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# Prospective Comparison of Point-of-Care Device and Standard Analyzer for Monitoring of International Normalized Ratio in Outpatient Oral Anticoagulant Clinic

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**Abstract**

Point-of-care testing (POCT) coagulometers are increasingly being used in the hospital setting and patients' self-testing. We determined the agreement of prothrombin time international normalized ratio (INR) results by POCT coagulometer and laboratory instrument through a comparative analysis and investigated whether the results of POCT coagulometer can reliably be used without being confirmed by standard laboratory analyzer. A total of 200 INR measurements by POCT coagulometer (CoaguChek XS Pro) and laboratory analyzer (Sysmex CS2000i) were compared using Passing-Bablok regression analysis and Bland-Altman plot. Agreement of the INR measurement was further analyzed in relation to dosing decision. The correlation of INR measurements between CoaguChek XS Pro and Sysmex CS2000i was excellent (correlation coefficient = 0.973). The overall mean difference was 0.21 INR $\pm$ 0.32 (range: 1.7-0.44). The mean difference was found to get increased as INR results increased and was 0.09 in the subtherapeutic range ($\leq$1.9 INR), 0.29 INR in the therapeutic range (2.0-3.0 INR), while 0.4 INR in the supratherapeutic range (>3.0 INR). The overall agreement was excellent ($\kappa = 0.916$) and overall 11 (5.5%) of 200 INR measurements showed a difference in dosing decision between the 2 instruments. The positive bias of POC-INR is evident in the supratherapeutic range which could affect the dosing decision requiring confirmation with the laboratory INR measurement.

**Keywords**

international normalized ratio, point-of-care testing device, anticoagulation, warfarin

## Introduction

Point-of-care tests (POCT) are the tests performed at or near patient site of care. Their application is increasing as they enable swift clinical decisions due to rapid therapeutic turnaround time.[1] In hemostasis field, a number of POCTs (activated clotting time, thromboelastography, platelet function, D-dimer, and so on) are available but measurement of international normalized ratio (INR) for monitoring warfarin therapy is the main test of this domain.[2] Despite the emergence of novel oral anticoagulants, warfarin is still the most commonly used oral anticoagulant worldwide.[3] Warfarin is monitored through INR which is a mathematical calculation based on prothrombin time. Owing to complex pharmacokinetics and pharmacodynamics of warfarin, it is necessary to keep the patient in a narrow therapeutic index (INR of 2-3) to prevent clot formation or expansion.[4] To determine INR, POCT could be performed easily with less frequent visits to the laboratory either at anticoagulation clinic or at home. Additionally, INR-POCT allows reduction of problems related to venipuncture, particularly in patients with difficult venous access and therefore can minimize errors in results of blood coagulation.[5] It also provides greater convenience for patients living in remote locations[6] and has been advocated for home monitoring and self-dose adjustment.[7] Quality assurance for POCT is no less important than for conventional laboratory-based analyses and incorporates all measures that are taken to ensure the reliability of testing and reporting. Therefore, general applicability of POCT-INR to particular patient populations requires

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validation. Hence, it is extremely important to compare INR results from point-of-care device with the results as generated by laboratory instrument. In 2013, anticoagulation clinic was initiated at our institute. We planned to monitor anticoagulation with POCT device in this clinic and therefore needed validation of the new tool. This study was undertaken to perform comparative evaluation of POCT-INR with the INR obtained in laboratory by standardized automated method to determine the agreement between 2 test results.

## Material and Methods

### Study Design and Study Population

This comparative study was conducted at Aga Khan University Hospital, Pakistan, from July 2013 to March 2014. A total of 100 individuals (20 healthy controls and 80 patients on warfarin) were enrolled. During study period, patients were recruited from outpatient anticoagulation clinic who visited for routine monitoring of oral anticoagulation therapy with warfarin prescribed either for treatment or prophylaxis of venous thromboembolism. Controls were the healthy individuals visiting our blood bank for donating blood. Study population was 18 years and older. The median age of study population was 36 years (range: 18-62) with 71 males and 29 females. All individuals were included after informed consent.

### Sample Collection and INR Measurements

Two drops of capillary whole blood and 3 mL of venous blood (in a tube containing 3.2% buffered sodium citrate) was collected from each individual for estimation of INR on point-of-care device (CoaguChek XS Pro; Roche Diagnostics GmbH, Mannheim, Germany) and laboratory instrument (Sysmex CS 2000i; Sysmex Corporation, Kobe, Japan), respectively. The venous sampling was performed by trained phlebotomist and samples were sent to laboratory where INR testing was performed within 2 hours of sample collection while the capillary blood testing was performed by trained nursing staff at the anticoagulation clinic. Both the capillary blood testing on POC device and laboratory instrument was determined in duplicate.

