Q: For years, my laboratory has used a thromboplastin reagent with a high International Sensitivity Index, or ISI, around 1.9. Now I read that labs should use a more responsive reagent with an ISI of 1.4 or less. How is this likely to affect my prothrombin time and International Normalized Ratio values? Will the PT in seconds be longer and the INR results stay close to the same or will the PTs be somehow the same and the INRs be lower?

A: The International Normalized Ratio method of reporting prothrombin time values was introduced in 1983 to standardize laboratory monitoring of oral anticoagulant therapy. Standardization was needed due to the significant variation in PT results caused by the marked variability in how different commercial thromboplastin reagents respond to the vitamin K-dependent clotting factors (II, VII, X) involved in the extrinsic and common pathways. The INR was developed to normalize the clotting time values by mathematically correcting for differences in reagent responsiveness.

Each lot of commercial thromboplastin reagent produced is tested against the International Reference Plasma, and the relationship is expressed as the International Sensitivity Index. The lower the ISI, the more responsive to changing factors the effects of warfarin therapy and the longer the PTs are for a given factor concentration. The INR is calculated as the PT ratio (patient PT divided by the geometric mean normal PT) raised to the power of the ISI. In an ideal situation, if a sample from an individual on stabilized warfarin therapy were tested using two thromboplastin reagents with two different ISIs, the PT would be higher with the more sensitive thromboplastin and lower with the less sensitive reagent, but the INR values would be equivalent.

The precision of the INR is dependent on the ISI through the following equation: coefficient of variation of the INR = CV (PT ratio) / ISI. Thromboplastins with a high ISI value, therefore, may lead to greater imprecision in INR values.

In an effort to improve interlaboratory variation, the 1998 College of American Pathologists Conference XXXI on Laboratory Monitoring of Anticoagulant Therapy published a recommendation that laboratories use thromboplastins with an ISI between 0.9 and 1.7, with a preference for reagents with an ISI toward the lower end of the scale. Although the effect of using more responsive thromboplastins on interlaboratory precision is modest, data from CAP interlaboratory proficiency testing programs generally validate this recommendation.

The use of more sensitive thromboplastins is further supported by how variation or errors in ISI values influence the INR, especially when ISI values approach 2.0 or greater. For example, given a PT ratio of 2.0, a 5 percent difference in ISI in a reagent with an ISI value of 2.0 causes the INR to vary from 3.7 to 4.3, while a reagent having an ISI of 1.0 causes the INR to vary from 1.9 to 2.1 (Fig. 1). Variation in ISI can occur due to local instrument effect altering the value of the manufacturer-assigned ISI, or it can reflect an error in assignment of ISI value due to inherent imprecision in the manufacturer-assigned ISI compared to the ISI value determined directly against the WHO reference plasma. Finally, using thromboplastin reagents with low ISI values results in a wider range of PT ratios to obtain an INR in the therapeutic range (Fig. 2), thus enhancing patient safety.

Despite introduction of the INR system, significant interlaboratory variation and inaccuracies persist in the INR. Laboratories can reduce this variation by using a sensitive thromboplastin, using a thromboplastin with an instrument-specific ISI value, properly determining the geometric mean PT for each lot of thromboplastin, and ensuring that the INR is calculated properly using the appropriate ISI for each given reagent lot.

Bibliography
Dorothy M. Adcock, MD Medical Director Exeterix Coagulation Aurora, Colo.

Q: We use NCCLS standard H3-A4 (June 1998) for the order of draw for venipuncture collections with multiple tubes. We are starting to change from glass to plastic tubes, and the manufacturer has advised us that the order of draw is different for plastic serum tubes. Has the NCCLS updated this standard? Are there updated standards for those tests that are affected by using plastic tubes instead of glass?

A: There are no updated NCCLS standards that address the impact of plastic tubes on the order of draw or the analytes being measured. The order of draw must be obtained from the manufacturer of the plastic tube collection system that you use. For example, some manufacturers, like Becton Dickinson and Company, coat their plastic serum tubes with silica to activate coagulation. In this case, the citrated (blue top) tube should be drawn before the plastic tube to ensure that silica is not inadvertently introduced into the citrated tube, thereby confirming the result of the prothrombin time/partial thromboplastin time with regard to the effect of plastic tubes on particular analytes, CAP Laboratory Generalist checklist questions for individual laboratories determine if specimen containers contribute to anticoagulation in the assays they perform. Labs should make this determination using a combination of literature review, analysis of manufacturer information, and direct testing.

Manufacturers should provide information that helps laboratories make the transition from glass to plastic containers. However, laboratories are responsible for deciding which tests are most appropriate for plastic collection tubes.

Robert Makar, MD, PhD Fellow in Transfusion Medicine Blood Transfusion Service Massachusetts General Hospital Boston

Q: Our very small facility provides care for a large rural area that runs from the Black Hills to Yellowstone, which means we serve local residents as well as tourists. We have our share of emergency visits for chest pain and other ailments, and our physicians are asking for B-type natriuretic peptide results. What is the most cost-effective testing for BNP?

A: To provide real-time BNP results in an outpatient clinic setting, especially for tourists who may need acute care and possibly hospitalization, the only point-of-care testing option is the Biosite BNP assay. Biosite recently released its Triage CardioProfilER system that provides a 15-minute result turnaround time for BNP, cardiac troponin I, creatine kinase-MB, and myoglobin on the Triage Meter-Plus testing platform. BNP analysis can also be performed separately. Only a few drops of whole blood are needed.

Bayer and Roche have larger platforms to measure BNP and N-terminal-proBNP, respectively, that can also provide turnaround times of less than 15 minutes. The cost per test is competitive for all three BNP assays.

We use the Biosite BNP assay in our emergency department. In this point-of-care setting, the test helps us triage patients, as well as manage therapy and assess risk.

Fred Apple, PhD Medical Director, Clinical Laboratories Hepatitis Clinic Medical Center Professor, Laboratory Medicine University of Minnesota Minneapolis

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Q: What is the cost of the Triage Meter-Plus testing platform? BNP analysis can also be performed separately. Only a few drops of whole blood are needed.

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**Editors Note:** This column is written by members of the Clinical Chemistry Editorial Board, which includes Paul A. Feingold, MD, PhD, professor of medicine at the University of Minnesota, and Richard A. Savage, MD, clinical professor of medicine at the University of Minnesota School of Medicine and vice president of clinical programs for Esoterix.

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