticoagulation therapy is continued vs the risk of thrombosis if anticoagulation therapy is discontinued, as well as the cost of alternative anticoagulation options. This subject has been reviewed with suggested alternative options based on an estimate of the preoperative and postoperative daily risk of bleeding or thrombosis.$^{40}$ With each of the following options, the length of time for warfarin dosage reduction and for the duration of heparin or low-molecular-weight heparin (LMWH) use preoperatively can be shortened by administering vitamin K$_1$ 24 to 48 h before surgery to reverse the warfarin effect. Traditionally, full dose, IV, unfractionated heparin has been the standard therapy for patients who need full anticoagulant protection that is readily reversible before a procedure. Its major drawback is the complexity and cost associated with IV heparin therapy and hospitalization. LMWH now offers another, simpler alternative approach. Johnson and Turpie$^{41}$ used LMWH in a prospective cohort study (dalteparin, 100 anti-Xa U/kg, subcutaneous [SC], bid) in 112 patients with mechanical heart valves, atrial fibrillation, or venous thromboembolism undergoing urologic, cardiac, eye, or dental procedures. Patients received an average of five doses before the procedure and 4.3 doses started 8 to 12 h after the procedure. Patients discontinued warfarin therapy for an average of 5.4 days. One patient experienced a major episode of bleeding in the rectus muscle at the injection site. There were no thromboembolic events. Timmout et al$^{42}$ reported on a prospective cohort of 27 patients with mechanical heart valves, atrial fibrillation, and venous thromboembolism who were at high risk for stroke. Patients received LMWH (dalteparin, 200 anti-Xa U/kg SC qd) on the 2 days before the procedure, and therapy was restarted 12 to 24 h after the procedure. Warfarin therapy was discontinued 4 days before the procedure. Among the
22 evaluable patients, there were two episodes of minor bleeding, and one patient experienced a transient ischemic attack. The investigators also demonstrated a $4,285 (Canadian) per patient savings as a result of using LMWH as an outpatient to avoid hospitalization. Last, Spandorfer et al.\(^4\) treated a cohort of 20 patients who had prosthetic cardiac valves, atrial fibrillation, or thrombophilia with LMWH (enoxaparin, 1 mg/kg SC bid) in preparation for a variety of invasive procedures. Warfarin therapy was started 5 to 6 days before the procedure, and LMWH therapy was started 36 h later and then stopped 12 to 18 h before the procedure. LMWH therapy was restarted at a mean of 13.5 h after the procedure. One patient experienced a significant drop in hemoglobin of 2 g/dL after the procedure. No thromboembolic complications developed. The results of these three studies suggest that LMWH is a simple and less costly alternative for full anticoagulation protection, but randomized, controlled trials are still needed to identify the best means of alternative anticoagulation therapy. Recommendations for the management of anticoagulation therapy during invasive procedures are presented at the end of this article.

Dental procedures represent a particularly common intervention for patients receiving anticoagulant therapy. A comprehensive review of the subject\(^1\) indicated that in most cases, no change in the intensity of anticoagulation is needed. To our knowledge, there are no well-documented cases in the literature of serious bleeding in this setting, but there are a number of documented cases of embolic events in patients whose warfarin therapy was discontinued for dental treatment. If there is a need to control local bleeding, tranexamic acid or epsilon amino caproic acid mouthwash has been used successfully without interrupting anticoagulant therapy.\(^4,12\)

### Adverse Events (Hemorrhage)

#### Definition of Major and Minor Hemorrhage

Precise estimates of hemorrhagic event rates are complicated by the inconsistency between classification schemes in clinical research studies.\(^12\) The goal of classification is to place a bleeding episode on a continuum of severity ranging from minor events, such as brief epistaxis that would not have been reported to a physician (but would, for example, be recorded as part of a clinical trial), to a fatal or life-threatening episode of bleeding. Fihn et al.\(^12\) established the following three categories: minor (reported, but not requiring additional testing, referrals, or visits); major (requiring treatment, medical evaluation, or at least 2 U blood); and life threatening (leading to cardiac arrest, surgical/angiographic intervention, or irreversible sequelae). Most other investigators, however, divide adverse events into minor and major categories, with major events including fatal or life-threatening bleeding episodes (eg, intracranial or retroperitoneal) or bleeding with a defined drop in hemoglobin level, leading to transfusion of a specified number of units of blood or to hospitalization. The reader must be aware of these discrepancies when interpreting the results from clinical studies. For purposes of comparison between studies, we suggest that investigators define hemorrhagic events into major and minor categories with qualifying criteria such as those examples listed above.

#### Risk Factors for Adverse Events

**Intensity of Treatment:** Bleeding is the main complication of oral anticoagulant therapy. The most important factor influencing the risk of bleeding is the intensity of anticoagulant therapy.\(^4,12–14\) Four randomized studies have specifically demonstrated that the risk of clinically important bleeding is reduced by lowering the therapeutic range from 3.0 to 4.5 to 2.0 to 3.0.\(^4–7\) A number of additional studies have shown what amounts to an exponential increase in hemorrhagic events as the INR increases > 5.0.\(^8,9,10,11,47\)

**Patient Characteristics:** Several patient characteristics have been shown to be associated with higher odds of bleeding during anticoagulation therapy.\(^4,12–14,47–56\) The patient factor most consistently demonstrated to be predictive of episodes of major bleeding is a history of bleeding (especially GI bleeding).\(^12,13,51\) Other factors that have been shown to be associated include a history of stroke and the presence of a serious comorbid condition, such as renal insufficiency, anemia, or hypertension.\(^12–14,47–56\) The relationship between older age and anticoagulant-associated bleeding is controversial. Several reports have suggested that older individuals are not at an increased risk for bleeding\(^12,48,49,57–67\) while others have described such an association.\(^8,13,47,52,54,68–72\) This issue is of clinical importance since older individuals often have conditions that warrant anticoagulation therapy and some recommendations for anticoagulation have been based in part on patient age.\(^71\) Establishing a causal association between old age per se and an increased risk of anticoagulant-associated bleeding is difficult since age may simply be associated with comorbid conditions, which themselves are risk factors for bleeding (eg, colonic polyps, concomitant medications, or poor anticoagulant control due to lack of compliance). Some studies indicate that older patients who have high-quality anticoagulation management, such as that provided by an anticoagulation clinic, have the same risk of bleeding as their younger counterparts.\(^77\) Some studies that attempted to separate the effect of age from comorbid conditions associated with age concluded that age in and of itself is not a major independent risk factor.\(^12,50,72,73\) while others have found it to be an independent risk factor.\(^14\) even after controlling for the intensity of the anticoagulant effect. Individuals who are otherwise good candidates for anticoagulation therapy should not have it withheld because of their age. However, elderly patients should be monitored more carefully in order to maximize their time in the therapeutic range (grade 2C, see “Recommendations” section).

