Accuracy of Capillary Whole Blood International Normalized Ratio on the CoaguChek S, CoaguChek XS, and i-STAT 1 Point-of-Care Analyzers

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Abstract

We evaluated the accuracy of capillary whole blood international normalized ratio (INR) on the CoaguChek S (Roche Diagnostics, Indianapolis, IN), CoaguChek XS (Roche Diagnostics), and i-STAT 1 (i-STAT, East Windsor, NJ) point-of-care (POC) analyzers compared with venous plasma INRs determined by a reference laboratory method. Overall agreement between POC and laboratory plasma INR was very good, with median bias between capillary whole blood and laboratory plasma INRs varying from 0.0 to –0.2 INR units on all devices. More than 90% of results on the CoaguChek XS and i-STAT 1 and 88% of CoaguChek S results were within 0.4 INR units of the reference laboratory method. The CoaguChek XS and i-STAT 1 demonstrated greater accuracy than the CoaguChek S as measured by the number of results that differed by more than 0.5 INR units from the reference method. Median bias between CoaguChek S capillary whole blood and laboratory plasma INRs changed over time, demonstrating the need for ongoing quality assurance measures for POC INR programs.

Point-of-care (POC) measurement of the international normalized ratio (INR) is increasingly common in outpatient, inpatient, nursing home, and home care environments. Multiple devices exist for measurement of INR from a capillary finger-stick sample, making real-time measurement and adjustment of warfarin dosages possible at sites where testing is undertaken. However, the accuracy, reliability, and safety of INR measurement by capillary finger stick remains controversial. Studies of POC INR accuracy are divided into those comparing INR measurement by capillary finger stick with matched venous plasma samples tested on a laboratory reference analyzer and those that use carefully prepared reference plasma or whole blood materials to test POC INR devices.1-7

Some previous studies comparing capillary finger stick with laboratory plasma INR values have found significant differences between results of POC and laboratory plasma INR. In these studies, the mean bias varied from –0.2 to 0.8 INR units, and percentage results within 0.5 INR units of the reference method varied from approximately 50% to approximately 80%.1-3 Systematic bias between POC and laboratory plasma INRs existed for all POC methods, especially at INR values of more than 3.0.1-3 In contrast, 2 other studies found nearly perfect agreement between POC and laboratory plasma INRs (mean bias less than 0.1 INR unit), with 85% to 100% of values matching the reference method within 0.5 INR unit.4,5 These various studies are difficult to compare owing to different POC devices used, differing laboratory reference methods used, and the patient populations (ie, range of INR values measured) studied.

Other investigators have prepared external quality assessment material to assess consistency between results of different POC INR devices or consistency of results from the same
device used at different centers. These studies have found that the relationship between POC and laboratory plasma INRs differs by device, strip lot used for a given device, and between centers using the same device.6,7 Another study used whole blood drawn by venipuncture to compare POC INR values on 2 devices to plasma INR results using a manual method that used World Health Organization thromboplastin standards. This study also found significant variation between POC and laboratory plasma INRs, especially at INR values greater than 3.0.8 These studies raise significant concerns about the quality and consistency of POC INR testing and its use in outpatient practices, although it is not clear how results obtained with whole blood or external quality assessment material relate to differences between capillary whole blood and venous laboratory plasma INRs. Because the practice of self-monitoring of INR is associated with reductions in thromboembolism and major bleeding episodes,9 it is important to identify the monitors that will provide optimal results for outpatient and self-monitoring of the INR.

In the present study, we evaluated the performance of the i-STAT 1 (i-STAT, East Windsor, NJ), CoaguChek XS (Roche Diagnostics, Indianapolis, IN), and CoaguChek S (Roche Diagnostics) POC INR monitors using capillary whole blood. The venous plasma INR from a single laboratory coagulation analyzer with a single lot of thromboplastin was used as the reference method for comparison of device accuracy. The results provide information on the degree of systematic bias and variability between POC and laboratory plasma INRs for recently available POC INR monitors.

**Materials and Methods**

The study was performed at 2 outpatient practice sites at the Mayo Clinic, Rochester, MN: Primary Care Internal Medicine and the Thrombophilia Clinic. Both areas see a high volume of patients undergoing long-term anticoagulation and have participated in POC INR programs for several years. Between the 2 sites approximately 2,000 POC INR measurements are performed monthly by 44 trained nurses and midlevel practitioners. Patients were selected for the study if they had stable anticoagulation measures with warfarin therapy for more than 1 month; patients receiving heparin preparations and new patients were excluded.

