# College of American Pathologists Conference XXXI on Laboratory Monitoring of Anticoagulant Therapy

## Laboratory Monitoring of Oral Anticoagulant Therapy

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● **Objective.**—To review the state of the art of laboratory monitoring of oral anticoagulant therapy, as reflected by the medical literature and the consensus opinion of recognized experts in the field, and to make recommendations for improvement in laboratory monitoring of oral anticoagulant therapy.

**Data Sources.**—Review of the medical literature, primarily from the last 10 years, and current laboratory practices by a panel of 8 international experts in the field of oral anticoagulant monitoring.

**Data Extraction and Synthesis.**—After an initial assessment of the literature, key points were identified. Experts were assigned to do an in-depth review of the literature and current practices relevant to each of the key points and to prepare a summary of their findings and recommendations. A draft manuscript was prepared and circulated to every participant in the College of American Pathologists Conference XXXI on Laboratory Monitoring of Anticoagulant Therapy prior to the conference. Each of the key points and associated recommendations was then presented for discussion at the Conference. Recommendations were accepted if a consensus of the 26 experts attending the Conference was reached. The results of the discussion were used to revise the manuscript into its final form.

**Conclusions.**—Consensus was reached on 12 recommendations concerning the laboratory monitoring of oral anticoagulant therapy. Detailed discussion of the rationale for each of these recommendations is found in the text of this article. Discussion of points on which consensus was not reached is also included in the text. It is hoped that widespread adoption of these recommendations will further improve the laboratory monitoring of oral anticoagulant therapy.

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T his review focuses on the laboratory and near patient monitoring of oral anticoagulant therapy (OAT). Laboratory monitoring of OAT represents one of the oldest forms of therapeutic drug monitoring. Despite this long history of clinical utilization, there continues to be controversy regarding optimal monitoring of therapy for patients on OAT. In addition, OAT continues to be associated with a significant risk of bleeding. The goal of this report is to address important issues facing physicians and laboratories monitoring patients on OAT. Consensus recommendations for monitoring of OAT are included, and a

level of evidence is assigned to each recommendation (see Tables 1 and 2). The information in this report is intended to improve laboratory performance in monitoring patients receiving these agents.

## EFFECTS OF PREANALYTIC VARIABLES ON THE INTERNATIONAL NORMALIZED RATIO

Prothrombin time (PT) is one of the most commonly performed clinical laboratory procedures. Although the PT procedure is relatively straightforward, correct results are dependent on appropriate sampling and testing techniques. Guidelines for the performance of PTs have been published by several groups, including the European Committee for Clinical Laboratory Standards (in association with the International Organization for Standardization) and the National Committee for Clinical Laboratory Standards (NCCLS).[1–3] A proposed revision of the NCCLS guideline has recently been circulated for consideration as part of the NCCLS consensus process.

A major variable in PT performance is the concentration of sodium citrate used to anticoagulate the patient sample. There is a significant difference between the international normalized ratio (INR) for samples collected in 109 mmol/L (3.2%) and 129 mmol/L (3.8%) trisodium citrate.[4–6] For one reagent the difference averaged 19%, with the higher citrate concentration yielding a higher INR.[4] In a recent study, 18% of samples collected into the 2 concentrations of citrate showed an absolute INR difference

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| Table 1. Levels of Evidence for Consensus Recommendations | | |
|---|---|---|
| Level 1 | The recommendation is based on well-designed prospective studies, preferably more than 1. |
| Level 2 | The recommendation is based on retrospective studies or multiple anecdotal studies that reach consensus. |
| Level 3 | The recommendation is based on isolated anecdotal studies or the consensus of expert practioners. |

**Table 2. Summary of Recommendations**

1. Based on the recommendation of the World Health Organization and recently proposed National Committee on Clinical Laboratory Standards (NCCLS) guidelines, it is recommended that 109 mmol/L (3.2%) citrate be used as the anticoagulant of choice for coagulation testing. (Level 1)
2. Specimens for the determination of prothrombin time, either spun or unspun, may be stored at room temperature (20°C–24°C) but should be processed and tested within 24 hours. (Level 2)
3. Thromboplastins with a manual international sensitivity index (ISI) between 0.9 and 1.7 are recommended. It is desirable to have an ISI toward the lower end of this scale. (Level 2)
4. Laboratories should be aware that coagulation instruments may affect the ISI, which can differ from the assigned value by a clinically important degree. (Level 1)
5. Laboratories should use reagent-instrument combinations for which the ISI is known. (Level 3)
6. The use of lyophilized calibrator plasmas to determine a laboratory's own method ISI is under study and represents a potential method of improving interlaboratory international normalized ratio (INR) variation. Use of INR-certified plasmas for screening of individual laboratory performance may improve interlaboratory INR variation. (Level 2)
7. Unfractionated heparin can increase the prothrombin time (PT)/INR. The effect is dependent on the method and heparin level. Laboratories should determine the sensitivity of their PT to heparin and, where possible, select a thromboplastin that is insensitive to heparin in the therapeutic range. (Level 2)
8. During the initiation phase of oral anticoagulant therapy, it is prudent to monitor patient status daily or at least 4–5 times per week, until some degree of consistency of the INR response to a stable dose is noted. (Level 2)
9. The frequency of testing in stabilized anticoagulated patients should be determined on an individual patient basis. In general, the INR should be determined at intervals not exceeding 4 weeks. (Level 2)
10. Lupus anticoagulants can alter the PT, and the effect is reagent-dependent. The effect may give rise to clinically important differences in INR values that may result in incorrect dosing. A normal baseline PT does not rule out an effect of a lupus anticoagulant on the INR during therapy. Alternative tests may be useful in monitoring these patients, and they may be best managed in coordination with a facility capable of performing these alternate assays. (Level 2)
11. Whole blood monitors may be used to determine the INR in patients on oral anticoagulant therapy. When more than 1 test system is used within an institution, each test system should be calibrated against the other test systems. (Level 2)
12. Patients participating in whole blood self-testing must receive appropriate training in the use of the test system and must be supervised by a physician or anticoagulant clinic familiar with the system. Quality control procedures should ensure that the instrument and reagent cartridge are functioning properly. (Level 3)

greater than 0.7 with a high sensitivity reagent (international sensitivity index [ISI] = 1.0), but a smaller effect with a less sensitive reagent (ISI = 1.94).[6] In another report, no significant difference was observed using a single sensitive reagent (ISI = 1.06).[7]

There was a consensus among conference participants that use of a single concentration of buffered sodium citrate would improve standardization of INR reporting. In the revision of the 1991 guideline, the NCCLS Subcommittee on Coagulation has agreed to recommend that a single sodium citrate concentration, 109 mmol/L, be used. A concentration of 109 mmol/L was selected because this is the concentration used for calibration of reagent ISIs, and it is the concentration recommended by international standards organizations.[8] In addition, spurious results due to overcitrated specimens caused by underfilling of tubes, variation in vacuum, or high hematocrit are more likely to occur with specimens collected in 129 mmol/L citrate.[7] There does not appear to be a problem with under-anticoagulation when using 109 mmol/L citrate, even with samples having hematocrits as low as 5%.[9] Use of 129 mmol/L citrate is still recommended for platelet aggregometry and testing of blood bank components (eg, quality control of cryoprecipitate).