**TTR:** A strong relationship between TTR and bleeding or thromboembolic rates has been observed across a large number of studies with different patient populations, different target ranges, different scales for measuring the intensity of anticoagulation (ie, PT, PT ratio, and INR),...
In a large representative study by Cannegieter et al., the relationship between TTR and major episodes of bleeding was approximately exponential; that is, small departures from the target range were associated with small-to-moderate increases in bleeding rates, while large departures from the target range were associated with large increases in bleeding rates. A similar relationship holds for TTR and thromboembolism rates, and when bleeding and thromboembolism are considered simultaneously, the overall relationship is U-shaped. Table 1 summarizes the data from those studies, assessing the quality of anticoagulation therapy as reflected by TTR. Most studies, however, fail to measure the quality of anticoagulation man-

<table>
<thead>
<tr>
<th>Study/Year</th>
<th>Predominant Management Model</th>
<th>PTR vs INR</th>
<th>TTR, %†</th>
<th>Range, %</th>
<th>Frequency of Monitoring</th>
<th>Method of Determining TTR</th>
<th>Major Diagnosis</th>
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<tr>
<td>Garabedian-Ruffalo et al 82/1985</td>
<td>UC PTR</td>
<td>64 — — —</td>
<td>% in range</td>
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<td>50 30 20</td>
<td>Every 25 d‡</td>
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<td>Beyth and Landefeld 85/1997</td>
<td>UC INR</td>
<td>33 16 51 —</td>
<td>—</td>
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<td>59 — — 19 d‡</td>
<td>% in range</td>
<td>Valves</td>
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<td>34 16 50 —</td>
<td>% in range</td>
<td>AF/valves</td>
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<td>68 6 26 15 d‡</td>
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<td>AF</td>
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<tr>
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<td>86 — — —</td>
<td>% in range</td>
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<tr>
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<td>75 — — —</td>
<td>Days in range</td>
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<td>AMS PTR</td>
<td>68 10 22 16 d‡</td>
<td>Days in range</td>
<td>Mixed</td>
<td></td>
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<tr>
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<td>59 12 29 —</td>
<td>—</td>
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<td>Days in range</td>
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<td>SPAF I 91/1991</td>
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<td>71 5 23 At least once a month</td>
<td>% in range</td>
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<td>% in range</td>
<td>AF</td>
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<tr>
<td>SPAF III 96/1996</td>
<td>RCT INR</td>
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<td>% in range</td>
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<td>48 24 26 Every 2-6 wk</td>
<td>% in range</td>
<td>AF</td>
<td></td>
<td></td>
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</tbody>
</table>

*RCT = randomized controlled trial; PTR = prothrombin time ratio; TT = thrombotest; Mixed = mixed indications for anticoagulation; valves = cardiac prosthetic valve; AF = atrial fibrillation; % in range = the proportion of PT tests in range divided by the total number of tests; days in range = the estimated days or time in range as determined by various methodologies; AFASAK = Atrial Fibrillation, Aspirin, and Anticoagulant Therapy; BAATAF = Boston Area Anticoagulation Trial For Atrial Fibrillation; SPAF = Stroke Prevention in Atrial Fibrillation; CAAFA = Canadian Atrial Fibrillation Anticoagulation; EAFT = European Atrial Fibrillation Trial; SPINAF = Stroke Prevention in Atrial Fibrillation Trial.

†TTR represents mean or median percentage of PTs or days in range.

‡Those studies that documented the achieved frequency of monitoring as opposed to the stated goal for monitoring interval.
agement as reflected by TTR. We believe that this is a deficiency that can lead to erroneous interpretation of results, and we urge investigators to measure TTR in their studies. There is still difficulty, however, in comparing TTR across studies because different methods are used to measure TTR. The most common method expresses the proportion of INR values within the therapeutic range as the number of INRs within the range divided by the number of PT tests. This method is biased and is likely to underestimate the TTR because the result is affected by the tendency of physicians to perform repeated tests soon after obtaining an out-of-range INR (eg, to verify the initial INR or to assess the effect of a dosage adjustment). Another approach is the cross-section of the files method, in which a given date is selected and the proportion of INRs within target range, using the most recent INR value, is calculated for each patient. The cross-section of the files method is unbiased but is inefficient as it fails to utilize test results between the assessment dates. Two other methods try to overcome these problems and assess actual days spent in or out of range. The equidivision method assumes that the change between the two consecutive INR measurements occurs halfway between the two tests. It has been shown to be reproducible but not valid. The linear interpolation method of Rosendahl et al is based on calculating the actual time in target range by first linearly interpolating between observed test values and then defining the TTR as the number of patient-days of follow-up that were within the target range divided by the total number of patient-days included in the follow-up period. The results of all of these methods depend on the choice of target INR range, and therefore, the TTR can be enhanced considerably if the target range is expanded, even in the absence of any actual improvements in the quality of anticoagulation therapy management. Another deficiency is that the various methods of assessment treat small departures from target range as identical to large departures, even though the former would have much less impact on clinical outcomes than the latter. These differences must be taken into account when comparing results across multiple studies. The data in Table 1 indicate the various methodologies used for determining TTR.

Frequency of Testing: The optimal frequency of monitoring the INR is dependent on many factors, including patient compliance, transient fluctuations in comorbid conditions, the addition or discontinuation of treatment with other medications, changes in diet, the quality of dose-adjustment decisions, and whether treatment is early or late in the course of therapy. Some investigators have attempted to develop predictive models with the goal of reducing the frequency of testing without sacrificing quality. The results of a few clinical trials suggest that TTR, and presumably fewer adverse events, can be maximized by more frequent testing. This is particularly true in studies utilizing patient self-testing in which access to testing is virtually unlimited. Horstkotte et al specifically addressed this issue in a study of 200 patients with mechanical cardiac valves in whom the percentage of INRs within the target range varied from 48%, when monitoring occurred at an average interval of 24 days, to 89%, when monitoring occurred at an average interval of every 4 days. These results, however, are inconclusive because of questions about how TTR was calculated and other methodologic issues.

