

# The International Normalized Ratio

## *A Guide to Understanding and Correcting Its Problems*

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**W**ith the increasing use of the international normalized ratio (INR) to monitor warfarin therapy, a number of problems with prothrombin time (PT) testing have been identified that have led some laboratory physicians to question the reliability of the INR.<sup>1</sup> This is ironic, because it was the introduction of the INR system that brought to light some of the long-standing problems with the technique of PT monitoring. However, these problems are not insurmountable if a compromise can be reached between the expectations of laboratory physicians and of clinicians. Thus, the laboratory physician seeks a perfect assay system, which in the case of the INR is unattainable at present, because of differences in PT reagents and methods. In contrast, the clinician is satisfied with a system of monitoring that provides safe and effective warfarin dosing. This goal can be achieved provided that certain details of PT testing are observed. In this communication, which is directed to practicing clinicians, the potential problems with the INR system are discussed, their clinical relevance is critically reviewed, and solutions are offered.

Warfarin treatment must be monitored closely because the anticoagulant response to fixed dosages varies among individuals,<sup>2</sup> and the efficacy and safety of warfarin are highly dependent on maintaining the anticoagulant effect within a defined therapeutic range.<sup>2-5</sup> Laboratory monitoring is usually accomplished by measuring the PT. The PT is measured by adding a thromboplastin reagent (which is either an extract of mammalian tissue rich in tissue factor or a recombinant preparation of human tissue factor in combination with phospholipid) to citrated plasma and recording the time for clotting to occur after recalcification. The PT is responsive to a reduction of three vitamin K-dependent clotting factors (prothrombin and factors VII and X), the levels of which decrease at a rate that depends on their respective half-lives.<sup>6</sup> The major reason why control of warfarin therapy using the PT

is problematic is because thromboplastin reagents vary in their responsiveness to warfarin-induced reduction in clotting factors, a variability that is dependent on their method of preparation.<sup>7,8</sup>

The urgent need to standardize PT reporting was highlighted by two recent reports in the United States<sup>9,10</sup> that demonstrated that PT reagents used in North America still differ markedly in their responsiveness to the anticoagulant effects of warfarin. As a result, widely divergent PT ratios may be obtained for the same plasma sample, depending on the thromboplastin reagent that is used,<sup>11</sup> a situation that can lead to inappropriate and dangerous anticoagulant dosing.

There are a number of potential solutions to this problem. The approach that is now recommended is to standardize PT monitoring by using the INR, a system that adjusts for the variable sensitivities of the different thromboplastin reagents. An alternative approach would be to use thromboplastin reagents that have a similar level of responsiveness to warfarin-induced re-

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**Relationship Between INR and PT Ratio Over an ISI Range of 1.0 to 2.8\***

INR	PT Ratio by ISI						
	1.0	1.4	1.8	2.0	2.3	2.6	2.8
2.0-3.0	2.0-3.0	1.6-2.2	1.5-1.8	1.4-1.7	1.4-1.6	1.3-1.5	1.3-1.5
2.5-4.0	2.5-4.0	1.9-2.7	1.7-2.2	1.6-2.0	1.5-1.8	1.4-1.7	1.4-1.6

\*INR indicates international normalized ratio; PT, prothrombin time; and ISI, International Sensitivity Index.

duction of coagulation factors. A third possibility might be to replace the PT with a test that does not use a thromboplastin reagent, avoiding the limitations caused by the variability in responsiveness of these materials. The latter two approaches will be discussed briefly before the problems associated with the INR system are reviewed.

#### STANDARDIZING THE RESPONSIVENESS OF THROMBOPLASTINS

This potential solution would require the cooperation of manufacturers to produce sensitive thromboplastin reagents with similar levels of responsiveness to warfarin-induced reduction of coagulation factors. This approach has been facilitated by the availability of human recombinant tissue factor, which makes it easier to produce sensitive thromboplastin reagents in commercial quantities.<sup>12</sup>

#### REPLACEMENT OF THE PT WITH OTHER TESTS

Other laboratory tests that are easier to standardize than the PT may be useful substitutes for monitoring warfarin treatment. The most promising of these is the prothrombin (factor II) antigen assay, which was reported to be better than the PT ratio at predicting clinical events in studies of patients treated with warfarin.<sup>13,14</sup> Unfortunately, however, an insensitive thromboplastin was used to measure the PT ratio in these studies, and it remains to be established whether the PT antigen assay will be

as effective and safe as the PT ratio when a sensitive thromboplastin is used. Further randomized trials are necessary to settle this issue. In addition, the utility of the prothrombin antigen assay may be limited because it is more expensive and more complicated to perform than the PT test. Until these issues are settled, the PT will continue to be the method of choice for monitoring warfarin treatment.