There has been considerable controversy regarding the length of time that specimens may be stored before PT testing is completed. The 1991 NCCLS guideline indicated that samples could be stored for up to 4 hours if maintained at 2°C to 4°C.[3] Van den Besselaar et al[10] demonstrated that storage of citrated blood or plasma at room temperature up to 6 hours was acceptable. Raskob et al[11] showed that storage at room temperature and overnight shipping did not significantly alter the INR results of patients on low-dose warfarin. Dwyre et al[7] observed no difference in the INR measured in appropriately anticoagulated plasma specimens stored at room temperature for 0, 4, or 24 hours, either on or off the cellular matrix. Recently, Baglin and Luddington[12] found no clinically significant change in INR when analysis was delayed for up to 3 days in samples stored as whole blood at room temperature.

The NCCLS Subcommittee on Coagulation has agreed to recommend in the revision of the 1991 guideline that samples may be stored spun or unspun at room temperature (~20°C to 24°C) for up to 24 hours. It is important to note that samples should not be stored for prolonged periods in the cold (4°C), since "cold activation" of factor VII may occur, leading to shortening of the PT and underestimation of the INR.

### Recommendations

1. Based on the recommendation of the World Health Organization and recently proposed NCCLS guidelines, it is recommended that 109 mmol/L (3.2%) buffered citrate be used as the anticoagulant of choice for routine coagulation testing.[3,7] (Level 1)

2. Specimens for the determination of the prothrombin time, either spun or unspun, may be stored at room tem-

**Table 3. Effect of International Sensitivity Index (ISI) and Coagulometer on Prothrombin Time (PT) and International Normalized Ratio (INR) Precision: 1996 College of American Pathologists Comprehensive Coagulation Survey CG2-C**

| | ISI 1.0 Instrument A | ISI 1.0 Instrument B | ISI 2.0 Instrument B | ISI 2.0 Instrument C |
|---|---|---|---|---|
| Sample CG2-11* | | | | |
| No. of laboratories | 42 | 26 | 131 | 97 |
| Mean PT, s | 49.5 | 50.4 | 25.2 | 22.9 |
| CV(PT) | 5.7% | 7.9% | 3.8% | 5.0% |
| Mean INR | 4.58 | 4.62 | 4.54 | 3.76 |
| CV(INR) | 6.1% | 7.2% | 8.5% | 7.8% |
| Sample CG2-13† | | | | |
| No. of laboratories | 42 | 26 | 132 | 99 |
| Mean PT, s | 32.9 | 33.2 | 20.0 | 18.4 |
| CV(PT) | 4.2% | 7.0% | 2.9% | 3.5% |
| Mean INR | 3.07 | 3.06 | 2.79 | 2.39 |
| CV(INR) | 5.5% | 6.9% | 7.1% | 7.7% |

\* Sample CG2-11 was composed of lyophilized pooled plasma from patients receiving high-dose oral anticoagulant therapy.
† Sample CG2-13 was composed of lyophilized, pooled plasma from patients receiving standard dose oral anticoagulant therapy.

perature (20°C to 24°C), but should be processed and tested within 24 hours.[7,10–12] (Level 2)

**Note.**—The recommendations for storage of plasma refer to patients on OAT. The stability of the PT for samples obtained from hospitalized patients with complex coagulopathies has not been established.

### SENSITIVITY OF THROMBOPLASTINS USED FOR MONITORING OAT

Thromboplastins used to perform PTs vary widely in their sensitivity to the coagulation defect induced by OAT; more sensitive reagents are characterized by a low ISI. It has been suggested that use of low-ISI reagents may improve laboratory monitoring of OAT.[13] Although an optimal ISI has not been rigorously defined by laboratory studies or clinical trials, there are a number of reasons why low-ISI reagents may be beneficial.

Sensitive thromboplastin reagents offer the potential for improved precision in the determination of the INR. The INR is calculated by raising the PT ratio (ie, the ratio of patient PT to the mean normal PT) to the power of the ISI as follows: $INR = (PT\ ratio)^{ISI}$. It follows that the analytic variation (coefficient of variation [CV]) of the INR is a function of the CVs of the PT ratio and the ISI from which it is calculated. Assuming, for the sake of simplicity, that there is no error in the ISI, we can derive the following formula for the CV of the INR[14]:

$$CV(INR) = CV(PT\ Ratio) \times ISI.$$

Consequently, the CV of the INR determination may be greater when the PT is performed with less sensitive thromboplastins having higher ISI values.[15] However, the CV(PT ratio) and ISI are not independent parameters; some studies have suggested that low-ISI reagents may be associated with a higher CV for the PT determination and thus a higher CV(PT ratio) as compared with a reagent with a higher ISI. Thus, the within-laboratory CV(INR) determined with a high-ISI reagent (and low CV[PT ratio]) is not always greater than the CV(INR) obtained with a low-ISI reagent (with a higher CV[PT ratio]).[16] Based on this precision model, the ideal ISI would be one where the product of the ISI and CV(PT) ratio is lowest. Obviously, other factors that contribute to the CV(PT), such as instrumentation, may contribute to the overall CV(INR) and may obscure the potential benefit of a low-ISI reagent,

particularly if they are associated with a significant increase in the CV(PT).

Data from interlaboratory proficiency testing programs provide support for this model, but the data are not conclusive. Data from the College of American Pathologists 1996 Comprehensive Coagulation Survey for the 3 largest reagent/instrument peer groups are presented in Table 3. These data generally support the above model, in that the CV(PT) (and thus the CV[PT ratio]) appears to be greater with more sensitive thromboplastins. However, the differences in CV(INR) may not meet statistical significance.

The choice of instrument has a direct effect on the true ISI of a reagent/instrument test system.[17] Variables, such as the instrument, that increase the CV(ISI) would be expected to also increase the CV(INR). Results from a recent international collaborative study showed significantly greater interlaboratory variation in INR values using the higher ISI reagent when testing thromboplastins of lower (1.0) and higher ISIs (1.9), using the same coagulometers.[18] This would suggest that higher ISI reagents would be associated with a higher interlaboratory CV(INR) due to the increased CV(ISI).

Consecutive United Kingdom National External Quality Assessment Surveys (NEQAS), compared the interlaboratory variation with 2 thromboplastins, 1 with a low ISI (1.1) and 1 with an intermediate ISI (1.4).[14,19] The interlaboratory variation was noted to be greater for the reagent having an ISI of 1.4. In another report based on National External Quality Assessment Surveys involving 3 thromboplastin reagents, the mean CV of the INR was lowest for the most sensitive reagent (ISI = 1.2) compared with the other 2 reagents (ISIs of 1.4 and 1.45).[20] However, a report from a Canadian proficiency program did not demonstrate a significantly lower interlaboratory variation of the INR for low ISI reagents in comparison with high ISI reagents, especially for higher INR levels.[21]

Another consequence of the exponential nature of the equation for calculating the INR is that the range of PT ratios corresponding to the therapeutic range decreases as the ISI increases (Figure).[19] In addition, the absolute prolongation of the patient PT (in seconds) relative to the mean normal PT becomes progressively smaller as the ISI increases. Thus, discrimination of the patient PT from normal may be reduced with higher ISI reagents, and clinical