Frequency of Hemorrhage

The frequency of hemorrhage associated with oral anticoagulant therapy is reviewed in detail in another article in this supplement (see page 108). The rate of hemorrhagic events must be interpreted not only in the context of the quality of anticoagulation management (eg, the model of anticoagulant care and TTR), but also with consideration of a number of the other factors discussed above, as well as factors such as whether therapy was monitored by the use of the PT or INR, whether the indications studied included patients with mixed diagnoses or a restricted indication, and whether the patients studied were new to anticoagulation therapy or were patients already established on a regimen of long-term therapy.

Nonhemorrhagic Adverse Events

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

Management of Adverse Events

Management of the Patient Who Bleeds During Warfarin Therapy

The short-term management of patients who bleed with an excessively prolonged INR has been discussed above. The long-term management of patients who bleed but who require ongoing protection against systemic embolism (eg, patients with mechanical heart valves or with...
atrial fibrillation and other risk factors) is problematic. There are two general principles that should be followed: (1) to attempt to identify and reverse the cause of bleeding; and (2) to examine the possibility of lowering the intensity of the anticoagulant effect. Every effort should be made to treat the cause of bleeding (eg, the use of aggressive antulcer therapy) if it is potentially reversible.

The risk of bleeding is strongly related to the intensity of the anticoagulant effect. Therefore, in patients who continue to bleed, every effort should be made to maintain the INR at the lower limit of the therapeutic range (ie, 2.0). Laboratory control of treatment should be optimized with frequent INR measurements and by ensuring that a sensitive thromboplastin (international sensitivity index [ISI], < 1.5) is used.106 For patients with mechanical prosthetic valves (and a persisting risk of increased bleeding), it would be reasonable to aim for an INR range of 2.0 to 2.5. For patients with atrial fibrillation (and a persisting risk of increased bleeding), the anticoagulant intensity can be reduced to an INR range of 1.5 to 2.0 with the expectation that efficacy will be reduced but not abolished.10 Alternatively, aspirin can be used to replace warfarin in patients with atrial fibrillation, but also with a reduced efficacy in high-risk patients.

Diagnostic Evaluation of Bleeding

When bleeding occurs, especially from the GI tract or urinary tract, it is important to consider the possibility of a serious, underlying occult lesion as the source of bleeding. A number of descriptive studies indicate the probability of finding such a lesion.68,107,108 Coon and Willis68 identified serious, underlying occult lesion as the source of bleeding. In a prosaic way, it is important to consider the possibility of a lesion that is not directly visible, such as a tumor or a vascular malformation. A careful physical examination, including a rectal examination, should be performed. In patients with anemia, a bone marrow aspiration may be necessary to rule out a hematological disorder. If an occult lesion is suspected, diagnostic tests, such as endoscopy, should be performed. If hematuria persists, further evaluation may be required, such as a cystoscopy or a renal biopsy.

Models of Anticoagulation Management

The effectiveness and safety of warfarin are critically dependent on maintaining the INR in the therapeutic range. This objective is facilitated by aiming for an INR that is in the middle of the INR range (ie, a goal of 2.5 for a designated range of 2.0 to 3.0, and a goal of 3.0 for a designated range of 2.5 to 3.5). The impact of maintaining good anticoagulant control was highlighted by reanalysis of the primary prevention trials in atrial fibrillation using an on-treatment analysis.1 The results of the on-treatment analysis showed that a majority of the events (both thromboembolic and bleeding) occurred when the PT ratio was outside the designated therapeutic range and that both the safety and efficacy of warfarin were increased by maintaining good anticoagulant control. Subgroup analyses of other cohort studies have also shown a sharp increase in the risk of bleeding when the INR is higher than the upper limit of the therapeutic range.10,11.114

Approaches to improve anticoagulant control include the use of (1) anticoagulation management services (AMSs) (ie, anticoagulation clinics) to manage therapy, (2) point-of-care (POC) PT testing that allows patient self-testing (PST) and patient self-management (PSM) of dose adjustments, and (3) computer programs to aid in dose adjustment.

Usual Care vs AMSs

There is growing evidence that better outcomes are achieved when anticoagulation is managed by an AMS compared to patients managed by their personal physicians (ie, usual care [UC]). The latter is the predominant model of therapy in North America,115 whereas anticoagulation clinics have long been the model of care in the United Kingdom and the Netherlands.116 Unfortunately, the available literature on the benefits of an AMS consist mostly of descriptive reports, case control studies, or nonrandomized prospective studies. Extrapolation of the rates of adverse events from many of the large randomized controlled studies to everyday practice is limited by the fact that indications studied are often restricted, patients are highly selected, and monitoring and management of anticoagulation are highly coordinated.

Tables 2 to 4 summarize the results of studies assessing the frequency of hemorrhage or thrombosis based on the model of care. These studies were selected based on the following criteria: published in 1980 or later (excluding abstracts); providing sufficient information to classify the model of care as either UC or an AMS; defining the criteria for major hemorrhage; identifying the rate of major hemorrhage; and providing information to determine the number of patient-years of therapy for comparative purposes. Table 2 summarizes three large retrospective observational studies on UC.13,51,55 Each study reports on patients followed up by private physicians in a particular locale. Results indicate a frequency of major hemorrhage of approximately 7.7% per patient-year of therapy, with recurrent thromboembolism of 5.1% per patient-year in one study. Table 3 summarizes the results achieved with an AMS from mostly retrospective observational analyses that met selection criteria.10,12,47,54,57,61,91,92,117 A majority
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Table 2—Frequency of Major Hemorrhage/Thromboembolism in Patients Managed Under a UC Model of Management*

<table>
<thead>
<tr>
<th>Study/Year</th>
<th>Patients, No.</th>
<th>Patient-yr, No.</th>
<th>Data Collection, yr</th>
<th>New or Established Patients</th>
<th>Indications</th>
<th>Recent TE†</th>
<th>Definition of Major Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gitter et al†/1995</td>
<td>261</td>
<td>221</td>
<td>1987–1989</td>
<td>Established</td>
<td>Ven art</td>
<td>8.1</td>
<td>0.45</td>
</tr>
<tr>
<td>Beyth et al†/1998</td>
<td>264</td>
<td>440</td>
<td>1986–1993</td>
<td>New</td>
<td>Ven art</td>
<td>5.0</td>
<td>0.68</td>
</tr>
</tbody>
</table>