#### THE INR

The INR scheme for PT standardization was approved by the Expert Committee on Biological Standardization of the World Health Organization in 1983 after extensive and prolonged study.<sup>15</sup> The INR corrects the PT ratios obtained with thromboplastin reagents with different degrees of responsiveness to the warfarin-induced coagulation defect by standardizing the result against a common international reference preparation. Standardization is achieved by converting the PT ratio observed with any local thromboplastin to a common standard, which is the INR. The INR is calculated as follows:  $INR = (\text{Observed PT Ratio})^c$ , where the PT ratio is the patient's PT value divided by the mean normal PT value and *c* indicates the power representing the International Sensitivity Index (ISI) for each thromboplastin. The INR system of reporting is based on a logarithmic relationship between the PT ratios of the test and reference preparation. The INR is the PT ratio that would be obtained if the international reference preparation, which has an ISI of 1.0, were used to perform the test. The ISI is the correc-

tion factor in the equation that relates the PT ratio of the local reagent to the reference preparation and is a measure of the responsiveness of a given thromboplastin to reduction of the vitamin K-dependent coagulation factors: the lower the ISI, the more "sensitive" the reagent and the closer the derived INR will be to the observed PT ratio.

The calculation of the INR is relatively simple and can be performed with a handheld calculator. For example, if the PT ratio is 1.5 and the ISI of the thromboplastin is 1.8, the  $INR = 1.5^{1.8} = 2.07$ . The relationship between the INR and PT ratio over a range of ISI values is shown in the **Table**.

After a slow start, the INR system of PT standardization is being adopted by an increasing number of hospitals in North America. Thus, whereas two reports from the United States in 1992 showed that only a very small proportion of centers were reporting the PT ratio as an INR, by mid-1993, about half of the participants in the College of American Pathologists proficiency testing program were doing so (D. A. Triplett, MD, oral communication, March 2, 1993). With the increasing use of the INR system to replace the PT ratio method of reporting, a number of problems have been identified, and the INR system has been criticized.<sup>1</sup> The remainder of this article will review these problems with the INR system, consider their clinical importance vis-à-vis the continued use of PT system of reporting, and suggest solutions.

#### PROBLEM 1

##### Lack of Reliability of the INR System When Used at the Onset of Warfarin Therapy

The PT is responsive to reduction in three of the four vitamin K-dependent procoagulants, factor II, factor VII, and factor X, but individual thromboplastin reagents vary in their sensitivity to decreases in these clotting factors,<sup>7,8</sup> particularly factors VII and X. Since

the three vitamin K-dependent clotting factors have varying rates of plasma clearance, their relative contribution to the prolongation of the PT will be different during the induction phase of warfarin therapy (first few days) than during the subsequent weeks to months of treatment.<sup>16</sup> Thus, during the first 2 to 5 days of warfarin treatment, the prolongation of the PT is mainly the result of a reduction in the level of functional factor VII, with some contribution from a decrease in factor X levels. In contrast, during longer-term anticoagulation, the prolongation of the PT reflects a decrease in all three vitamin K-dependent coagulation factors, which are usually reduced to a similar extent.

To overcome the problem of the variable responsiveness of thromboplastins to factors VII and X, plasma samples collected during the induction phase are not used to calibrate thromboplastins. Instead, the INR scheme is based on ISI values derived from the plasma of patients whose conditions have stabilized while receiving anticoagulant treatment for at least 6 weeks.<sup>15</sup> Given this practice, there is the potential for the INR to be unreliable early in the course of warfarin therapy if reagents that are relatively insensitive to depletion of factors VII and X are used.

This problem was investigated by McKernan and associates,<sup>16</sup> who performed serial PT testing for 5 to 40 days after oral anticoagulant therapy was started in 15 patients. All plasma samples were tested in parallel with five different thromboplastins (including the international reference preparation). A wide range of INR values was observed when the same plasma was tested with the different thromboplastins. The variance appeared to be most marked during the first 4 days of warfarin therapy but persisted throughout the period of study. Two factors explained the divergence in INR values among the different thromboplastins. These were (1) differences in the responsiveness of the reagents to decreases in individual vi-

itamin K-dependent coagulation factors and (2) inaccurate calibration of reagents by manufacturers. Although the variance was considerable, the clinical relevance of these differences is uncertain, because they would have resulted in only modest changes in warfarin doses during the first 14 days of treatment. Furthermore, among the different thromboplastins, the INR values were less variable than the PT ratios during the initial stages of treatment. Thus, this study clearly demonstrates that the INR system of reporting is superior to the non-standardized PT ratio, even when used to monitor patients soon after warfarin therapy has been started.