The CoaguChek XS Pro uses a human recombinant thromboplastin (International sensitivity index [ISI] = 1.01) and employs electrochemical current detection to measure clot formation. In capillary whole blood testing, the mean coefficient of variation of the CoaguChek XS Pro INR determination was claimed to be less than 4.5% by the manufacturer, and the analytic measurement range was 0.8 to 8.0 INR.

The citrated venous blood samples Sysmex CS2000i were processed and analyzed according to the routine procedures of the laboratory. Sysmex CS 2000i utilizes a clotting-based assay for prothrombin time estimation using Innovin (Dade Innovin, Siemens Healthcare Diagnostics Products GmbH, Germany)as thromboplastin reagent with an ISI of 0.9. The laboratory measurements using Sysmex CS2000i was considered the reference standard method.

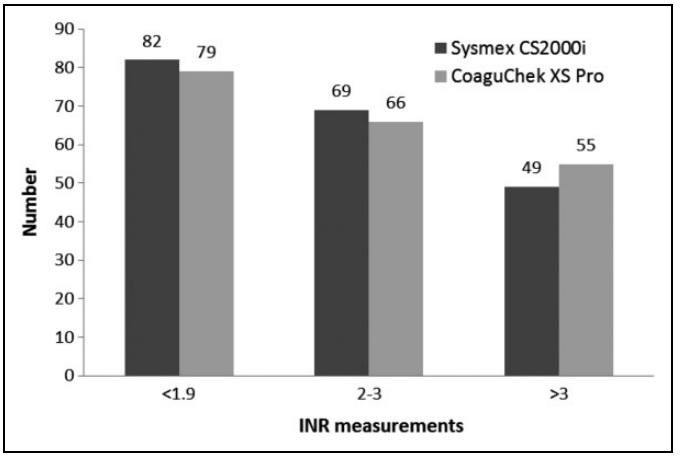


**Figure 1.** The distribution of INR measurements by CoaguChek XS Pro and Sysmex CS2000i. INR indicates international normalized ratio.

*Quality control.* Manufacturer's recommendation for calibration was followed and it was assured that both the test and the comparative methods remain in proper quality control throughout the evaluation period. Two levels of internal control were provided by the manufacturer: levels 1 and 2 with respective INR of 1.18 ± 0.04 and 2.95 ± 0.12, respectively. Operators ran 2 levels of control upon starting and toward the end of container of test strips as recommended by manufacturer.

### Statistical Analysis

The INR measurements were analyzed using Pearson correlation coefficient, Passing-Bablok regression analysis, and Bland-Altman plot. Bland-Altman plot was used to identify mean difference and 95% limits of agreement of the INR results between CoaguChek XS Pro and Sysmex CS2000i. The overall correlation and difference were compared in a total of 200 measurements and were further compared in 3 INR ranges (<1.9 INR, 1.0-2.0 INR, and 2.0-3.0 INR). Agreement of INR measurements was also assessed according to the 3 ranges of dosing decision (subtherapeutic, therapeutic, and supratherapeutic ranges) with cutoff values of <1.9 INR, 2.0-3.0 INR, and >3.0 INR, respectively. Cohen κ value was used for assessing agreement. Statistical analysis was performed using Excel Stat Biomed 2017, SAS 9.3, and SPSS 21 version, and *P* values less than .05 were considered statistically significant.

### Ethical Approval

The study was initiated after ethical approval from institutional ethical review committee [#2569-Pat-ERC-13]. Informed consent was taken from each individual before enrollment in study. The study results were not neither discussed nor disclosed to the manufacturer.