*Ven art = mixed indications in the venous and arterial system; NA = not available; hct = hemoglobin count; TE = thromboembolism.
†Values expressed as percent per patient-year of therapy; fatal hemorrhagic events also included with major hemorrhage.

of the earlier studies used a PT ratio to monitor therapy, thereby potentially providing more intense therapy. Higher rates of bleeding are noted in these earlier studies compared to the last three that employed an INR to monitor therapy. Table 4 summarizes the four studies in which investigators used clinical outcomes to compare two models of care in a single setting.53,82,118,119 All of these studies used a before-and-after design, and none were prospective randomized trials. In two studies,53,82 the same patient groups were observed first in a UC setting and then in an AMS setting. The third study118 involved two defined cohorts of patients, and the fourth report119 provided data on the following three sequential inception cohorts: an initial AMS; then a UC cohort; followed by a second AMS cohort. Although none of these trials were randomized, each reported an impressive reduction in the incidence of major hemorrhage and thromboembolism, and the one study that evaluated death due to bleeding or thromboembolism found a reduction that approached statistical significance (p = 0.09).119

Although these results suggest that the coordinated approach of an anticoagulation clinic is superior to UC, the studies were not randomized and therefore, they need to be validated. A recently completed prospective randomized trial (the MAST trial)120 should provide more definitive information in this regard as preliminary evidence suggests.18

Cost-effectiveness of UC vs AMS

Because of improved outcomes with fewer hospitalizations and emergency department visits, the management of anticoagulation therapy by an AMS may prove to be cost effective. Gray et al121 estimated a savings of $860 per patient-year of therapy in 1986 due to reduced hospital days in a study of patients treated by an AMS vs UC. Chiquette et al119 found a savings of $1,621 per patient-year of therapy in their comparative study due to a significant reduction in hospitalizations and emergency department visits. Last, Wilt et al118 found an extremely high rate of savings ($4,072 per patient-year of therapy) due to reduced utilization of services. These observations need to be validated by randomized studies.

POC PST and PSM

Recent technological advances in POC PT measurement offer the potential for both simplifying and improving oral anticoagulation management in the professional setting as well as at home. POC monitors measure a thromboplastin-mediated clotting time that is then converted to a plasma PT equivalent by a microprocessor and expressed as a PT or INR. Three monitors are approved for PST at home.122 (Table 5).

The validity of this methodology was initially established in 1987 by Lucas et al123 using a monitoring instrument (Coumatrak; Biotrack Inc; Freemont, CA) that showed an r value of 0.96 between reference plasma PTs and capillary whole-blood PTs in 858 samples from 732 subjects (ie, control subjects, warfarin-treated patients, and heparin-treated patients). Within-day precision using two different levels of control subjects revealed coefficients of variation (CVs) of 4.9% and 2.9%. The accuracy of the instrument was not compromised by hematocrit measurements ranging from 23 to 54%. Other studies have confirmed the accuracy of the instrument (r = 0.95)124 compared to reference laboratory methods (r = 0.91).125

POC instruments, however, do have limitations, as demonstrated by other studies. Using a derivative of the Biotrack ProTime monitor (Biotrack 512; Ciba Corning; Medfield, MA), Jennings et al126 found poor comparability between the instrument and the thrombotest, with the former underestimating the INR by a mean of 0.76 INR units. The precision of the instrument was considered to be good (CV, 7.5% and 4.5%, respectively). McCurdy and White,127 with another derivative of the Biotrack monitor (Coumatrak; DuPont; Wilmington, DE), found that the capillary method yielded the most accurate results in an INR range of 2.0 to 3.0, but that the results of the two methods became discrepant as the INR increased. Tripodi et al128 found with the Biotrack 512 model that by recalibrating the ISI of the instrument’s thromboplastin
against the secondary international reference preparation (IRP) for rabbit thromboplastin, it was systematically higher (ISI, 2.715) than that reported by the manufacturer (ISI, 2.036). Like McCurdy and White, they found that the monitor underestimated the results as the INR increased (ie, INR > 4.0). However, this error was not instrument-related but the result of a faulty ISI; the error did not occur when the INR was recalculated using their recalibrated ISI.

In a second class of PT monitors (CoaguChek; Roche Diagnostics; Indianapolis, IN), Oberhardt et al reported an r value of 0.96 in 271 samples compared to standard laboratory methods. Rose et al determined within-day precision for normal and abnormal control plasmas with CVs of 3.7% and 3.6%, respectively. An r value of 0.86 was obtained from 50 outpatients compared with reference plasma PTs. Fabbrini et al also found reasonable precision (CV, 6% and 4%) with excellent correlation coeffi-

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Table 3—Frequency of Major Hemorrhage/Thromboembolism in Patients Managed Under an AMS*