Additional evidence that it is safe to use the INR system during the initial stages of warfarin therapy is provided by the results of randomized trials in which the INR was used to monitor treatment, even though PT reagents with different sensitivities were used to titrate warfarin doses. Anticoagulant therapy monitored this way proved to be both effective and safe for the prevention and treatment of venous thrombosis, for the prevention of systemic embolism in patients with prosthetic heart valves, and for the secondary prevention of myocardial infarction.<sup>3</sup>

Despite its loss of reliability in the initial stages of warfarin therapy, when thromboplastin reagents with different ISI values are used, the INR system is more reliable than the unconverted PT ratio, and from the point of view of clinical management, it appears to be an effective and safe method of monitoring warfarin therapy.

#### Potential Solutions

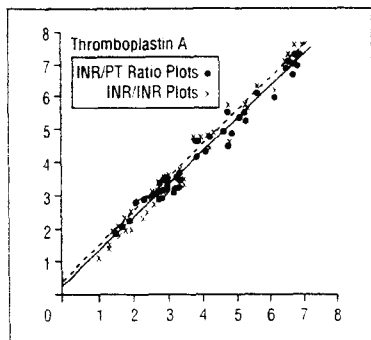
On the basis of the data described above, some investigators have suggested that the PT ratio should be used to monitor patients in the early stages of warfarin therapy and the INR should be restricted to monitoring patients receiving long-term anticoagulant therapy. Not only is this approach im-

practical and confusing, it is also not supported by the evidence. There is evidence that the PT ratio is less reliable than the INR even during the induction phase of warfarin treatment. Although there may be limitations of the INR during this period, they do not adversely affect patient treatment and certainly do not justify abandoning the INR system. Furthermore, it is likely that the problems with the INR during the early stages of warfarin therapy would be minimized if sensitive thromboplastins were used.

## PROBLEM 2

### INR System Loses Accuracy and Precision When Thromboplastins With High ISI Values Are Used

Given that the INR is calculated by raising the PT ratio to the power of the ISI as follows:  $INR = PT \text{ ratio}^{ISI}$ , it is not surprising that the calculated result is less accurate when the PT test is performed with insensitive thromboplastins that have high ISI values.<sup>17,18</sup> For the same reason, the inaccuracies are greater with higher PT ratios. Although these concepts are supported by a number of studies,<sup>17-19</sup> the study by Moriarty and associates<sup>17</sup> will be discussed in some detail because it exemplifies the problem and suggests a solution. Comparing 12 thromboplastins against a secondary reference thromboplastin, these investigators tested 20 control plasma samples and 60 plasma samples from patients who had been treated with warfarin for at least 3 weeks. The ISI values of the thromboplastins varied from approximately 1.0 to 2.2. The points describing the relationship between the observed PT ratios were plotted in two ways: as INR values on both the horizontal and vertical axes and as an INR on the horizontal axis and PT ratio on the vertical axis. Representative examples of the results with three different thromboplastins are summarized here: thromboplastin A, with an ISI value of 0.98 (**Figure 1**); thromboplastin B, with im-

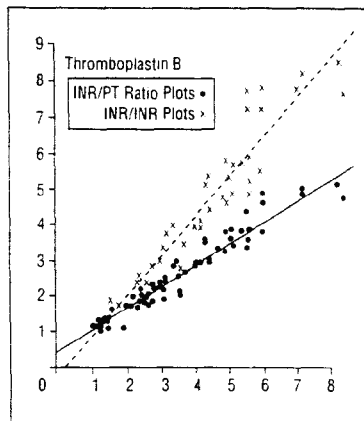


**Figure 1.** Relationship between observed prothrombin time (PT) ratios and international normalized ratio (INR) values for thromboplastin A (Australasian reference thromboplastin 9-88), with an International Sensitivity Index of 0.98. The dashed and solid lines are the regression lines for the INR/INR plots and the INR/PT ratio plots, respectively.

an ISI value of 1.3 (**Figure 2**); and thromboplastin C, with an ISI value of 2.2 (**Figure 3**).