## Results

A total of 400 INR measurements were performed from 100 anticoagulated patients through duplicate testing on each

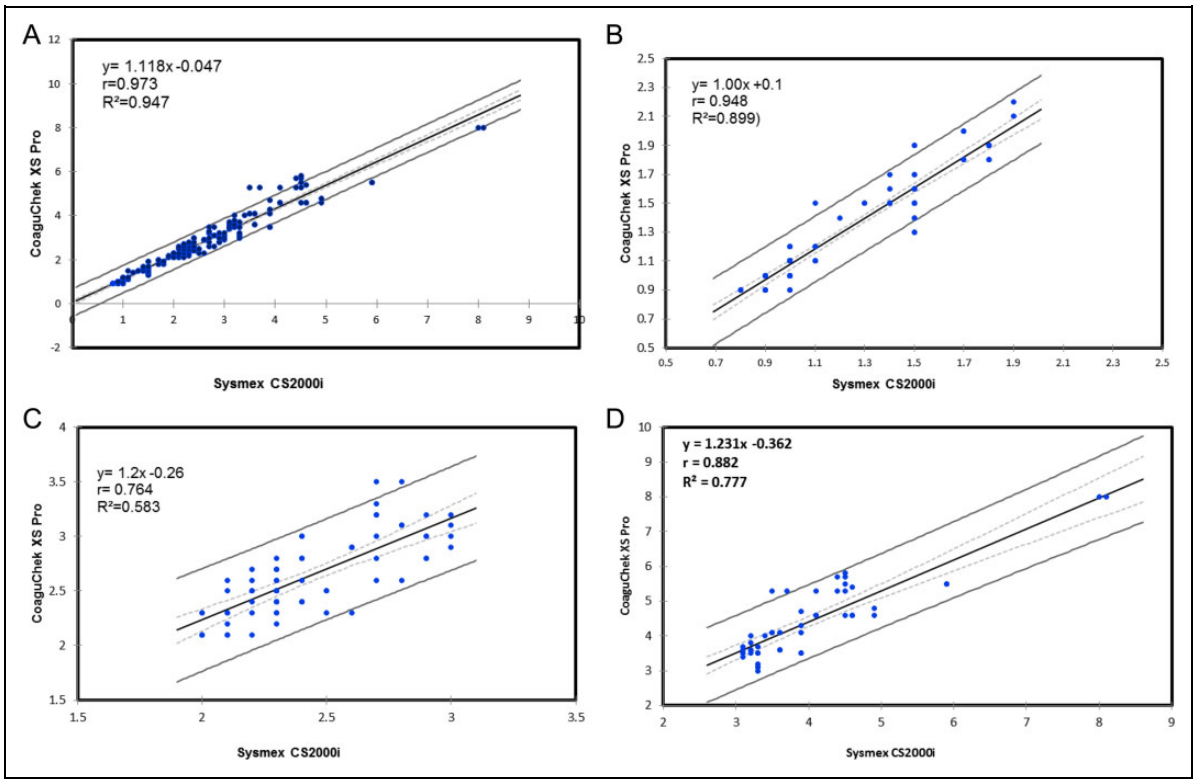


**Figure 2.** Comparison of INR measurements between the CoaguChek XS Pro and the Sysmex CS2000i using Passing-Bablock regression analysis. A, In a total of 200 measurements, Passing-Bablok regression analysis gave a slope of 1.118 (95% CI: 1.07 to 1.16) and an intercept of −0.047 (95% CI: −0.14 to 0.03). B, International normalized ratio of <1.9, it gave a slope of 1.00 (95% CI: 1.00 to 1.17) and an intercept of −0.1 (95% CI: −0.10 to 0.10). C, International normalized ratio 2-3, it gave a slope of 1.2 (95% CI: 1.00 to 1.50) and an intercept of −0.26 (95% CI: −1.0 to 0.2). D, International normalized ratio >3.0, it gave a slope of 1.23 (95% CI: −1.0 to 0.2) and an intercept of −0.047 (95% CI: −0.16 to 0.40). CI indicates confidence interval; INR, international normalized ratio.

individual sample on laboratory instrument (Sysmex CS2000i; n = 200) and POCT device (CoaguChek XS Pro; n =200).

Based on the Sysmex CS2000i, the mean INR was 2.34 ± 1.25 (range: 0.80-8.07), whereas on CoaguChek XS Pro, the mean INR was 2.55 ± 1.37 (range: 0.9-8.0). The distribution of INR measurements by Sysmex CS2000i and CoaguChek XS Pro is presented in Figure 1. The overall correlation of the INR measurements between the 2 methods was excellent without significant deviation from linearity. The Pearson correlation coefficient in all 200 measurements was ($r$) = 0.973 (95% confidence interval [CI]: 0.96-0.98; $P < .0001$).