<table>
<thead>
<tr>
<th>Study/Year</th>
<th>Patients, No.</th>
<th>Patient-yr, No.</th>
<th>Data Collection, yr</th>
<th>New or Established Patients</th>
<th>Indications</th>
<th>Target PTR</th>
<th>INR</th>
<th>Major (Henorrhage†)</th>
<th>Fatal</th>
<th>Recurrent TE‡</th>
<th>Definition of Major Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forfar 7/1982</td>
<td>541</td>
<td>1,362</td>
<td>1970–1978</td>
<td>Both</td>
<td>Ven art</td>
<td>1.8–2.6</td>
<td>4.2</td>
<td>0.14</td>
<td>NA</td>
<td></td>
<td>Significant bleeding requiring medical advice (exclude bruises and epistaxis)</td>
</tr>
<tr>
<td>Errichetti et al 12/1984</td>
<td>141</td>
<td>105</td>
<td>1978–1983</td>
<td>Both</td>
<td>Ven art</td>
<td>1.3–2.0</td>
<td>6.6</td>
<td>NA</td>
<td>NA</td>
<td></td>
<td>Bleeding leading to hospitalization, transfusion, or discontinuing therapy</td>
</tr>
<tr>
<td>Conte et al 12/1986</td>
<td>140</td>
<td>153</td>
<td>1975–1984</td>
<td>Both</td>
<td>Ven art</td>
<td>1.7–2.5</td>
<td>2.6</td>
<td>NA</td>
<td>8.4</td>
<td></td>
<td>Bleeding leading to hospitalization, discontinuing, or reversal of therapy</td>
</tr>
<tr>
<td>Petty et al 12/1988</td>
<td>310</td>
<td>385</td>
<td>1977–1980</td>
<td>Both</td>
<td>Ven art</td>
<td>NA</td>
<td>7.3</td>
<td>0.77</td>
<td>NA</td>
<td></td>
<td>Life-threatening bleeding (GI, intracranial, subdural, or death), discontinuing therapy</td>
</tr>
<tr>
<td>Charney et al 12/1988</td>
<td>73</td>
<td>77</td>
<td>1981–1984</td>
<td>Both</td>
<td>Ven art</td>
<td>1.5–2.5</td>
<td>0</td>
<td>0</td>
<td>5.0</td>
<td></td>
<td>Bleeding leading to hospitalization or discontinuing therapy</td>
</tr>
<tr>
<td>Bussey et al 12/1989</td>
<td>82</td>
<td>199</td>
<td>1977–1986</td>
<td>New</td>
<td>Ven art</td>
<td>NA</td>
<td>2.0</td>
<td>NA</td>
<td>3.5</td>
<td></td>
<td>Bleeding leading to hospitalization, transfusion, vitamin K, or fresh frozen plasma</td>
</tr>
<tr>
<td>Seabrook et al 12/1990</td>
<td>93</td>
<td>158</td>
<td>1981–1988</td>
<td>New</td>
<td>Ven art</td>
<td>1.5–2.0</td>
<td>3.8</td>
<td>0</td>
<td>2.5</td>
<td></td>
<td>Bleeding leading to hospitalization, transfusion, or discontinuing therapy</td>
</tr>
<tr>
<td>Fihn et al 12/1993</td>
<td>928</td>
<td>1,950</td>
<td>NA</td>
<td>New</td>
<td>Ven art</td>
<td>1.3–1.5</td>
<td>1.7</td>
<td>0.2</td>
<td>7.5</td>
<td></td>
<td>Fatal or life-threatening bleeding (CPR, 1.5–1.8 surgery angiography, irreversible damage, hypotension, hct &lt; 20, ≥ 3 U blood)</td>
</tr>
<tr>
<td>van der Meer et al 12/1993</td>
<td>6,814</td>
<td>6,085</td>
<td>1988</td>
<td>Both</td>
<td>Ven art</td>
<td>2.4–5.3</td>
<td>3.3</td>
<td>0.64</td>
<td>NA</td>
<td></td>
<td>Fatal bleeding, intracranial bleeding, transfusion, or surgery, all muscle and joint bleeding</td>
</tr>
<tr>
<td>Cannegieter et al 12/1995</td>
<td>1,608</td>
<td>6,475</td>
<td>1985 to present</td>
<td>Both</td>
<td>Mech valves</td>
<td>3.6–4.8</td>
<td>2.5</td>
<td>0.33</td>
<td>0.7</td>
<td></td>
<td>Fatal or bleeding leading to hospitalization</td>
</tr>
<tr>
<td>Palareti et al 12/1996, 12/1997</td>
<td>2,745</td>
<td>2,011</td>
<td>1993–1995</td>
<td>New</td>
<td>Ven art†</td>
<td>2.0–3.0</td>
<td>1.4</td>
<td>0.24</td>
<td>3.5</td>
<td></td>
<td>Fatal bleeding, intracranial bleeding, ocular bleeding with blindness, joint, retroperitoneal bleeding, surgery or angiography, &gt; 2 g blood, transfusion ≥ 2 U</td>
</tr>
</tbody>
</table>

*Mech valves = mechanical cardiac prosthetic valve. See Tables 1 and 2 for abbreviations not used in text.
†Values expressed as percentage per patient-year of therapy; fatal hemorrhagic events also included with major hemorrhage.
‡INR, 2.5 to 4.5.
cients (r = 0.92 and 0.91) compared with reference plasma PTs in two different groups of patients.

Tripodi et al132 evaluated the calibration of the ISI in the CoaguChek system based on an IRP and found that they were extremely close to those adopted by the manufacturer for both whole blood and plasma. Although the CVs of the slopes of the regression lines comparing the system with an international reference were excellent (ie, a CV of 2.2 for both whole blood and plasma on the instrument compared with the international reference), the instrument reported significantly higher INRs (whole blood INR, 3.20; plasma INR, 3.41; reference system INR, 2.92) using the manufacturer’s calibration. The differences were due to a lower mean normal PT adopted by the manufacturer.

Kaatz et al133 evaluated both classes of monitors (CoaguChek and Biotrack) as well as four clinical laboratories against the criterion standard established by the World Health Organization (WHO) using an international reference thromboplastin level and the manual tilt-tube technique. They found that laboratories using a more sensitive thromboplastin showed close agreement with the criterion standard, whereas laboratories using an insensitive thromboplastin showed poor agreement. The two monitors fell

### Table 5—Capillary Whole-Blood (POC) PT Instruments*

<table>
<thead>
<tr>
<th>Instrument</th>
<th>Clot Detection Methodology</th>
<th>Home Use Approval</th>
<th>Type of Sample</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biotrack ProTIME Monitor 1000</td>
<td>Clot initiation: thromboplastin</td>
<td></td>
<td>Capillary WB and venous WB</td>
</tr>
<tr>
<td>Coomatrak†</td>
<td>Clot detection: cessation of clotting</td>
<td>Yes (CoaguChek only)</td>
<td>Capillary WB, venous WB, and plasma</td>
</tr>
<tr>
<td>Biotrack 512 coagulation monitor†</td>
<td>Clot detection: cessation of blood flow through capillary channel</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CoaguChek Plus†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CoaguChek Pro†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CoaguChek Pro/DM†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CoaguChek thrombolytic assessment system</td>
<td>Clot initiation: thromboplastin</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Clot detection: cessation of movement of iron particles</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ProTIME Monitor</td>
<td>Clot initiation: thromboplastin</td>
<td>Yes</td>
<td>Capillary WB and venous WB</td>
</tr>
<tr>
<td>Hemochron Jr†</td>
<td>Clot detection: cessation of blood flow through capillary channel</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GEM PCL‡</td>
<td></td>
<td>Yes</td>
<td>Capillary WB and venous WB</td>
</tr>
<tr>
<td>Avocet PT 1000</td>
<td>Clot initiation: thromboplastin</td>
<td>Yes</td>
<td>Capillary WB, venous WB, and plasma</td>
</tr>
<tr>
<td></td>
<td>Clot detection: thrombin generation detected by fluorescent thrombin probe</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*WB = whole blood.