Consent was obtained from 100 patients undergoing long-term anticoagulation who attended routine monitoring appointments at the Primary Care Internal Medicine or Thrombophilia clinics in 2 study periods. During study period 1, between October 2006 and April 2007, 50 patients were enrolled who consented to capillary whole blood INR measurement on the CoaguChek S and i-STAT analyzers. During study period 2, between May 2007 and July 2007, 50 additional patients were enrolled who consented to capillary whole blood INR measurement on the CoaguChek S and CoaguChek XS analyzers. Separate finger-stick capillary collections were used for each analyzer (ie, 2 finger sticks per patient). The CoaguChek S measures blood clotting by mechanical end point. Blood on the test strips is mixed with rabbit thromboplastin to initiate clotting. Tiny iron particles on the test strip are moved by alternating electrical fields, and the end point is reached when the blood clot stops the iron particles from moving. The i-STAT and CoaguChek XS measure clotting by electrochemical current detection following activation of blood clotting by recombinant thromboplastin. During parts of the study, a national recall of the CoaguChek S device mandated repeated testing with a second CoaguChek device using the same drop of blood. For these measurements, the average result of the 2 measurements was used for data analysis. There were 11 CoaguChek S, 2 i-STAT 1, and 3 CoaguChek XS instruments used during the 2 study periods.

After completion of the clinic visit (typically within 15 minutes), patients were sent immediately for plasma INR assessment. Blood samples were obtained by venipuncture in collection tubes containing 3.2% sodium citrate. Blood was centrifuged at 1,500g for 10 minutes, followed by analysis on an MDA 180 coagulation analyzer (Trinity Biotech, Bray, Ireland) using a Dade Innovin reagent (Dade Behring, Deerfield, IL) with an assigned international sensitivity index value of 1.0. The same lot of Innovin reagent was used on the same laboratory analyzer for all 100 venous plasma INR measurements. During study period 2, there were 2 patients with laboratory plasma INR values of more than 6.0 INR units, and these were excluded from analysis. The study protocol was approved by the Mayo Clinic Institutional Review Board.

Accuracy of POC INR devices was determined by comparing median bias between capillary whole blood and laboratory plasma INRs. The statistical significance of differences in median bias between devices was assessed by using GraphPad InStat, version 3 for Windows 2000 (GraphPad Software, San Diego, CA), with a P value of less than .05 considered significant. Bland-Altman plots were used to compare differences between POC and laboratory INRs across the range of values measured.

**Results**

During study period 1, 50 patients had capillary whole blood INR determinations made by CoaguChek S and i-STAT monitors, followed by venous blood sampling for INR determination in the central laboratory as the reference method. Of 50 patients, 10 had laboratory plasma INR values of more than 3.0 INR units. The median bias between capillary whole blood INR on the CoaguChek S and
laboratory plasma INR was 0.0 INR units, with 5 of 50 capillary samples exceeding 0.5 INR units of the reference method. For the i-STAT analyzer, the median bias between capillary whole blood and plasma INR was −0.1, although only 1 of 50 capillary samples differed by more than 0.5 INR units of the reference method. The difference in median bias between the CoaguChek S (0.0 INR units) and i-STAT (−0.1 INR units) was not statistically significant (P > .05).

To assess the clinical significance of these differences, we counted the number of whole blood INR measurements that would have resulted in a different warfarin dosage compared with the plasma INR, using a clinical protocol designed to keep INR in the range of 2.5 to 3.5. For the CoaguChek S, there were 14 of 50 whole blood measurements that would have resulted in a different warfarin dosage compared with the matching plasma INR, whereas for the i-STAT, there were 12 of 50 potential dosing discrepancies.

During study period 2, 48 patients had capillary whole blood INR determinations made by the CoaguChek S and CoaguChek XS, followed by venous blood sampling for laboratory plasma INR determination. Of 48 patients, 18 had a venous plasma INR of more than 3.0 INR units. The median bias between the capillary whole blood INR on the CoaguChek S and the laboratory plasma INR was −0.2 INR.

![Figure 1](image1.png) Bland-Altman plots (difference between capillary whole blood and laboratory plasma international normalized ratio [INR] vs mean of whole blood and laboratory INR) for the CoaguChek S (Roche Diagnostics, Indianapolis, IN) (A) and i-STAT 1 (i-STAT, East Windsor, NJ) (B) devices. Data were collected during study period 1.

![Figure 2](image2.png) Bland-Altman plots (difference between capillary whole blood and laboratory plasma international normalized ratio [INR] vs mean of whole blood and laboratory INR) for the CoaguChek S (A) and CoaguChek XS (B) devices (Roche Diagnostics, Indianapolis, IN). Data were collected during study period 2.
units, with 3 of 48 capillary whole blood specimens exceeding 0.5 INR units of the reference method. The difference between median bias on the CoaguChek S during study period 1 (0.0 INR units) and study period 2 (~0.2 INR units) was statistically significant (P < .01). For the CoaguChek XS instrument, the median bias between capillary whole blood and laboratory plasma INRs was 0.0 INR units, with 1 of 48 capillary whole blood specimens differing by more than 0.5 INR units from the reference method. The difference in median bias between the CoaguChek S (~0.2 INR units) and CoaguChek XS (0.0 INR units) was statistically significant (P < .05).

