Oral Anticoagulant Therapy
Urgent Need for Standardization
Jack Hirsh, MD

Over the last 20 years, important advances have been made in the clinical use of oral anticoagulants and in our understanding of their mechanism of action. Clinical trials have demonstrated that oral anticoagulants are effective antithrombotic agents,1 that the incidence of bleeding is influenced strongly by the intensity of the anticoagulant effect,2-5 and that for many clinical indications the use of a less intense therapeutic range decreases the rate of bleeding without reducing efficacy.2-10 In addition, the development of a standardized international normalized ratio (INR) method for reporting the prothrombin time (PT) has provided a means to ensure that a uniform intensity of oral anticoagulant therapy is used worldwide.11 Unfortunately, evidence from two recent surveys12,13 indicates that PT reporting is not standardized in many laboratories in the United States, and as a consequence, many patients are not deriving maximum benefit from these recent advances. This is of particular importance to cardiologists who are responsible for the care of large numbers of patients on chronic oral anticoagulant therapy. Although the PT test is simple, low cost, and potentially very useful, it is clear that PT results are being reported incorrectly by many laboratories in the United States. This deficiency could be corrected if the reporting of the PT were standardized by use of the INR system of reporting.

The purpose of this review is to discuss the reason why standardization of PT reporting is important for optimal patient care, to present the evidence from recent studies that PT reporting is substandard in many laboratories in the United States, and to suggest ways of correcting this deficiency.

The PT is responsive to depression of three of the four vitamin K-dependent procoagulant clotting factors (prothrombin and factors VII and X). These factors are reduced by warfarin at a rate proportionate to their respective half-lives.14 The PT assay is performed by adding a mixture of calcium and thromboplastin to citrated plasma. The term “thromboplastin” refers to a phospholipid–protein extract of tissue, usually lung, brain, or placenta, that contains both tissue factor and the phospholipid necessary to promote the activation of factor X by factor VII. The activation of coagulation produced by adding thromboplastin to plasma for the PT assay is illustrated in Figure 1. Thromboplastin complexes with and activates factor VII (to factor VIIa), and the thromboplastin/factor VIIa complex then activates factor X to form factor Xa. Factor Xa forms a complex with factor Va, which then converts prothrombin to thrombin. Thrombin then clots the plasma by converting fibrinogen to fibrin. A variety of thromboplastins are available in commercial PT reagent kits, and these differ markedly in their ability to activate factor X. A “responsive” thromboplastin is a relatively weak activator of factor X and, therefore, produces a greater prolongation of the PT for any given coumarin-induced reduction in clotting factors.

Because of the variability of commercial thromboplastins, laboratories using different reagents will obtain (and report) discrepant PT results when the test is performed on an identically anticoagulated plasma sample.15-21 This difference in responsiveness of various thromboplastins to coumarin-induced anticoagulant effect has already had profound clinical consequences. First, it was responsible for clinically important differences in the dosages of oral anticoagulants used to treat the same conditions in different countries19; this difference in responsiveness continues to be responsible for clinically important differences in the dosages of anticoagulants used to treat the same conditions in different parts of the United States.12,13 Second, it led to an inadvertent increase in the therapeutic range in North America in the late 1960s when hospitals changed from local preparations of responsive thromboplastins to commercial preparations of less responsive thromboplastin reagents22; this change in thromboplastins resulted in less prolongation of the PT for any given coumarin-induced reduction of coagulation factors, with an associated increase in the risk of bleeding.

To solve the problem of variability in responsiveness of commercial thromboplastins, an INR was established,11,23,24 which is a calibration system based on a linear relation between the logarithm of the PT ratios obtained with the reference and test thromboplastins. This calibration model was adopted by the World Health Organization (WHO) in 1982 and is used to standardize the reporting of the PT by converting the PT ratio observed with any local thromboplastin into an INR, which is calculated as follows: INR=(patient PT/mean normal PT)c, where c is the power value representing the international sensitivity index (ISI) for each thromboplastin. The ISI 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 "responsive" is the reagent and the closer the derived INR to the observed PT ratio. The INR is, therefore, the PT ratio that would be obtained if the WHO reference thromboplastin, which by definition has an ISI of 1.0, had been used to perform the PT. Laboratories can now obtain ISI values for each new lot of thromboplastin from the major manufacturers in the United States on request and, therefore, can easily calculate an INR value for each PT result. For example, if the observed PT ratio is 2.0 and the thromboplastin has an ISI of 2.4, then inserting these figures into the formula INR = PT ratio\(^{ISI}\), the INR = 2.0\(^{2.4}\) = 5.3. A specially designed nomogram has been developed\(^{25}\) that provides INR values from the prothrombin ratio value obtained with thromboplastin reagents over a range of ISI values without the need for calculations (Figure 2).

The problem produced by failure to standardize PT reporting has been highlighted by the results of two recent surveys of laboratory practices in the United States.\(^{12,13}\) The findings are disturbing for several reasons. The first is that most of the more than 200 laboratories surveyed indicated that they report PT results without any attempt at standardization, despite the well-described observation that commercial thromboplastin reagents vary in their responsiveness to the anticoagulant effects of warfarin.\(^{15-21}\) The second is that the information provided to Bussey et al\(^{12}\) from three major North American manufacturers indicates that the ISI values of their thromboplastins vary from 1.4 to 2.8, an even wider variation than was reported previously,\(^{15}\) which indicates that the term "typical North American thromboplastin" can no longer be used. The third is that the survey by Ansell\(^{13}\) of 88 laboratories in Massachusetts indicates that close to 70% of the laboratory

**FIGURE 1.** Flow diagram showing activation of coagulation produced by adding thromboplastin to plasma for PT assay.

**FIGURE 2.** Relation between the prothrombin time ratio and the international normalized ratio (INR) over a range of international sensitivity index (ISI) values. At an ISI value of 1.0, the prothrombin time (PT) ratio is identical to the INR. As the ISI value of the thromboplastin increases, the INR for a given PT ratio also increases. Reprinted with permission.\(^{25}\)
supervisors had little or no understanding of the meaning of the terms ISI and INR and that only 5% reported the PT result as an INR. When Ansell checked the lot numbers of the different thromboplastins used in the hospitals surveyed, he found that their ISI values varied from approximately 1.8 to 2.8.