With thromboplastin A (ISI, 1.0), the regression lines representing the INR/INR and INR/PT ratio plots were virtually identical (**Figure 1**). In addition, the variance was minimal, and virtually all of the data points fell on the regression lines, which had a slope of 45°. These data demonstrate that a very responsive thromboplastin (with an ISI of 0.98, almost identical to that of the reference preparation) is accurate and precise over a wide range of INR values.

When a thromboplastin of intermediate sensitivity (thromboplastin B; ISI, 1.3) was used, there was considerable divergence between the regression lines representing the INR/INR and INR/PT ratio plots. Although there was also a greater scatter of points around the regression line in the INR/INR plot, the slope of the line was still approximately 45° (**Figure 2**). In addition, as expected, the PT ratio was considerably lower than the INR, and this difference was increased with increasing intensity of anticoagulation. These findings indicate that a thromboplastin with an ISI of 1.3 is likely to produce less accurate INR results than a thromboplastin with an ISI close to 1.0. Regardless of which thromboplastin is used, however, the results



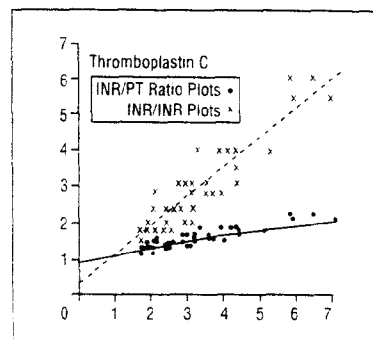
**Figure 2.** Relationship between observed prothrombin time (PT) ratios and international normalized ratio (INR) values for thromboplastin B (Simplastin Excel S, lot OC-136), with an International Sensitivity Index of 1.30. The dashed and solid lines are the regression lines for the INR/INR plots and the INR/PT ratio plots, respectively.

are more accurate when expressed as INR values than as PT ratios.

The results with the less sensitive thromboplastin C (ISI, 2.2), a mid-range North American thromboplastin, are shown in **Figure 3**. There is marked divergence between the regression lines representing the INR/INR and INR/PT ratio plots. This divergence is already evident at an INR of 2.0, where the corresponding PT ratio is approximately 1.3, and is extreme with an INR of 5.0, where the corresponding PT ratio is approximately 2.0. In addition, the ability to discriminate between an INR of 3.0 (which is the upper level of the therapeutic range and represents a relatively safe level of anticoagulation) and an INR of 5.0 (which is potentially dangerous) is poor. The slope of the regression line is less than 45°, although not greatly less, indicating that even with this less responsive thromboplastin, the INR system remains valid. However, the scatter of individual points around the regression line is considerable, demonstrating again the potential for loss of accuracy and precision with less responsive thromboplastins.

#### Potential Solution

The problem of loss of accuracy and precision of the INR system can be



**Figure 3.** Relationship between observed prothrombin time (PT) ratios and international normalized ratio (INR) values for thromboplastin C (BioMerieux 69260, lot 02601), with an International Sensitivity Index of 2.19. The dashed and solid lines are the regression lines for the INR/INR plots and the INR/PT ratio plots, respectively.

solved by using sensitive thromboplastins with ISI values close to 1.0. However, even with poorly responsive thromboplastins, conversion to the INR system provides more accurate results than reporting the results as a PT ratio.

#### PROBLEM 3

##### Loss of Accuracy of the INR With Automated Clot Detectors

The INR system is based on a mathematical relationship between the PT ratios obtained with test thromboplastin and the international reference preparation using a manual method of clot detection. However, most modern laboratories now use automated clot detectors, introducing a new variable. This variable does affect the accuracy of the INR system.<sup>20-25</sup> Studies have shown that the observed INR of the same plasma sample can vary even when instruments of the same make and model are used,<sup>25</sup> but is the magnitude of the variability clinically important? This issue was addressed in a recent report by Poller and associates.<sup>20</sup> Using the same responsive thromboplastin (ISI, 1.12), over 100 laboratories measured the PT for plasma samples obtained from warfarinized patients and from normal controls. The PT test was performed either by the manual method or with

ratory control PT instead of a properly defined mean normal PT can lead to erroneous INR calculations, particularly with nonresponsive reagents. The mean normal PT is determined by measuring the PT for fresh plasma samples obtained from at least 20 healthy individuals (and preferably a larger sample from both sexes over a range of age groups). Since the distribution of PT values is not normal, log-transformation and calculation of a geometric mean is recommended. Alternatively, the median can be used, since this is a close approximation of the geometric mean. The mean normal PT should be determined with the same reagent and on the same instrument as the patient's PT.<sup>29</sup>

#### Potential Solution

Laboratory personnel should be educated about the differences between mean normal PT and control PT and should be instructed to calculate the mean normal PT using fresh plasma samples from at least 20 healthy subjects.