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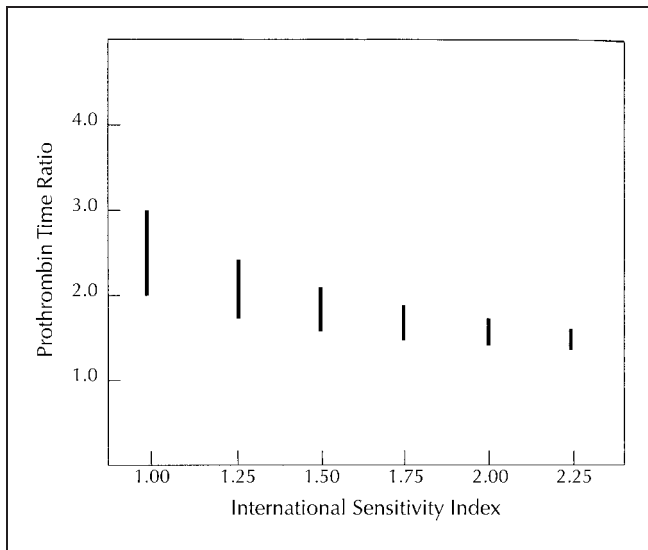
The relationship between the prothrombin time (PT) ratio that corresponds to an international normalized ratio range of 2.0 to 3.0 and the international sensitivity index (ISI) of the reagent is shown in this figure.[19] As the ISI of the reagent increases, the PT ratio corresponding to the therapeutic range decreases and narrows. Thus, reagents with a low ISI have a wider range of PT ratios that correspond to the therapeutic range.

refinement of dosage may become more difficult. Furthermore, an increase in ISI does not represent a linear decrease in responsiveness; for example, a thromboplastin with an ISI of 2.0 has far less than half of the responsiveness of a thromboplastin with an ISI of 1.0. This results from the logarithmic relationship between the INR and the PT ratio.[8]

It has been suggested that reagents with a low ISI may be beneficial in the early stages of anticoagulation owing to their sensitivity to depression of factors VII and X, factors which decrease first with warfarin treatment.[13] However, anticoagulant efficacy appears to be more related to a decrease in the level of prothrombin than to a decrease in either factor VII or X. A recent study suggests that there is no clinical advantage for a more rapid increase in the PT associated with use of higher initial doses (eg, 10 mg) of warfarin.[22] By analogy, there may be little advantage to using a reagent that is particularly sensitive to the level of factor VII. Indeed, there are unpublished anecdotal reports that some very sensitive reagents may show a marked prolongation of the PT during the initial phase of anticoagulation, perhaps overestimating the degree of anticoagulation.

Although the INR is generally accepted as the measurement of choice for monitoring OAT, diagnostic PTs are ordered in a variety of settings (eg, preoperative screening, liver disease, prior to some invasive procedures, evaluation of potential drug-induced coagulopathies, and hereditary coagulopathies). When PTs are reported using low-ISI reagents, the absolute value in seconds may be misinterpreted by clinicians who are accustomed to less sensitive reagents (and shorter PTs). There may also be confusion with activated partial thromboplastin time values that are similar in numerical value (eg, 25–35 seconds). Extensive educational efforts to acquaint clinicians with the response and expected results with these thromboplastins are needed as they are introduced into practice.

Some institutions have responded to this problem by reporting only the INR (see below).

Most automated coagulometers are designed to cut off if no clot is detected within a specified period of time. With low-ISI reagents, some coagulometers cut off at INRs of approximately 10.0. Patients with an INR above the coagulometer cutoff may not be fully assessed in terms of the appropriate therapy to reverse the anticoagulation.[13] However, the accuracy and precision of the INR in this high region is poor and should not be relied on totally for management decisions. This is due, in part, to the fact that when the INR is very prolonged, very small differences in the biologic level of factors may have an inordinate impact on the clotting time.

We identified only 2 studies evaluating the effect of reagents of different ISIs on clinical outcome. Brophy et al[23] looked at 2 reagents (ISI 1.3 and 1.9) in a blinded, prospective study of 84 patients with an INR target of 2.5 and concluded that there was no significant difference in the percentage of INRs in the therapeutic range, mean daily warfarin dose, number of dosage adjustments, or bleeding events when patients were monitored with either of these 2 reagents. Only 1 thrombotic complication was reported (in the sensitive reagent group). Barcellona et al[24] looked at 2 reagents (ISI 0.82 and 1.46) in a blinded, prospective, crossover study of 67 patients with an INR target range of 2.0 to 4.5 and concluded that there was no significant difference in outcome as measured by similar end points. However, thrombotic and bleeding complications were not reported in this study. More studies are needed to address this issue.

### Recommendation

Thromboplastins with a manual ISI between 0.9 and 1.7 are recommended. It is desirable to have an ISI toward the lower end of this scale.[13,14,25] (Level 2)

**Note.**—We recognize that less sensitive reagents are commonly being used in US laboratories and that changing to more sensitive reagents will require time and cooperation from manufacturers.

### THE INSTRUMENT EFFECT ON THE METHOD ISI

It is well-established that the choice of coagulometer has an effect on the stated ISI of the working thromboplastin.[26–33] As noted above, an international collaborative study established the effect on the ISI for 3 different types of coagulometers when high and low ISI reference thromboplastins were tested.[18] Not only was the ISI of the thromboplastin assigned by the manual method altered, but the ISI varied significantly between different individual coagulometers of the same model. Of 6 widely used reagent-instrument systems, the tendency in 5 was to appreciably lower the ISI compared to the manually assigned ISI.

More recently, field studies have been undertaken by the European Concerted Action on Anticoagulation (ECAA) in 16 European countries, with 155 centers participating.[34] In these multicenter trials, the effect of coagulometers on ISI using the same reference thromboplastins and the same certified test plasmas was investigated. It was also possible to compare coagulometer effects using low- and high-ISI thromboplastins. The results indicated that there was a difference in the effect on clotting times of normal and abnormal lyophilized plasmas. The PT of the normal plasma was shorter with the human ECAA reagent used on

the coagulometers as compared to the manual technique. In contrast, the PT results of the abnormal samples with the coagulometers were similar to the manual technique. This resulted in an alteration in the PT ratio obtained with the coagulometers due to the shift in the normal PTs (L.P.P., unpublished data, 1997).

The clinical significance of this instrument effect is currently unknown. Theoretically, the instrument is most likely to affect the accuracy of INR determination. If the assigned ISI is incorrect, a bias in the results will be evident. This would most likely be a consistent and persistent bias, which could lead to chronic under- or over-anticoagulation of patients.

Some thromboplastin manufacturers have sought to address the problem of instrument effect by providing instrument-specific ISI values for their reagents (system ISIs). Unfortunately, some manufacturer-assigned ISIs have been shown to be inaccurate for some reagent-instrument systems.[33] Manufacturers should assume the responsibility of providing accurate, certified, instrument-specific ISI for reagents used by their customers. However, this may not be easily accomplished in all cases, since there are over 250 reagent/instrument combinations in use in North America, based on College of American Pathologists proficiency survey data. It would help interlaboratory standardization if laboratories would use reagent/instrument combinations for which the ISIs have been established by the manufacturer. Laboratories should avoid using a reagent on an instrument for which the ISI has not been characterized by either the laboratory or reagent manufacturer. Local ISI calibration may be required to verify the true working ISI and minimize interlaboratory variability in the INR.

### Recommendations

1. Laboratories should be aware that coagulation instruments may affect the ISI, which can differ from the assigned value by a clinically important degree.[17,18] (Level 1)

2. Laboratories should use reagent/instrument combinations for which the ISI has been established. (Level 3)

### LOCAL CALIBRATION OF THE ISI

The variability between test systems suggests that individual laboratories may need to calibrate their own test system. The most reliable method of local calibration of the PT test system would be the World Health Organization protocol, using an international reference preparation (IRP) with the manual (tilt tube) method on 20 fresh normal and 60 fresh patient samples.[8] This is clearly not a practical method for most clinical laboratories because of the restricted availability of IRPs, the fact that few laboratorians are proficient in the manual technique, the workload required to complete the study, and the availability of 60 fresh patient samples.