†Instrument based on the original Biotrack ProTIME Monitor 1000 and licensed under different names. The latest version available is the CoaguChek Pro and Pro/DM (as models evolve they acquire added capabilities). Earlier models are no longer available.

‡Simplified versions of the ProTIME Monitor. Hemochron Jr is manufactured by International Technidyne. GEM PCL is manufactured by Instrumentation Laboratory, Lexington, MA.
between these two extremes. As in the study by McCurdy and White, the Coumatrak underestimated the INR at values > 2.5, whereas the CoaguChek simply showed more scatter at INR values > 2.75. INR determinations of the Coumatrak monitor and the CoaguChek were only slightly less accurate than those of the best clinical laboratories.

A third class of POC capillary whole-blood PT instrumentation (ProTIME Monitor; International Technidyne Corporation; Edison, NJ) differs from the previously described instruments in that this instrument performs a PT in triplicate (i.e., three capillary channels) and simultaneously performs a level 1 and level 2 control (i.e., two additional capillary channels). In a multi-institutional trial, the instrument INR correlated well with the reference laboratory with tests performed by either the health-care provider (venous sample, r = 0.93) or the patient (capillary sample, r = 0.93). PT results for fingersticks performed by both the patient and the health-care provider were equivalent and correlated highly (r = 0.91).

In a separate report involving 76 warfarin-treated children and 9 healthy control subjects, Andrew et al found a correlation (r = 0.89) between venous and capillary samples. Both results, compared with venous blood tested in a reference laboratory (ISI, 1.0), revealed correlation coefficients of 0.90 and 0.92, respectively.

A fourth type of PT monitor (Avocet PT 1000; Avocet Medical; San Jose, CA) has been studied in 160 subjects and was found to yield good correlation with a reference laboratory INR when compared to capillary blood (r = 0.97), citrated venous whole blood (r = 0.97), and citrated venous plasma (r = 0.96). Within-day precision was acceptable (citrated whole blood CV, 4.8% and citrated plasma CV, 5.5%, respectively).

Despite the studies noted above, steps are still needed to ensure conformity of POC PT monitors to the WHO INR PT standardization scheme. The WHO ISI calibration procedure is not practicable on the monitors. It demands parallel testing using a conventional PT test and the manual technique with a thromboplastin IRP using citrated blood samples taken at the same time or from the same blood specimen as the uncitrated whole blood tested with the monitor. Specimens from 60 warfarin-treated patients and 20 healthy subjects are required for the ISI calibration. The recently revised WHO guidelines further specify that the calibration be performed by the manufacturer at more than one center. A simpler procedure for ISI calibration of POC monitors is needed and a method based on the use of certified lyophilized plasma calibrants is being evaluated in a current European Concerted Action on Anticoagulation multicenter study.

PST

Self-testing and/or self-management by the patient using POC instruments represents another model of care with the potential for improved outcomes as well as greater convenience. Self-testing provides a convenient opportunity for increased frequency of testing when deemed necessary. The use of the same instrument provides a degree of consistency in instrumentation, and self-testing provides the potential for greater knowledge and awareness of therapy leading to improved compliance.

White et al in a small randomized controlled study, assessed patients' abilities to measure their own PT following hospital discharge with warfarin dosing managed by their health-care providers. These self-testing patients (n = 23), when compared with a control group treated by an AMS (n = 23), spent a greater percentage of the TTR (87% vs 68%, respectively; p < 0.001) and were significantly less likely to be in the subtherapeutic range during the follow-up period (6.3% vs 23%, respectively; p < 0.001). This study was underpowered to detect differences in outcomes of hemorrhage or thrombosis.

Anderson et al confirmed the feasibility and assessed the accuracy of PST at home in a prospective cohort of 40 individuals who monitored their own therapy over a period of 6 to 24 months. Based on either a narrow or expanded therapeutic range, they observed a mean level of agreement per patient with reference plasma PTs of 83% by narrow criteria and 96% by expanded criteria. Ninety-seven percent of the patients preferred home testing to standard management. Andrew et al similarly evaluated the use of a home PT monitor (ProTIME; International Technidyne; Edison, NJ) in 82 adults and 11 children. No difference was detected between INR results obtained from the home PT monitors and the laboratory, and the results were highly correlated (r = 0.92). Ninety-five percent of participants preferred using the PT monitor over the usual laboratory testing.

Beyth and Landefeld randomized 325 newly treated elderly patients, 163 of whom had their doses managed by a single investigator based on INR results from PST at home compared with 162 treated by their private physicians (UC) based on venous sampling. Over a 6-month period, the investigators recorded a rate of major hemorrhage of 12% in the latter group vs 5.7% in the self-testing group. This finding was based on an intention-to-treat analysis. For those patients actually performing self-testing, there was only a 1.2% incidence of major hemorrhage.

PSM

In 1974, Erdman et al first tested the concept of PSM of oral anticoagulation based on physician-derived guidelines with PTs obtained on plasma samples by routine laboratory instrumentation. In nearly 200 patients with prosthetic heart valves who were managing their own therapy, they found a greater degree of satisfactory anticoagulation (98% of 195 patients enrolled) compared with a retrospective survey of standard management patients who achieved only a 71% degree of adequate anticoagulation.

Ansell et al analyzed the results of PSM with the Biotrack instrument over a span of 7 years in a cohort of 20 patients ranging in age from 3 to 87 years with diverse indications for anticoagulation. Compared with an age-matched, sex-matched, and diagnosis-matched control group treated by an AMS, self-managed patients were found to be in the therapeutic range for 88.6% of the PT determinations compared with 68% for the control subjects (p < 0.001). There were also fewer dose changes for
study patients (10.7%) than for control subjects (28.2%; p > 0.001), while complication rates did not differ between the groups. Patient satisfaction was extremely high with this mode of therapy, based on a patient survey of attitudes.