When the correlation was further assessed in the ranges of ≤1.9 INR (n = 82), 2.0-3.0 INR (n = 69), and >3.0 INR (n = 49), the Pearson correlation coefficient was 0.948 (95% CI: 0.92-0.97, $P < .0001$), 0.764 (95% CI: 0.64-0.85, $P < .0001$), and 0.882 (95% CI: 0.80-0.93, $P < .0001$), respectively (Figure 2). The mean difference between the INR measurements generated with the CoaguChek XS Pro and the Sysmex CS 2000i instrument was 0.21 INR ± 0.32 (range: 1.7-0.44).

For differences with 95% limits of agreement, the Sysmex CS2000i INR measurements differed from the CoaguChek XS Pro INR measurements by −0.43 INR to 0.85 INR. The mean difference of INR measurements increased as INR values increased, and CoaguChek XS Pro exhibited increasing positive bias compared with Sysmex CS2000i at higher INR measurements.

The mean difference of the INR measurements was 0.09 (±1.96 standard deviation [SD], −0.13 to 0.32) in the lower range (<1.9 INR), 0.20 (±1.96 SD, −0.65 to 0.25) in the range of 2.0 to 3.0 INR, and 0.4 (±1.96 SD, −0.63 to 0.1.45) in >3.0 INR range, respectively (Figure 3).

### Clinical Evaluation

The agreement of INR measurements between CoaguChek XS Pro and Sysmex CS2000i was further assessed according to the 3 INR ranges (subtherapeutic, therapeutic, and supratherapeutic ranges) related to dosing decision. The overall agreement was excellent (κ = 0.916; 95% CI: 0.862-0.964), and 11 (5.5%) of 200 INR measurements showed a difference in dosing decision between the 2 instruments (Table 1).

## Discussion

Point-of-care INR devices were initially implemented to monitor oral anticoagulation by vitamin K antagonist,[8-11] and thereafter, its use has been extended to monitor coagulation state in