An alternative would be to use a set of calibrator plasmas with assigned INR values. There are several issues associated with the use of calibrator plasmas that need to be addressed, including the type of plasma (OAT patient samples or in vitro depletion of vitamin K–dependent factors), the nature of plasma (fresh, frozen, or lyophilized), assignment of INR values to the calibrators, the minimum number of calibrators necessary for local calibration, and the statistical method for calculating the local ISI. These issues have been addressed in a series of recent studies,

but, as discussed below, the results are not yet conclusive.[18,35,36]

The use of certified lyophilized plasmas depleted in vitro of vitamin K–dependent factors was originally proposed by Miale and coworkers in a series of reports in the late 1960s and early 1970s.[37–39] This proposal did not gain widespread acceptance because the plasmas were only certified against one commercial thromboplastin in the absence of an IRP thromboplastin, and there was no standard system for reporting results. Artificially depleted plasmas continue to have several advantages over plasmas from patients on OAT, including availability of larger volumes, wider selection of INR values across the therapeutic interval, and reduced risk of virus transmission. Although it can be argued that larger volumes of anticoagulated patient plasmas could be obtained by pooling donations from patients on OAT, this procedure would make a spectrum of INR values more difficult to obtain because of the averaging in such a pool. There would also be an increased risk of virus transmission, both because of the pooling and because testing for human immunodeficiency virus would be less dependable. However, it has also been argued that it is important to use lyophilized OAT plasmas because these plasmas give different results than artificially depleted plasmas, presumably owing to the presence of proteins induced by vitamin K antagonists.[40–42]

The ECAA has found that there is a difference between the results with lyophilized depleted plasmas and lyophilized OAT plasmas in ISI value assignment, but both of these differed by a similar amount from a conventional fresh plasma ISI calibration.[35] There was little to choose from between the 2 types of plasma in terms of reliability; both differed from the fresh plasma calibration by approximately 5%, and from each other by 11%. The differences from the fresh plasma calibration are presumably due to artifactual changes related to lyophilization and do not appear to be excessive with either type of lyophilized plasma. According to the ECAA report, lyophilized plasmas appear to permit reasonably reliable local ISI calibrations using the manual technique with the human brain IRP and recombinant thromboplastin. It should be noted that these conclusions may not be applicable to other reagent-instrument systems.[43]

Although lyophilization seems a simple solution to the difficulties associated with storage and shipment of calibrator plasmas, there are problems associated with lyophilized materials. Lyophilization can induce changes in the plasma and how it responds in clotting assays. Complicating this effect is the observation that the magnitude of the changes is not the same for all reagents or instruments.[44,45] The measured INR of lyophilized calibrator plasmas may depend on the thromboplastin reagent and instrument used. Van den Besselaar[46] has suggested that reagent-specific INR values for calibrator plasmas appear to be more reliable than either a single INR value assigned with an IRP or the overall mean INR determined with a range of reagents. With more than 250 test systems in use in the United States, calibration of reference plasmas for all the test systems would be a daunting task. In contrast to these findings, several other recent multicenter collaborative studies have demonstrated that the concept of lyophilized plasmas, with INR values certified in terms of an IRP, may provide a practical approach to the requirements of local INR correction for the users of coagulometers.[18,31,40,47]

Another major consideration is the minimum number of calibrator plasmas required to give a reliable local ISI calibration. The number of abnormal lyophilized plasmas for such calibrations has varied from 2 (as recommended by Houbouyan and Goguel[42]), to 5 (as recommended in some commercial kits), to 20 (as reported in several national and international studies).[18,31,48] The reliability of smaller numbers than the 60 plasmas recommended for conventional fresh plasma calibrations has been studied in detail. The effect of progressively reducing the number of individual plasmas from the conventional 60 to 5 abnormal plasmas, while retaining a constant proportion of normal plasmas in the calibration, has been observed in an ECAA study.[49] The precision of the resulting calibration, expressed as the CV of the slope of the calibration line, and the reliability of the resulting INR were not appreciably affected until the number of abnormal plasmas was reduced to 20 combined with 7 normal plasmas. With a further reduction in the number of plasmas, there was a dramatic increase in both parameters, that is, a rapid rise in CV and a large increase in the incidence of clinically significant INR deviations. It has been suggested that by pooling larger numbers of individual OAT patient plasmas and using these as calibrators, as few as 5 such ''pools'' can give as precise a calibration as 20 single calibrator plasmas (A.M.H.P.B., unpublished data, 1997).

Another problem limiting the potential reliability of local ISI calibration is the complex calculation required for the orthogonal regression analysis to determine the ISI. With the use of certified lyophilized plasmas, it could be argued that the simpler method of linear regression analysis, which is widely available and incorporated in the software of some coagulometers, might be acceptable. In the ECAA study, it was shown that linear regression was acceptable for the manual method only and is not generally applicable to coagulometers.[36] However, it has been suggested that the use of large pool calibrator plasmas results in significantly less scatter than with individual plasmas, and the 2 types of regression analysis appear nearly identical in this setting (A.M.H.P.B., unpublished data, 1997). Hubbard et al[50] have explored an alternate approach to this problem. They suggested that the calibrator plasmas can be used to establish a ''standard curve'' for the INR, with patient values being read directly off the curve.

A recent international multicenter study involving 37 laboratories shows the potential for improvement with a calibration system. The laboratories measured PTs on 20 IRP-certified lyophilized plasma calibrators using 2 supplied ''common'' thromboplastins on 3 brands of coagulometers and derived ''local system'' ISIs.[18] The laboratories also determined the PT and INR on a series of 10 lyophilized plasmas from patients on OAT. Of note, the ''true'' working ISI frequently differed from the ISI assigned by a manual technique. The variation in the locally calibrated working ISI was highest for the reagent with the highest ISI. In the absence of local calibration of the ISI, there was significant deviation of the INR from the predetermined INR value (range, 10.74% to 19.43% signed variation). This deviation was largely corrected by the local calibration exercise (range of deviation after calibration, −3.32% to 5.43%). Of note, the largest deviation with the noncalibrated systems was seen with the lowest ISI reagent. These results suggest that local calibration may lead to improvement in INR determination.

Based on the findings of the ECAA study, sets of 20 artificially depleted plasmas certified in terms of the human and rabbit thromboplastin IRP are now being made available commercially in Europe and the United States. In addition, there are a number of other calibration ''kits'' containing variable numbers of plasmas from both donors on OAT and artificially depleted plasmas currently available commercially in the United States. These calibration kits should be used carefully, as some may be valid only for specific reagent/instrument combinations.

### Recommendation

The use of lyophilized calibrator plasmas to determine a laboratory's own method ISI is under study and represents a potential method of improving interlaboratory INR variation. Use of INR-certified plasmas for screening of individual laboratory performance may improve interlaboratory INR variation.[18,31,42,48] (Level 2)

### THE EFFECT OF HEPARIN ON THE INR

The effect of heparin on the PT has been addressed in several studies published over the past 15 years.[51–54] Clearly heparin can affect the PT and INR. The magnitude of this effect is a function of the sensitivity of the thromboplastin, the presence and concentration of a heparin neutralizer in the thromboplastin reagent, and the plasma heparin concentration. Reagents that are insensitive to the action of heparin show little effect, whereas thromboplastin reagents that are sensitive can show an appreciable effect.