In a retrospective analysis, Bernardo reported on 216 patients who managed their own therapy between 1986 and 1992 and found that 83.1% of the PT results were within target therapeutic range and that no serious adverse events had occurred. Horstkotte et al performed a randomized controlled study of 150 patients with prosthetic heart valves who managed their own therapy (n = 75) compared with a control group (n = 75) who were managed by their private physicians (UC). The patients who self-managed 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 and only 59% of INRs were in therapeutic range. The self-managed individuals experienced a 4.5% per year incidence of any type of bleeding and a 0.9% per year rate of thromboembolism compared with 10.9% and 3.6% rates, respectively, among patients in the physician-managed group (p = 0.038 between the two groups). Hasenkam et al confirmed the effectiveness of self-management in 20 patients with prosthetic valves, reporting that these patients were in the therapeutic range 77% of the time compared to 53% of the time for 20 retrospectively matched control patients. Sawicki ran a preliminary analysis of 50% of the target patient enrollment. Three hundred five patients using PSM achieved a greater frequency of INRs in range (78.3%) than did 295 UC patients (60.5%). There was a significant difference in major adverse events between groups as well (UC group, 15%; PSM group, 9.5%; p = 0.03).

Although a growing number of studies indicate the superior performance of PSM over UC, there is little evidence comparing them to care provided by an AMS. PST and PSM require special patient training to implement, and therapy should be managed by a knowledgeable provider. A definitive recommendation cannot yet be made as to the overall value of PST or PSM.

Data Management and Computerized Dosing

An obstacle to the safety and effectiveness of warfarin therapy is the poor quality of dose management as currently practiced. Data from clinical trials on success in achieving TTR are difficult to evaluate because of problems of how TTR is determined and whether narrow or expanded ranges are considered, as noted above. Correlating such results with adverse event rates is also complicated by the fact that the older literature based results on a PT ratio, whereas therapy based on an INR with low and high intensity levels of treatment is a relatively recent phenomenon. Nevertheless, where data are available (Table 1), results indicate a wide range of success in achieving TTR. A UC model appears to yield the worst results with a TTR between 33% and 64%. Even in randomized controlled trials in which patient care is often highly structured, TTR varies between 48% and 83%. Achieved TTR appears to be the best in either an AMS model or with PSM (ie, approximately 60 to 90%). Computer assistance by the use of dedicated programs may, however, improve dose management and TTR. Although programs differ, they typically calculate whether dose adjustment is necessary from a user-defined table of trend rules for each therapeutic range. If it recommends dose adjustment, the current INR is compared to the target INR and the difference in INR is used in a proprietary equation to calculate the new dose. The time to the next dose is also set by the program using a set of variables comparing the current INR, the interval from the last test, the number of previous changes, and the number of previous INR values within the target range.

A number of older studies have evaluated computer programs to improve warfarin dosing. The first randomized study in 1993 showed that three contemporary computer programs all performed as well as an experienced medical staff of an AMS in achieving a target INR of 2.0 to 3.0, but the computer achieved significantly better control when more intensive therapy was required (INR, 3.0 to 4.5). In another randomized study of 101 long-term anticoagulated patients with prosthetic cardiac valves, computerized adjustments in warfarin dosage proved comparable to manual regulation in the percentage of INR values maintained within the therapeutic range, but they required 50% fewer dose adjustments. The first multicenter randomized control trial of one computerized dosage program in 1998 showed a 22% overall improvement of control with the program (Dawn AC; 4S Information Systems, Cumbria, United Kingdom) compared to performance by the medical staff. The computer program gave significantly better INR control than experienced medical staff for all 285 patients for all target INR ranges. The study also showed that the natural increased caution of medical staff in dosing patients at a higher INR range is not shared by the computer. It cannot be assumed, however, that all computer programs will be equally successful, and new programs will require independent validation by randomized controlled studies to determine the extent of their ability to accurately predict dosage control.

Special Situations

Pregnancy

Oral anticoagulants cross the placenta and can produce a characteristic embryopathy, CNS abnormalities, fetal bleeding, or increased rates of fetal death. These
complications are discussed in detail elsewhere in this supplement (see page 122). The incidence of warfarin embryopathy is greatest during 6 to 12 weeks’ gestation, and warfarin should be avoided during this period of pregnancy. Since CNS abnormalities, fetal bleeding, and fetal death may occur throughout pregnancy, oral anticoagulants, if possible, should be avoided throughout the entire pregnancy. Recent evidence suggests that the risk of adverse fetal outcomes relates in part to the maternal daily dose of oral anticoagulants. Vitale and colleagues reported for sodium warfarin that the incidence of spontaneous abortions and fetal abnormalities significantly increased if the daily dose exceeded 5 mg. The one potential indication for warfarin use during pregnancy is for patients with mechanical heart valves who have a high risk of embolism. Uncontrolled studies have suggested that heparin may be less effective than warfarin for prophylaxis in this setting. For other indications, heparin or LMWH is preferred when anticoagulants are indicated in pregnancy. There is convincing evidence that warfarin does not induce an anticoagulant effect in the breast-fed infant when the drug is administered to a nursing mother.

Antiphospholipid Syndrome

Lupus anticoagulants are known to be associated with an increased risk of thrombosis. Consequently, it is not uncommon for patients receiving lupus anticoagulants to be placed on a regimen of oral anticoagulant therapy. Evidence from observational studies suggests that clinical outcomes are improved when the therapeutic range for patients receiving lupus anticoagulants is closer to 2.5 to 3.5 rather than 2.0 to 3.0. The reasons why a higher INR may be beneficial are not known. One potential explanation is that the requirement for a higher INR is due to lupus anticoagulants interfering with the PT. Lupus anticoagulants typically cause prolongation of the activated partial thromboplastin time, but they may also cause mild prolongation of the PT or, in the presence of specific antibodies to prothrombin, significant prolongation of the PT. The degree of prolongation of the PT induced by lupus anticoagulants appears to be dependent on the reagent used. One study found that INR values from patients with lupus anticoagulants receiving oral anticoagulants differed from 0.4 to 6.5 between reagents. However, two studies have demonstrated standardization of INR values using either calibrated reference plasmas or locally assigned analyzer-specific ISI values can significantly reduce this variability. These latter techniques appear to enable oral anticoagulants to be reliably monitored using the INR system for some, but not all, reagents. Other techniques for monitoring oral anticoagulant therapy for patients receiving lupus anticoagulants include the measurement of prothrombin activity, native prothrombin concentration, and the prothrombin and proconvertin test. The validity and reliability of these latter tests have not been rigorously evaluated in controlled clinical trials for patients with lupus anticoagulants.

Recommendations

Practical Dosing

1. For the initiation of and maintenance dosing of warfarin, commence therapy with an average maintenance dose of 5 mg (grade 2A compared to a dose of 10 mg). Starting doses of < 5 mg might be appropriate for elderly patients, patients with impaired nutrition or liver disease, and in patients with a high risk for bleeding.