#### PROBLEM 6

##### High INR Values in Overanticoagulated Patients Can Produce Unnecessary Alarm

The expanded scale and logarithmic relationship of the INR system results in much higher values in overanticoagulated patients than values obtained with the PT ratio using less responsive thromboplastins. For example, if a thromboplastin with an ISI of 2.8 is used, an INR of 21.7 is equivalent to a PT ratio of 3.0, and an INR of 13.0 is equivalent to a PT ratio of 2.5. While a PT ratio of 2.5 is unlikely to evoke feelings of panic or even of concern, the inexperienced physician is likely to be alarmed by an INR of 13.0. An approach to reversing a high INR has been suggested in a recent publication and is summarized below.

#### Potential Solution

A standard approach to treating patients with high INR values has been developed. The following protocol<sup>3</sup> is offered:

1. If the INR is above the therapeutic range but below 6.0, if the patient is not bleeding, and if rapid reversal is not indicated for reasons of surgical intervention, the next few doses can be omitted, and warfarin therapy can be resumed at a lower dose when the INR is in the therapeutic range.

2. If the INR is above 6.0 but below 10.0 and the patient is not bleeding, or if rapid reversal is required because the patient needs elective surgery, phytonadione (vitamin K<sub>1</sub>) can be given subcutaneously at a dose of 0.5 mg to 1 mg with the expectation that a demonstrable reduction of the INR will occur at 8 hours and that, in many patients, the INR will be in the therapeutic range of 2.0 to 3.0 within 24 hours. If the INR remains high at 24 hours, an additional dose of 0.5 mg of phytonadione can be given. Warfarin treatment can then be resumed at a lower dose.

3. If the INR is above 10.0 but below 20.0 and the patient is not bleeding, a higher dose of phytonadione (3 to 5 mg) should be given subcutaneously with the expectation that the INR will be reduced substantially at 6 hours. The INR should be checked after 6 hours, and the dose can then be repeated if necessary. Subcutaneous injection of vitamin K is preferred over intravenous injection in these circumstances because rapid intravenous infusion of phytonadione can produce anaphylactoid reactions.

4. If a very rapid reversal of an anticoagulant effect is required because of serious bleeding or major warfarin overdose (eg, INR >20.0), phytonadione at a dose of 10 mg should be given by slow intravenous infusion (eg, over 20 to 30 minutes), and the INR should be checked every 6 hours. The dose of phyto-

nadione may have to be repeated every 12 hours and supplemented with plasma transfusion or prothrombin complex concentrate, depending on the urgency of the situation.

5. In case of life-threatening bleeding or serious warfarin overdose, replacement with prothrombin complex concentrate is indicated, supplemented with intravenous phytonadione, 10 mg, which should be repeated as necessary depending on the INR.

6. If continued warfarin therapy is indicated after high doses of phytonadione have been administered, heparin can be given until the effects of phytonadione have been reversed and the patient becomes responsive to warfarin therapy.

#### CONCLUSIONS

Historically, the INR system, which is based on a mathematical model, was developed to normalize the variability in PT ratios that results from the marked differences in sensitivity of commercial thromboplastin reagents to the anticoagulant effects of warfarin. The INR system can be precise and valid when a sensitive thromboplastin and a manual method of clot detection are used. However, it loses precision and accuracy when used to convert PT ratios obtained with less-sensitive thromboplastin reagents or when automated clot detection systems are used. These problems can be minimized by using sensitive thromboplastins with low ISI values and calibrating automated systems with well-characterized plasma calibrants.