Many of the data in this area derive from studies that reported PTs in seconds or ratios before widespread acceptance of the INR. At therapeutic concentrations of heparin, the additional prolongation in the PT in 2 studies was approximately 1 to 5 seconds.[51,52] Obviously, this difference could equate to a significant change in the INR, based on the reagent sensitivities that were being used in the United States at the time of these studies (1987 and 1991). Furthermore, at heparin concentrations of 0.6 to 0.8 U/mL, the additional prolongation in some patients exceeded 10 seconds. This degree of prolongation could be a very significant source of error. There is anecdotal evidence that some thromboplastins are sensitive to low-molecular-weight heparins (A. Giles, MD, unpublished data, 1997). The magnitude of the effect, if any, appears to depend on both the brand of low-molecular-weight heparin and the thromboplastin.

Data from College of American Pathologists proficiency surveys with heparin added to normal lyophilized plasma show a range of effects on the INR.[55] For example, a specimen containing 0.5 U/mL of heparin in pooled normal plasma was tested by over 4000 participating laboratories. The mean INR reported for 52 graded peer groups, where each peer group was composed of a single reagent-instrument combination, ranged from 0.92 to 1.51. In contrast, the mean INR for a pooled normal plasma sample ranged from 0.98 to 1.09. The effect may be even greater in OAT patient samples owing to the combination of defects.

The effect of heparin may be reduced or eliminated by using a reagent containing a heparin-neutralizing substance, such as polybrene or protamine sulfate. Some manufacturers have introduced thromboplastin reagents with these substances present. The effectiveness of these substances in neutralizing low-molecular-weight heparin has not been established. Laboratories should be aware of the

level of sensitivity of their thromboplastin to heparin and, where possible, select a thromboplastin that is insensitive to heparin in the common therapeutic range. If this is not possible, an option to consider would be to add various concentrations of heparin to plasmas of known INR values and to determine the extent of prolongation. This determination would be especially important for heparin concentrations in the usual therapeutic range. This procedure should be followed whenever the reagents are changed, and the information should be made available to physicians treating the patient, perhaps by including the information on the laboratory report.

In cases where heparin interference may be a problem, another option is pretreatment of the plasma sample with heparin adsorbent anion exchange resins or enzymatic digestion methods.[56,57] A problem with the former option is that anion exchange resins can remove coagulation factors (eg, IX and X) and may lead to an erroneous INR.[58] Anecdotal experience with enzymatic digestion suggests that it does not have a significant effect on the INR value (D.A.T., unpublished data, 1997).

### Recommendation

Unfractionated heparin can increase the prothrombin time and INR. The effect is dependent on the method and heparin level. Laboratories should determine the sensitivity of their PT to heparin and, where possible, select a thromboplastin that is insensitive to heparin in the therapeutic range.[51–55] (Level 2)

### REPORTING THE INR IN CONDITIONS OTHER THAN OAT

The subcommittee did not reach a consensus on the issue of reporting INR values for conditions other than OAT. The arguments for and against reporting these values are briefly summarized below. Some laboratories report only the INR for all PT measurements since the INR is simply a mathematical conversion of the PT using the ISI. Other laboratories have opposed converting to more sensitive thromboplastins because the higher PTs (in seconds) might be confusing to clinicians accustomed to the shorter PTs obtained with less sensitive reagents, particularly in those instances when a PT is ordered for a reason other than OAT (eg, preoperative orders or assessment of liver disease). For example, with a typical sensitive thromboplastin, when the INR is in the range of 2.0 to 3.0, the PT is in the range of 25 to 37 seconds. Some clinicians seeing a PT in this range may confuse these results with the activated partial thromboplastin time. The thought is that it might help clinicians become more comfortable with what the screening result actually means if only INRs are routinely reported.

There is evidence to support the conclusion that the INR value is appropriate for use in patients beginning anticoagulation as well as in patients with other coagulation disorders (eg, liver impairment).[59,60] The degree of PT prolongation appears to be greater for patients on OAT than for patients with liver disease or disseminated intravascular coagulation, but the PT (and thus INR) was shown to be linearly correlated when reagents of varying ISI were compared.[61] Koepke[62] has proposed reporting the INR in lieu of the PT for all patients, but has suggested the best way to accomplish this would be to have a national consensus conference.

The main argument against broad utilization of the INR

is that it was devised as a means of establishing consistency in PT results between laboratories on samples obtained from patients receiving OAT. One must recognize that the PT is obtained for 1 of 2 reasons: diagnostic evaluation and OAT monitoring. It is not known how well the INR correlates with the diagnosis or outcome in clinical settings such as liver disease, evaluation of potential coagulopathies induced by drugs or other conditions, and hereditary or other acquired coagulopathies. For example, there are no data available on the correlation of clinical bleeding with the INR in patients undergoing liver biopsy. What does an INR mean when one obtains a result on a patient who has congenital factor VII deficiency? There is concern that, in the absence of such data, the INR/ISI system could be blamed for adverse outcomes in patient settings for which it was not meant to be utilized.

Another argument against the routine use of reporting the INR value alone is the problem of interpreting mildly prolonged PTs. On occasion, mild prolongation of the PT may be the only clue to a clinically significant coagulopathy. However, the upper range of normal is obscured by the exponential nature of the INR calculation. For example, the upper limit of normal for 2 reagents may correspond to a PT ratio of 1.2. This would correspond to an INR of 1.2 for a reagent with an ISI of 1.0 and an INR of 1.4 for a reagent with an ISI of 2.0. The problem would then be in the interpretation of INR values in the range of 1.3 to 1.4.

### FREQUENCY OF MONITORING OAT

The monitoring of OAT can be divided into at least 3 phases, namely, the initiation phase, the stable phase, and the transition phase. During the initiation phase, there is consensus that monitoring daily or at least 4 to 5 times per week is prudent until some degree of stability of the INR response to a stable dose is noted.[63] Frequently, a daily INR is obtained while patients are in the hospital, with a single INR determination ordered about a week after discharge. This may create problems if the dose response has not been stabilized or if the patient is still receiving significant amounts of heparin until near the time of discharge. Failure to stabilize the dose response may lead to significant overdosage as the INR response continues to increase in the unmonitored outpatient setting. Concurrent heparinization may lead to overestimation of the true therapeutic level due to interaction between heparin and the PT as described above. Sick and elderly patients may have a pronounced warfarin effect that may not be appreciated if their hospitalization is short and they are not followed closely during the early outpatient period. Careful monitoring of the patient is required until a stable dose response is achieved, whether the patient is an inpatient or outpatient.

The optimal frequency for monitoring patients during the stable phase is not known. It is known that (1) patients who have an INR that varies greatly over time have a higher risk of bleeding complications and (2) because of both the variability and the association with bleeding, these patients need to be monitored more closely. In a brief letter, Howard and Mulligan[64] reported on a prospective study carried out at an anticoagulation clinic. Patients were randomized to either appointments every 6 weeks (n = 85) or appointments every 12 weeks (n = 94), and were followed for 40 weeks. There was no statistically significant difference in the control of anticoagulation be-

tween the 2 groups, as measured by the mean difference from target INR. No episodes of bleeding or thrombosis were observed in either group. Rospond et al[65] found that those patients who completed 3 months of stable anticoagulation without a change in their INR were only half as likely to need a dosage change at their next visit as were patients who completed their first monthly visit period. One of the authors (H.I.B.) recently evaluated a local health maintenance organization population and found that 30% to 50% of the time patients were going for more than 2 months without an INR being measured. The INRs were in the therapeutic range only 30% to 50% of the time (H.I.B., unpublished data, 1997).

Without reference to any published data, The American College of Chest Physicians Consensus Conference on Anticoagulant Therapy states: ''If the PT response remains stable, the frequency of testing can be reduced to intervals as long as every 4 to 6 weeks. If adjustments to the dose are required, then the cycle of more frequent monitoring is repeated until a stable dose response is again achieved.''[13] In the experience of this subcommittee, the frequency of monitoring should be determined on an individual patient basis, but in general should not exceed 4 weeks.