Management of Nontherapeutic INRs

1. For patients with INRs greater than the therapeutic level but < 5.0 who do not have significant bleeding, lower the dose or omit a dose and resume therapy at a lower dose when the INR is at the therapeutic level. If the INR is only minimally greater than the therapeutic range, no dose reduction may be required (grade 2C).

2. For patients with INRs > 5.0 but < 9.0 with no significant bleeding, omit the next one or two doses, monitor the INR more frequently, and resume therapy at a lower dose when the INR is at the therapeutic level. Alternatively, omit the dose and administer vitamin K1, 1 to 2.5 mg orally, particularly if the patient is at increased risk of bleeding. If more rapid reversal is required because the patient requires urgent surgery, administer vitamin K1, 2 to 4 mg orally, with the expectation that a reduction of the INR will occur in 24 h. If the INR is still high, administer an additional dose of vitamin K1, 1 to 2 mg orally (all grade 2C compared with no treatment).

3. For patients with INRs > 9.0 with no significant bleeding, hold off on warfarin therapy and administer a higher dose of vitamin K1, 3 to 5 mg orally, with the expectation that the INR will be reduced substantially in 24 to 48 h. Monitor the INR more frequently and administer additional vitamin K1 if necessary. Resume therapy at a lower dose when the INR reaches the therapeutic level (all grade 2C compared with no treatment).

4. For patients with INRs > 20 with serious bleeding, hold off on warfarin therapy and administer vitamin K1, 10 mg by slow IV infusion, supplemented with fresh plasma or prothrombin complex concentrate, depending on the urgency of the situation. Administration of vitamin K1 can be repeated every 12 h (grade 2C).

5. For patients with life-threatening bleeding, hold off on warfarin therapy and administer prothrombin complex concentrate supplemented with vitamin K1, 10 mg by slow IV
Management of Oral Anticoagulation During Invasive Procedures

1. For patients with low risk of thromboembolism (eg, patients without venous thromboembolism for > 3 months or patients who have experienced atrial fibrillation who do not have a history of stroke), stop warfarin therapy approximately 4 days before surgery, allow the INR to return to a near-normal level, briefly administer postoperative prophylaxis (if the intervention itself creates a higher risk of thrombosis) using low-dose heparin, 5,000 U SC, and simultaneously begin warfarin therapy (grade 2C).

2. For patients with intermediate risk of thromboembolism, stop warfarin therapy approximately 4 days before surgery, allow the INR to fall, cover the patient with low-dose heparin, 5,000 U SC, beginning 2 days before surgery or with a prophylactic dose of LMWH, and then commence low-dose heparin (or LMWH) and warfarin therapy after surgery (grade 2C).

3. For patients with high risk of thromboembolism (eg, patients with a recent [< 3 months] history of venous thromboembolism, patients with a mechanical cardiac valve in the mitral position; or an old model of cardiac valve [ball/cage]), stop warfarin therapy approximately 4 days before surgery, allow the INR to return to a normal level, begin therapy with full-dose heparin or full-dose LMWH as the INR falls (approximately 2 days before surgery). Heparin can be administered as an SC injection on an outpatient basis, can then be given as a continuous IV infusion after hospital admission in preparation for surgery, and can be discontinued 5 h before surgery with the expectation that the anticoagulant effect will have worn off at the time of surgery. It is also possible to continue the administration of SC heparin or LMWH and to stop therapy 12 to 24 h before surgery with the expectation that the anticoagulant effect will be very low or will have worn off by the time of surgery (all grade 2C).

4. For patients with low risk of bleeding, continue warfarin therapy at a lower dose and operate at an INR of 1.3 to 1.5, an intensity that has been shown to be safe in randomized trials of gynecologic and orthopedic surgical patients. The dose of warfarin can be lowered 4 or 5 days before surgery. Warfarin therapy then can be restarted after surgery and supplemented with low-dose heparin, 5,000 U SC, if necessary (grade 2C).

5. For patients undergoing dental procedures who are not considered to be at high risk for bleeding, we recommend that warfarin therapy not be discontinued. In patients at high risk for bleeding, we recommend that warfarin therapy be discontinued (all grade 2C).

6. For patients undergoing dental procedures in whom local bleeding must be controlled, tranexamic acid or epsilon amino caproic acid mouthwash can be administered without interrupting anticoagulant therapy (grade 2B).

Risk Factors for Adverse Events (Hemorrhage)

1. For individuals who are otherwise good candidates for anticoagulation therapy, do not withhold therapy because of a patient’s age (grade 1C).

2. Monitor elderly patients more carefully to maximize the TTR.

Models of Anticoagulation Management

1. In comparing UC with AMS, we recommend that clinicians employ a systematic process to manage oral anticoagulation dosing that includes a knowledgeable provider, reliable PT monitoring, and an organized system of follow-up, patient communication, and education (grade 1C).

2. POC PST is for selected individuals who are willing and able to perform self-testing and are suitably trained. We recommend this model as an alternative to a UC model of INR monitoring and management to achieve a greater TTR (grade 2B).

3. Computer software programs for dose management must be considered individually based on well-designed clinical outcome studies. We recommend consideration of those software programs demonstrated to provide dosing decisions equivalent to a better than physician management, especially in high-volume anticoagulation programs (grade 2B).

REFERENCES

16 Kirkwood TBL. Calibration of reference thromboplastins and standardization of the prothrombin time ratio. Thromb Haemost 1993; 49:238–244
36 Cosgriff SW. The effectiveness of an oral vitamin K1 in controlling excessive hypoprothrombinemia during anticoagulant therapy. Arch Intern Med 1965; 45:12–22
46 Souto JC, Oliver A, Znaiaz-Jansoro I, et al. Oral surgery in...
36S Sixth ACCP Consensus Conference on Antithrombotic Therapy


Horstkotte D, Fiper C, Wiemer M, et al. Improvement of
100 Verhagen H. Local hemorrhage and necrosis of the skin and underlying tissues at starting therapy with dicumarol or dicumaeil. Acta Med Scand 1954; 148:455–467

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Managing Oral Anticoagulant Therapy
Jack Ansell, Jack Hirsh, James Dalen, Henry Bussey, David Anderson, Leon Poller, Alan Jacobson, Daniel Deykin and David Matchar

*Chest* 2001;119; 22S-38S
DOI 10.1378/chest.119.1_suppl.22S

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