During study period 2, 14 of 48 CoaguChek S whole blood INR values would have resulted in dosing discrepancies by using the same clinical protocol as in study period 1. In contrast, only 8 of 48 warfarin dosages would have changed based on the CoaguChek XS whole blood INR result compared with the plasma INR result.

Owing to a national recall of the CoaguChek S device, 37 of 50 capillary samples during study period 1 were measured in duplicate (same finger stick) on 2 different CoaguChek S devices, and the average of the 2 results was used for data analysis. Mean and median bias did not differ significantly for patients who had duplicate analysis of samples on the CoaguChek S compared with patients who had a single measurement (P > .05). During study period 2, 16 of 48 capillary samples were measured in duplicate using 2 different CoaguChek S devices. Mean and median bias also did not differ between duplicate and single analysis of capillary whole blood INR during this study period (P > .05). Thus, duplicate measurement of INR, using the same capillary puncture but 2 different CoaguChek S devices, does not seem to impact the amount of bias observed between capillary whole blood and plasma INRs. All measurements with the i-STAT and CoaguChek XS devices were made on a single instrument.

The overall percentage of results (combining CoaguChek S data from study periods 1 and 2) within 0 to 0.2, 0.3 to 0.4, 0.5 to 0.6, 0.7 to 1.0, and more than 1.0 INR unit of the reference method is shown in Figure 3. The i-STAT and CoaguChek XS devices both had more than 90% of results within 0.4 INR units of the reference method, and the CoaguChek S had slightly more outliers (Figure 2). Overall there were 8 (8%) of 98 CoaguChek S, 1 (2%) of 50 i-STAT, and 1 (2%) of 48 CoaguChek XS results that differed by more than 0.5 INR units from the reference method.

Discussion

Several previous studies have demonstrated systematic bias of POC INR monitors compared with various laboratory reference methods, especially for patients with INR values of more than 3.0. CoaguChek S device found that the capillary whole blood INR was not significantly different from the laboratory plasma INR across a wide range of INR values. One new device, the CoaguChek XS, was also found to produce capillary whole blood INR values that closely matched those of a laboratory plasma method, although this study included few patients with INR values of more than 3.0.

The present study compared the performance of the CoaguChek S device and 2 new POC INR monitors, the CoaguChek XS and i-STAT 1, with a laboratory plasma reference method using Innovin as the thromboplastin. All devices were compared with a single reference method using 1 laboratory analyzer and 1 lot of thromboplastin on that analyzer to minimize the impact of the reference method used on comparison of POC INR monitor performance. The patients studied had INR values from 1.0 to 6.0 INR units, with approximately one third of patients having laboratory plasma INRs of more than 3.0. The median bias between capillary whole blood and laboratory plasma INRs varied from ~0.2 to 0.0 INR units. Thus, large systematic bias between capillary whole blood INR and laboratory plasma INR was not observed for any of the devices tested.

There were fewer patients with capillary whole blood INRs differing by more than 0.5 INR units from the reference method on the CoaguChek XS (1 of 48) and i-STAT 1 (1 of 50) devices compared with the CoaguChek S (8 of 98). Thus, the newer POC INR devices should allow for more accurate assessment of anticoagulation status, especially in patient populations expected to have higher INR results. Examination of the Bland-Altman plots (Figures 1 and 2) and measurement
of potential dosing discrepancies related to each device suggest that the CoaguChek XS demonstrated the best overall performance, although the study was limited by the number of patients included and the fact that different patients were assessed with the various meters.

The median bias between CoaguChek S capillary whole blood and laboratory plasma INRs changed significantly between study periods 1 and 2. Previous studies using external quality assessment material or reference plasma found that the relationship between POC INR and reference method INR differs over time, by center and/or user, and by lot of test strips used.6,7 Another study that used frozen plasma samples to measure INR values on 10 different CoaguChek S strip lots found significant differences between lots.11 However, no study has yet measured variability in the relationship between capillary whole blood INR and laboratory plasma INR over time using a single reference method.

We found that over several months the relationship between CoaguChek S capillary whole blood and laboratory plasma INRs changed significantly. It is not clear whether this may be attributed to differences in strip lots, instrument- or user-dependent effects, and/or patient characteristics during the 2 study periods. However, it is clear that ongoing assessment of the relationship between capillary whole blood and laboratory plasma INRs is necessary within the context of a POC INR program. This might be done coincidentally with each change in strip lots, although each POC INR program should determine the most practical manner for this assessment.

Large systematic bias between capillary whole blood and laboratory plasma INRs was not observed with any of the 3 POC INR devices studied. The CoaguChek XS and i-STAT 1 devices had greater accuracy than the CoaguChek S device, based on number of POC INR values that exceeded 0.5 INR units of the reference method. The relationship between CoaguChek S capillary whole blood and laboratory plasma INRs changed significantly during a period of several months, highlighting the necessity for ongoing assessment of POC INR device accuracy for POC INR programs.

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