A major reason for interest in longer times between monitoring is the cost and inconvenience to the patient associated with frequent laboratory testing. The advent of patient self-testing may change the overall perspective on some of these issues. For example, a large prospective trial in Germany comparing frequent self-testing with routine oral anticoagulant monitoring found that patients who self-tested did so on a more frequent basis and that the self-testing was associated with tighter control of the anticoagulant therapy, a lower rate of venous thromboembolism, and a lower rate of clinical bleeding.[66] This study suggests that there may be an advantage to more frequent monitoring of patients.

Transition phases of OAT therapy occur when other medications are added to or removed from the patient's regimen or when the underlying medical condition of the patient changes. A variety of drugs may affect the response to oral anticoagulants; therefore, it is prudent to monitor patients whenever there is any change in their regimen. Changes in the patient's underlying medical condition may also affect the response to OAT. For example, OAT therapy needs to be monitored more carefully in the patient with worsening congestive heart failure or in the patient with significant gastroenteritis. Significant changes in the diet may also affect the response to OAT owing to fluctuation in the amount of vitamin K in the diet.[67]

Long-term monitoring of OAT is dependent on appropriate presentation of data over time. There appears to be a consensus, but no specific recommendation, that laboratories should attempt to present patient results via a flow sheet. This is most readily accomplished using computer systems. Outcome results using a commercial software package have been promising, and other commercial products are available or in trial.[68] Incorporation of warfarin dosage as well as INR results would seem to be minimal requirements for a workable system.

### Recommendations

1. During the initiation phase of oral anticoagulant therapy it is prudent to monitor patient status daily or at least 4 to 5 times per week, until some degree of consistency of the INR response to a stable dose is achieved.[13,63,65] (Level 2)

2. The frequency of testing in stabilized OAT patients should be determined on an individual patient basis. In general, the INR should be determined at intervals not exceeding 4 weeks.[64–66] (Level 2)

## EFFECT OF CONCURRENT LUPUS ANTICOAGULANTS, LIVER DISEASE, OR CONGESTIVE HEART FAILURE ON MONITORING OF OAT

Lupus anticoagulants (LAs) are phospholipid-dependent antibodies that are detected by abnormalities in laboratory clotting tests. Criteria for their diagnosis have been established and include (1) prolongation of a phospholipid-dependent clotting test, (2) evidence of inhibition as demonstrated by mixing studies, (3) evidence of phospholipid dependence, and (4) lack of specific inhibition of any one coagulation factor and/or lack of another cause for the abnormal clotting test.[69] Although LAs are usually associated with prolongation of the activated partial thromboplastin time, they may also be associated with prolongation of the PT. In most cases, the degree of prolongation is mild and dependent on the PT reagent; in some cases, more significant prolongation of the PT may be associated with a true acquired deficiency of prothrombin.[70] Although the effect of LAs on the PT is usually mild in the absence of prothrombin deficiency, the concern is that the combination of a factor deficiency and an LA could lead to significantly greater prolongation of the PT than would be seen with the factor deficiency (ie, OAT) alone.

Moll and Ortel,[71] in a prospective case study of 34 patients with LAs, presented evidence that LAs can significantly influence PTs and lead to INRs that may not accurately reflect the true level of anticoagulation; in general, the INRs in these patients underestimated the level. In 50% of 22 patients who were not receiving OAT, PTs were elevated and varied significantly with the thromboplastins tested. For LA patients on OAT, the INRs using different thromboplastins varied greatly, with the difference between the highest and lowest values for any one patient ranging from 0.4 to 6.5. It should be noted that PTs were measured on a single, mechanical endpoint coagulometer using 9 different thromboplastins whose ISIs ranged from 0.93 to 2.41. The ISIs were assigned by the manufacturer for use with ''mechanical coagulometers.'' Della Valle et al[72] found that an INR of 2 to 3 with a recombinant thromboplastin correlated to an INR of 3.1 to 4.6 with a less sensitive thromboplastin in LA patients on warfarin. A recent abstract presented findings in 2 patients indicating that the effect of LAs on the INR was strongly reagent dependent.[73]

Refuting these data, Lawrie et al[74] investigated the laboratory variation in INR for 35 patients, 14 with LA documented by standard criteria and 21 non-LA patients. The authors used an optical endpoint instrument and 8 different thromboplastins, comparing the effect of the manufacturer's assigned ISI (range, 0.95–1.36) with local ISI assignment. They showed that the variation in INR of both groups of patients using the manufacturer-assigned ISIs was significant and similar (CV = 12.5% for non-LA and CV = 12.4% for LA patients). With locally assigned ISIs, the variation was markedly reduced (CV = 5.8% for non-LA and CV = 6.5% for LA patients). They concluded that inappropriate use of a generic, non–instrument-specific ISI

can lead to ambiguous INR results, but that there was no specific effect associated with LAs.

There is strong epidemiologic evidence that patients with LAs may need higher INRs to achieve protection against recurrent thromboembolism. Two retrospective studies have suggested maintaining the INR between 2.5 and 3.5 for secondary prophylaxis in patients with LA and a prior thromboembolic event (especially if it was an arterial event).[75,76] Failure to maintain this higher level of anticoagulation resulted in an unacceptably high incidence of recurrent thrombosis. This may be related to the effect of LAs on the PT and the tendency of the INR to overestimate the extent of anticoagulation in this setting.[71] These higher levels of anticoagulation were associated with a higher incidence of hemorrhage.

In general, chronic liver disease appears to be less of a problem than acute liver disease, since most of these patients have compensated cirrhosis and have a reasonably stable response to warfarin. The occult chronic alcoholic patient may present a more difficult problem, since in this setting warfarin-induced skin necrosis or thrombosis may occur more readily with a standard initiating dose. In general, dosing of warfarin may need to be done very cautiously to avoid over-anticoagulation in patients with documented or suspected liver disease. Precautions should include initiating therapy with a smaller dose than usual, increasing the dose in smaller increments than usual, and anticipating a longer time frame to achieve a steady state. When a flare-up of chronic hepatitis, acute hepatitis, or heavy drinking develops, a major decrease in clotting factor synthesis can occur, which can contribute to serious bleeding. There is no reliable way to avoid problems with these patients except to monitor them very closely; this usually means once or twice a week.

The target INR for patients with liver disease has not been well established. The general practice is to use the standard INR target range. However, there is little evidence to indicate whether a given INR in a patient with liver disease indicates the same degree of anticoagulation as in a patient without liver disease. The deficiency of additional factors, especially factor V, may alter the dose response to warfarin. In this setting, it is possible that a ''therapeutic'' INR may be achieved before there has been adequate suppression of prothrombin.

Anything that interferes with liver function may alter the INR. Patients with congestive heart failure severe enough to have passive congestion of the liver may develop wildly fluctuating INR responses to warfarin, depending on the status of their failure. Rospond et al[65] found that patients with congestive heart failure had more variability in their PTs, although this failed to achieve statistical significance. Clinically, there is a concern that changes in congestive heart failure status often produce significant changes in the INR. However, data that clearly indicate what the response will be in an individual patient are lacking. The key is to monitor patients with unstable congestive heart failure closely.