Although the INR system is far from perfect, it is the only practical solution currently available. With all of its faults, it is much better than an unadjusted PT system. Although the laboratory physician would like a perfect system with little or no variability, this goal is unattainable unless a standardized sensitive reagent is universally adopted. In contrast, the clinician wants a sys-

one of three different automated devices. Using the manual method, the "true" INR levels of the three thromboplastins were 2.21, 2.80, and 4.34, respectively. With all three instruments, the derived INR values differed from those obtained with the manual method. In addition, the results obtained with the three automated methods were more variable than those obtained with the manual method. The variance in ISI determinations could be reduced significantly by calibrating the instrument with 20 lyophilized plasma samples that had been certified centrally using the manual method. Without this type of calibration, INR values with automated instruments deviated by a mean of about 10% from the true INR. However, such differences may not be clinically important, provided that a sensitive thromboplastin (ISI value close to 1.0) is used. With less sensitive thromboplastins, the instrument effect is more obvious, but this effect can be offset and a reliable result can be obtained by performing local calibration with plasmas with certified INR values for each new batch of thromboplastin reagent.

#### Potential Solution

The problem resulting from the use of automated instruments to measure the INR can be minimized by using sensitive thromboplastins (ISI values close to 1.0) and by calibrating each new batch of thromboplastin with lyophilized plasmas with certified INR values. The problem cannot be resolved by reporting the results as a PT ratio.

#### PROBLEM 4

##### Lack of Reliability of the ISI Result Provided by the Manufacturer

A number of investigators have noted that the ISI value provided by the manufacturer for each new batch of thromboplastin reagent may be incorrect.<sup>1,16,17,27,28</sup> The error is usu-

ally suspected and identified when investigators calibrate a new lot of thromboplastin against an old lot. For example, in one recent report, the inaccuracy was identified when a new lot of thromboplastin reagent from the same manufacturer produced INR values that were inconsistent with those obtained with the prior lot.<sup>1</sup> The manufacturer was contacted and, after review, revised the ISI value of the new lot from 2.23 to 2.05. When the INR values were recalculated using the revised ISI, the discrepancy was partly corrected, but divergent INR values were still observed in the upper range. A local calibration was then performed using the prior thromboplastin reagent as the reference standard, and a local sensitivity index of 1.75 was obtained for the new thromboplastin. The authors concluded that better standardization of thromboplastin reagents was required among manufacturers, preferably with thromboplastins restricted to those with an ISI close to the international reference thromboplastin of 1.0. They also suggested that reliable secondary reference thromboplastins calibrated against the World Health Organization preparation should be more widely available for distribution so that local laboratories can perform their own calibrations.

It is clear that manufacturers should be required to provide reliable ISI values for each new lot of thromboplastin reagent, since failure to do so leads to inaccurate warfarin monitoring, with the potential for clinical disaster. The recommended calibration protocol for calculating the ISI of a thromboplastin is to perform the PT test with a reference thromboplastin and to test the thromboplastin on plasma samples from 20 healthy individuals and from 60 patients receiving oral anticoagulant therapy for at least 6 weeks. Although too cumbersome for clinical laboratories, this exercise is within the capability of manufacturers and should be ex-

pected by consumers (clinical laboratories and practicing physicians), by government, and by medical regulatory bodies. Alternatively, an independent national standards laboratory could be established to calibrate each lot of thromboplastin, providing independent verification for clinical laboratories. If manufacturers could be relied on to provide accurate ISI values, a large part of the problem would be solved. However, as already discussed, some discrepancies can still occur because of the effects of different automated instruments on the INR. Although the instrument-related problem is relatively minor if responsive thromboplastins are used, it can be troublesome with less responsive thromboplastins. Poller and associates<sup>26</sup> have reported that calibrations can be performed locally by using lyophilized plasmas with known INR values to calculate an instrument-specific ISI for each new lot of thromboplastin. Thus, the problem is solvable.

#### Potential Solution

The problem can be solved by ensuring that manufacturers assign reliable ISI values to their thromboplastins. Clinical laboratories should select sensitive thromboplastins with low ISI values (<2.0 and preferably <1.5). If less sensitive thromboplastins are used, local calibrations should be performed with certified lyophilized plasma samples with known INR values to determine the instrument-specific ISI.

#### PROBLEM 5

##### Incorrect Calculation of the INR Resulting From Use of Inappropriate Control Plasma

The PT ratio is calculated by dividing the patient's PT by the mean normal plasma PT. The mean normal plasma PT is not interchangeable with a laboratory control PT, since these values can be substantially different.<sup>29</sup> Therefore, the use of a labo-

tem that permits safe and effective warfarin dosing independent of the reagent or the method used to perform the PT test. By using sensitive thromboplastins with reliable ISI values and reporting the results as an INR, the laboratory physician can allow the clinician to achieve this goal.

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