Guidelines for therapeutic ranges for the control of oral anticoagulants have been proposed by a task force on antithrombotic therapy of the American College of Chest Physicians. These were revised at a recent meeting and are shown in Table 1. A moderate-intensity anticoagulant effect equivalent to an INR of 2.0–3.0 is recommended for most indications, except for patients with mechanical prosthetic valves, for whom an INR of 2.5–3.5 is recommended. The PT ratios corresponding to INRs of 2.0–3.0 and 2.5–3.5 for thromboplastins with ISI values of 1.0 to 2.8 are also shown in Table 1. The magnitude of variability in PT ratios for thromboplastins with ISI values that range from 1.4 to 2.8 (which represents the range of ISI values of thromboplastins used in North America) is striking. Thus, for the less intense INR of 2.0–3.0, the PT ratio for a thromboplastin with an ISI of 1.4 is 1.6–2.2, whereas for the more intense INR of 2.5–3.5 and a thromboplastin with an ISI of 2.8, the PT ratio is only 1.4–1.6. Considered from the point of view of a targeted PT ratio of 2.0, the INR would be 2.6 for a thromboplastin with an ISI of 1.4, and the INR would be 7.0 for a thromboplastin with an ISI of 2.8. Thus, if a targeted PT ratio of 2.0 were being used in two different laboratories in the United States, the INR could be 2.6 in one and 7.0 in the other. Because there is good evidence from randomized trials and from cohort studies that a relation exists between the intensity of the anticoagulant effect and clinically important bleeding, it must be concluded that the lack of standardized PT reporting by the majority of the laboratories surveyed is exposing some patients to an unnecessary risk of bleeding. In addition, poor standardization produces variable PT results when an identical anticoagulated blood sample is tested at different laboratories, and as a consequence, results in erratic laboratory control and frequent and unnecessary alterations in the dosage of oral anticoagulants, with the attendant inconvenience to patient and physician and increase in health care costs.

The problem of variability in responsiveness of thromboplastin reagents has been solved in many European countries by the introduction of the INR system of reporting. It can also be solved in North America but will require a concerted effort on the part of laboratory directors and clinicians. The first step is to educate laboratory supervisors and physicians that a problem exists. The next step is to put a system in place that ensures that each new batch of thromboplastin reagent is calibrated carefully by the manufacturer and that a reliable ISI is provided to the laboratory. Laboratories could then report their PT results as an INR. Because there have been anecdotal reports of inaccurate calibration by manufacturers and there is no national system for quality control of ISI values, laboratories should have ready access to a reference preparation or to a central facility that could check the ISI of new batches when required. Ideally, the quality control of the manufacturers' ISI values should be monitored by a national agency, because faulty calibration could impair the safety and efficacy of anticoagulant therapy.

If these steps were taken, the reliability of PT reporting would be improved greatly. Other steps involve fine-tuning of the system, because the INR system loses some precision when poorly responsive thromboplastins are used and when certain automated coagulation detection systems are used. The first problem can be overcome by encouraging laboratories to use one of a number of responsive commercial thromboplastins (preferably with an ISI of less than 1.5) that are now readily available, and the second can be overcome by requesting that manufacturers calibrate their thromboplastins for the automated coagulation detection system used in different laboratories and provide the laboratory with a suitably adjusted ISI value. These latter two technical problems are much less important causes of unreliable oral anticoagulant monitoring than the present practice in many North American centers of reporting PT results without any attempt at standardization.

The message provided by the two recent surveys is clear. Nonstandardized reporting has the potential to

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<thead>
<tr>
<th>Indication</th>
<th>INR</th>
<th>ISI</th>
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<tbody>
<tr>
<td>Prophylaxis of venous thrombosis (high-risk surgery)</td>
<td>1.0</td>
<td>1.4 1.8 2.4 2.8</td>
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<tr>
<td>Treatment of venous thrombosis</td>
<td></td>
<td></td>
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<tr>
<td>Treatment of pulmonary embolism</td>
<td></td>
<td></td>
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<tr>
<td>Prevention of systemic embolism</td>
<td></td>
<td></td>
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<tr>
<td>Tissue heart valves</td>
<td>2.0–3.0</td>
<td>1.6–2.2 1.5–1.8 1.3–1.6 1.3–1.5</td>
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<tr>
<td>Mechanical prosthetic heart valves</td>
<td></td>
<td></td>
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<tr>
<td>Acute myocardial infarction (to prevent systemic embolism)</td>
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<tr>
<td>Valvular heart disease</td>
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<td>Atrial fibrillation</td>
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<tr>
<td>Recurrent systemic embolism</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mechanical prosthetic valves (high risk)</td>
<td>2.5–3.5</td>
<td>1.9–2.4 1.7–2.0 1.5–1.7 1.4–1.6</td>
</tr>
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INR, international normalized ratio; PT, prothrombin time; ISI, international sensitivity index.
compromise patient care and should no longer be tolerated by physicians caring for patients who are being treated with oral anticoagulants. It is clearly time for all manufacturers to provide reliable ISI values for each new batch of thromboplastin and for all laboratories to adopt the INR system of reporting.

References

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