### ALTERNATIVE ASSAYS FOR MONITORING OAT

The prothrombin-proconvertin (PP) test uses a commercial thromboplastin, Simplastin A (Organon Teknika Corp, Durham, NC), which contains supplemental bovine factor V and fibrinogen. The clotting times of diluted patient plasmas are converted to percent of control pooled plasma using a log-log plot. Because this assay involves a

1:10 dilution of plasma, which may reduce the effect of LAs, it may be useful in patients with LAs, as suggested by Rapaport and Le.[77,78] They recommended that the test be used initially to adjust the warfarin dose to a PP test of between 15% and 20%. Then, once this level is achieved, a traditional PT should be obtained to determine the patient-specific INR target. Once the target INR has been defined, the patient may be followed with a routine PT. Moll and Ortel[71] have also recommended the PP test as a means of monitoring LA patients. These authors report that an INR of 2.0 to 3.5 was equivalent to a PP test of 27% to 9% in patients without LA. Haraldsson et al[79] reported data supporting this finding; they showed a good linear correlation between the INR calculated from a PT (reagent ISI = 2.0) versus the INR calculated from the PP (reagent ISI = 1.1).

There are several problems with the PP test approach. The reagent thromboplastin in undergoing reevaluation by the manufacturer and is not available in the United States. The correlation with the INR would be expected to depend on the individual thromboplastin that the laboratory is using at the time. Therefore, the process might have to be repeated whenever the laboratory changes reagent lots or even changes lots of the same reagent. Lastly, the relationship to the INR might also change over time as the concentration of the LA changes.

Measurement of factor II or X (either chromogenic or one-stage clotting assay based on at least 3 dilutions) may be used to assess anticoagulation intensity in LA patients.[71,74,80] Suggested levels vary, and correlation with an appropriate therapeutic INR remains to be established. An assay for native (fully carboxylated) prothrombin antigen has been suggested as an alternate assay for monitoring OAT in these patients, but a therapeutic range has not been clearly established.[81,82] Fragment 1 + 2, thrombin-antithrombin complex, activated factor VII, and D-dimer may be used as indicators of suppression of clotting activation. These tests may provide supporting data when one is uncertain if the level of anticoagulation achieved is adequate, or if there is suspicion of an ongoing clotting process.[83]

#### Recommendation

Lupus anticoagulants can alter the PT, and the effect is dependent on the reagent. The effect may give rise to clinically important differences in INR values, which may result in incorrect dosing. A normal baseline PT does not rule out an effect of an LA on the INR during therapy. Alternative tests may be useful in monitoring these patients, and they may be best managed in coordination with a facility capable of performing these alternate assays.[71,72,77,78] (Level 2)

### UTILIZATION OF WHOLE BLOOD COAGULOMETERS FOR MONITORING OAT

Whole blood coagulation monitors permit determination of a PT or activated partial thromboplastin time on a small amount of whole blood, which is usually obtained by a fingerstick. These whole blood monitors have an advantage because the test results are rapidly available to the operator of the instrument. In the setting of OAT monitoring, these instruments permit rapid assessment of the therapeutic response and adjustment of dosage. For this reason, these instruments have become popular with OAT management clinics. In addition, more recent studies sug-

gest that these instruments can be used appropriately by patients or family members to determine PTs in the home setting.

With the introduction of new technologies comes questions of the accuracy and precision of the new method, and whole blood coagulation monitors are no exception. Ideally, the whole blood PT result should be the same as the plasma measurement. A number of methods have been described that might be used to show such equivalence. Bland and Altman[84] have suggested that the proper way to compare a criterion standard method and a new method is to create a plot of the difference between the new measure and the average of the standard and the new measure. The NCCLS has published a standard procedure for method comparison that uses linear regression and bias plots between a reference or "comparison" method and the method being tested.[85] The British Standards Institution suggests a "coefficient of repeatability" as a measure of comparison.[86] Kaatz et al[87] looked at this issue in quite some detail in an evaluation of the accuracy of monitor measurements and presented several methods for comparing results.

Due to the number of statistical methods in the literature and the complexity of trying to compare 2 methods that use different sample types (whole blood vs anticoagulated plasma) obtained in different ways (fingerstick vs venipuncture), the conference participants were unable to reach a consensus as to which method is optimal for comparing whole blood analyzers to traditional plasma-based coagulometers. Adding to this complexity is the fact that some studies compare direct, fingerstick, non-anticoagulated whole blood with citrated plasma, while others compare citrated whole blood with the latter.

Looking at the available data, several evaluations of the most common methodology for whole blood PT measurement (thromboplastin-based, clot detection by capillary blood flow cessation) in general have shown that in the common therapeutic range of an INR of 2.0 to 3.0, there is acceptable agreement.[78,87–91] There may be a significant bias above this range, in that some whole blood analyzers appear to underestimate the INR when compared with plasma-based system.[90,91] However, in another study, there appeared to be a clinically significant bias throughout the range of INRs reported, with the whole blood analyzer underestimating the INR by a mean difference of 0.8.[92] In a recent prospective cohort study reported by Bussey et al[93] patients were followed by both whole blood–based and laboratory plasma-based INRs. The fingerstick system was judged to be superior in that it showed less variability and was less likely to indicate erroneous dosage changes. Additional randomized, prospective clinical outcome studies comparing whole blood and plasma-based systems are needed.

Reports on the performance of a second type of whole blood PT monitor (thromboplastin-based, clot detection by iron particle movement) in general have shown acceptable correlation.[94,95] One report showed increased scatter for INRs above 2.75, but acceptable agreement when compared with plasma-based systems using low-ISI thromboplastins.[90] Of note, an evaluation of the ISI of this system demonstrated acceptable calibration based on World Health Organization criteria.[96]

A recently developed whole blood PT monitor (thromboplastin-based, clot detection by capillary blood flow cessation) measures the clotting time for the patient plasma in triplicate and simultaneously measures the clotting time of internal lyophilized controls. This instrument has been evaluated in a multi-institutional trial.[97] Acceptable correlation between the laboratory-based INR and the portable monitor was obtained by either healthcare providers or patients. Ease of patient training was further demonstrated in a subsequent study.[98]

Quality control remains an important issue for the whole blood coagulation analyzers. Current College of American Pathologists laboratory accreditation guidelines require the laboratory to define a quality control system for each analyte or analyte system. For most analytes, it has been implicit that at least 2 levels of liquid quality control samples be incorporated into a "run," with a run being defined by the laboratory. The advent of portable devices utilizing disposable cartridges has added a new complexity to traditional quality control. As each cartridge represents a self-contained testing unit, it is not possible to establish quality control methods for the reagents actually used for testing the patient sample. Another variable that has entered the picture is the development of "electronic controls," which test the function of the instrument without using (or assessing) any cartridges.

Currently, each laboratory director must determine what quality program is adequate for his or her laboratory. At a minimum, it seems appropriate to test a sample of each lot or shipment of cartridges with at least 2 levels of liquid control material before they are used for clinical purposes. In addition, liquid controls may be useful for periodic checking of the cartridges during storage to assess the possibility of cartridge deterioration. Electronic controls may be incorporated into the overall program to assure that the instrument is working appropriately on a day-to-day basis. It should be noted that quality control material is included in the cartridges for one whole blood coagulation monitor. In many ways, this simplifies the quality control process and provides real-time data on the performance of this system.

In spite of a lack of consensus on this issue, monitoring of OAT using whole blood analyzers has increased, and 2 systems for home monitoring have recently received approval from the Food and Drug Administration in the United States. Currently, whole blood analyzers are widely used in clinics, and in the future self-monitoring will clearly grow. Studies demonstrating acceptable oral anticoagulant control based on achieving therapeutic INRs are available, but appropriate studies of clinical outcome are rare.[99] A major problem may occur when more than 1 method of PT determination is used within an institution. Very confusing results may be reported if the testing systems (whether whole blood or plasma-based) are not calibrated to each other. Therefore, if more than 1 test system is used to monitor OAT within an institution, it is important for each system to be calibrated against the other(s).

### Recommendation

Whole blood monitors may be used to determine the INR in patients on OAT. When more than 1 test system is used within an institution, each test system should be calibrated against the other test system(s).[90–93] (Level 2)

### PATIENT SELF-TESTING FOR MONITORING OAT

The role of patient self-testing as a model of care can be defined by examining the problems with traditional monitoring of OAT, and it can be justified if improved out-

comes at reasonable costs can be demonstrated. Patient self-testing cannot be looked at in isolation; it is part of a model of care in which patient self-management is the ultimate end point. Traditional monitoring of OAT is time-consuming for the patient and the clinician, and the labor intensity of management has been cited as one reason for nonuse of oral anticoagulants.[100,101] Traditional OAT management has a legacy of poor outcomes, with patients frequently out of the therapeutic range, a rate of major hemorrhage of approximately 1% to 4% per patient year of therapy, and a similar magnitude of recurrent thrombosis.[102,103] There are many reasons for these results, but failure to maintain therapeutic levels of anticoagulation is a major factor.

There is abundant evidence showing that significant improvement can be achieved by managing patients in a coordinated fashion utilizing an anticoagulation management service. Such programs typically achieve consistent levels of therapeutic effectiveness, with INRs in therapeutic range 60% to 80% of the time compared to less than 50% of the time for routine office management. This experience poses the question of whether OAT management can be further improved by involving the patient in the testing process. Patient self-testing (and potentially patient self-management) offers greater access to INR monitoring, which is associated with more timely results, more consistency of instrumentation and reagents, better convenience, and perhaps most importantly, a model of care that engenders patient empowerment and involvement.

Point-of-care PT testing was first introduced for use in the office, clinic, or hospital. An extensive experience has accumulated over the last 10 years; this experience has verified both the accuracy and precision of this technology, as well as its limitations.[87–91,93,96,99] Patient self-testing is the next logical step in the development of this technology, and a number of studies have demonstrated the ability of patients to perform self-testing and obtain an accurate result.[66,97,98,102,105] Early on, White et al[104] showed the potential value of having patients perform their own fingerstick for PT monitoring following hospital discharge. In a randomized study, 23 patients instructed in the use of the capillary system were discharged and asked to perform their own testing. The patients were instructed to report the results to the anticoagulation clinic for dose adjustments. Compared with a standard treatment group, these patients spent a greater percentage of time within the therapeutic range (93% vs 75%; $P = .003$) and were significantly less likely to be in a subtherapeutic range during the follow-up period (6.3% vs 23%; $P < .001$) than the standard treatment group. In a more recent trial of patient self-testing, Anderson et al[105] also confirmed the feasibility of such monitoring in 40 patients over a period of 6 to 24 months and demonstrated reasonable accuracy and patient satisfaction with this method of care.

Home PT monitoring is analogous to glucose monitoring, which raises the possibility of patient self-management of dose adjustments as diabetics do with insulin therapy. Although warfarin monitoring is not as intense as glucose monitoring for insulin therapy, it still requires relatively frequent assessment of its biological effect and frequent dose adjustments. This concept is not new; it was tested 20 years ago in a study by Erdman et al.[106] These investigators developed a protocol for patient self-adjustment of warfarin dosing based on physician-derived guidelines while the prothrombin times were still ob-

| Clinical Outcomes | Self-Managed Patients | Control Patients | P Value |
|---|---|---|---|
| No. of patients | 20 | 20 | >.10 |
| Weekly warfarin dose | 37.5 | 34.8 | >.10 |
| Mean duration, mo, in study (range) | 44.7 (3–87) | 42.5 (3–86) | >.05 |
| No. of PTs (mean per patient) | 2153 (107.7) | 1608 (80.4) | >.10 |
| Mean interval between PTs, d | 13.8 | 16.0 | <.001 |
| PTs above range, % | 5.2 | 10.3 | <.001 |
| PTs below range, % | 6.3 | 21.8 | <.001 |
| PTs in range, % | 88.6 | 68.0 | <.001 |
| Dose changes, % | 10.7 | 28.2 | <.001 |
| Incorrect dose changes, % | 3.1 | . . . | . . . |

**Table 4. Results of Long-Term Patient Self-Management of Oral Anticoagulation[107]**

tained on plasma samples by routine laboratory instrumentation. They claimed a greater degree of satisfactory anticoagulation (98% of 195 patients enrolled) than was found in a retrospective survey of standard management patients who only achieved a 71% degree of adequate anticoagulation.

More recently, Ansell et al[107,108] updated the results of a pilot study of patient self-testing and self-management using point-of-care methodology in 20 patients followed over a 7-year time course. Patients ranged in age from 3 to 87 years and had diverse indications for OAT. They performed their own PT tests at home and adjusted their warfarin dose based on physician guidelines. The results are summarized in Table 4. The study group was compared with matched controls managed by an anticoagulation service. Self-managed patients were found to be in the therapeutic range for 88.6% of PT determinations, compared to 68% of PT determinations in the controls ($P < .001$). Also, study patients required fewer dose changes than controls (10.7% vs 28.2%, $P < .001$). Complication rates did not differ between the groups, and study patients were extremely satisfied with this mode of therapy, according to a survey questionnaire.

Bernardo[109] has reported a similar experience from her work in Germany, where patient self-management is becoming widespread. A study of 216 self-monitored and self-managed patients between 1986 and 1992 found that 83.1% of the PT results were within the target therapeutic range, and no serious adverse events occurred. Most recently, Horstkotte et al[66] published in abstract form the results of a randomized prospective study of 150 patients with prosthetic heart valves who managed their own therapy (n = 75) as compared with a control group (n = 75) managed by their private physicians. The self-managed patients tested themselves approximately every 4 days and achieved a 92% degree of therapeutic effectiveness as determined by the INR. The self-managed patients experienced a 4.5% per year incidence of any type of bleeding and a 0.9% per year rate of thromboembolism, compared with a 10.9% per year and 3.6% per year rate, respectively, in the physician-managed group ($P = .038$ between the 2 groups). In a related study, these investigators also demonstrated that a frequency of INR testing of every 4 days appeared to be optimal.[110]

Appropriate quality control remains an unresolved issue for patient self-testing. Clearly, a program to assure

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the accuracy and reliability of the test system is required. In one whole blood coagulation instrument, the quality control material is incorporated into the test cartridge, simplifying the process for this system. In other test systems, periodic evaluation of liquid controls should be part of the program. One suggestion for quality control of patient self-testing involves one set of liquid controls for each box of purchased cartridges, regular electronic control testing before each measurement, and repetition of the measurement to check for precision and accuracy whenever the INR result is either out-of-range or a predetermined number of INR units different from the last INR result.

These studies indicate that patient self-testing and patient self-management offer the potential to lower the risk-benefit profile of anticoagulant therapy; to improve patient satisfaction and patient compliance; and, by reducing the labor intensiveness of physician management, to encourage the more widespread use of warfarin. By improving safety and efficacy, such therapy has the potential to be even more cost-effective. These outcomes, however, need to be verified by randomized controlled studies comparing patient self-testing and monitoring to the current "gold standard" of management by an anticoagulation management service. In particular, because of the potential for serious side effects, the safety of this approach to clinical management of these patients needs to be firmly established before it is widely adopted.

## Recommendation

Patients participating in whole blood self-testing must receive appropriate training in the use of the test system and must be supervised by a physician or anticoagulant clinic familiar with the system. Quality control procedures should ensure that the instrument and reagent cartridge are functioning properly.[104–106] (Level 3)

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