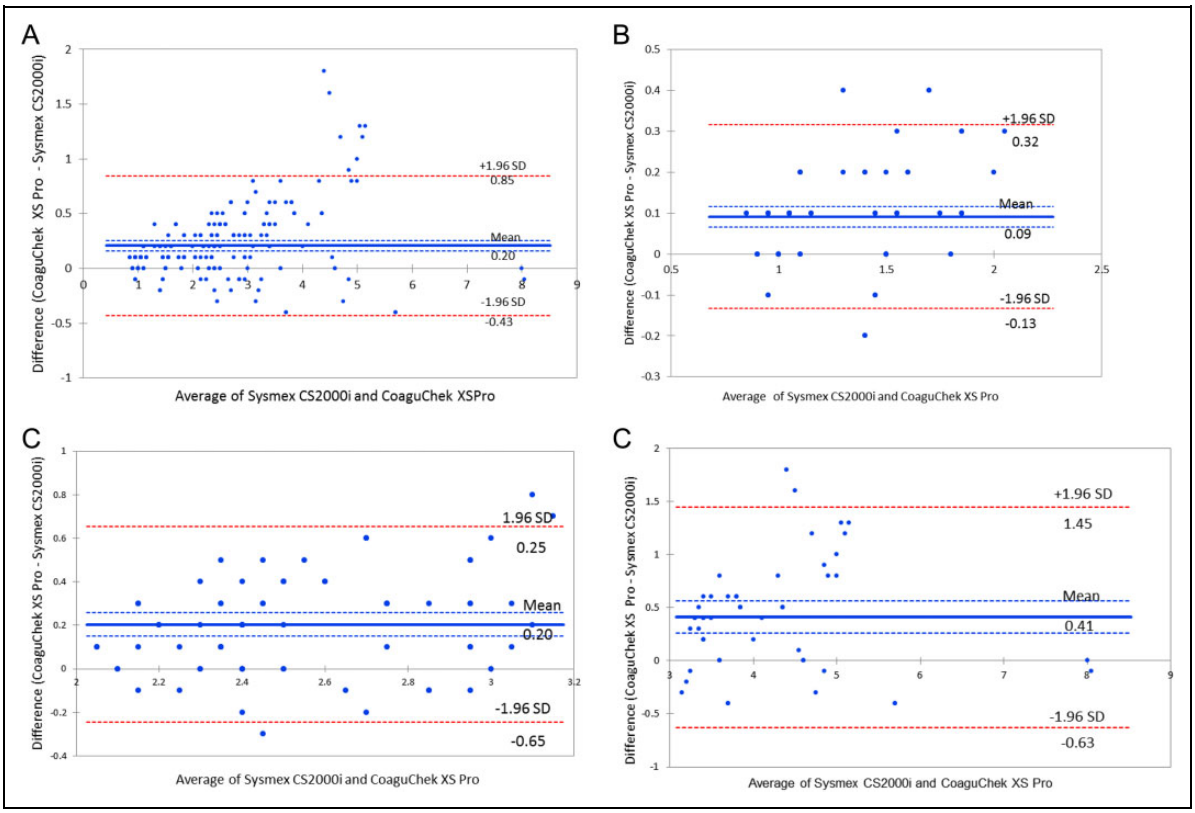


**Figure 3.** A, Comparison of INR measurements between the CoaguChek XS Pro and Sysmex CS2000i using Bland-Altman plots in a total of 200 measurements. B, International normalized ratio of <1.9. C, International normalized ratio in the range of 2 to 3. D, International normalized ratio of >3.1. The difference between 2 values in the *y*-axis is plotted against the average of Sysmex CS2000i and CoaguChek XS Pro results in the *x*-axis. INR indicates international normalized ratio.

**Table 1.** Agreement of INR Measurements Between CoaguChek XS Pro and Sysmex CS 2000i.[a]

| | CoaguChek XS Pro | | | |
|---|---|---|---|---|
| | ≤1.9 | 2-3 | ≥3.1 | Total (%) |
| Sysmex CS 2000i | | | | |
| ≤1.9 | 79 | 3 | 0 | 82 (41%) |
| 2-3 | 0 | 62 | 7 | 69 (34.5%) |
| ≥3.1 | 0 | 1 | 48 | 49 (24.5%) |
| Total (%) | 79 (39.5%) | 66 (33%) | 55 (27.5%) | 200 |

Abbreviations: CI, confidence interval; INR, international normalized ratio.
[a]κ: 0.916 (95% CI: 0.862-0.964).

the operating room,[12] emergency department,[13] and for patient self-testing at home.

The performance evaluation of POC-INR devices have been conducted in a number of studies in the past several years with varying results of precision and accuracy. In a review by Christensen and Larsen, the precision and accuracy of POCT coagulometers were found to be acceptable for use in clinical settings.[3] Whereas contradictory findings were stated in another systemic review where authors did not considered POCT INR measurements to be superior to laboratory INR.[14]

Using a POC-INR measurement device at our anticoagulation clinic, we found that INR measurements by CoaguChek XS Pro showed positive bias as INR values increased (>2 INR) when compared with laboratory INR as measured by Sysmex CS2000i. Similar observations were made by a number of studies that showed an increased INR difference at higher INR values.[15,16] In addition to the overall correlation and agreement, we further compared the INR results in subtherapeutic (<1.9 INR), therapeutic (2-3 INR), and supratherapeutic (>3.1 INR) range and found bias not only in the supratherapeutic but therapeutic range as well (Figures 2 and 3).

Studies conducted by Deom et al and Lawrie et al suggested that POC-INR can reliably be used for dosing decision for vitamin K antagonist,[17,18] whereas in a study by Celenza and Skinner, POC-INR testing is accurate to exclude significant coagulopathy, but laboratory INR is still needed to confirm supratherapeutic INR.[13] An another study performed in a setting of anticoagulation clinic revealed that 33% of INR measurements with the POC-INR were different from standard laboratory INR and resulted in different therapeutic decision.[15]

In this study, 11 (5.5%) of 200 INR measurements resulted in different dosing decision for warfarin therapy between POC-INR and laboratory INR. International normalized ratio measurements generated by POC device exhibited positive bias, compared with laboratory INR, for values at the high end of

the INR range (>2). Our data are in line with Donaldson et al and implies that dosing decision based on POC-INR would be different from that of laboratory-determined INR.[15]

With the availability of more convenient and cost-effective microfluidics technology of POC-INR, it has become the standard of care for patients on chronic warfarin therapy. It enables health-care providers to perform prompt warfarin dosing adjustment decision-making and face-to-face education with the patient. Dose adjustment rests on INR results, hence POC-INR results need to be accurate.

As for the clinical decision is concerned, we found no change in decision-making for dose adjustment in 2 instruments results for INR less than 1.9. However, positive bias observed in the therapeutic as well as supratherapeutic INR range suggests that it should be confirmed through standard laboratory analyzer. This study is limited in that the sample size in the >3.0 INR range was small as compared to the subtherapeutic and therapeutic range. Further studies with equal randomization in different INR ranges would delineate the performance evaluation of POC-INR. It might be convenient using POC-INR where facility of laboratory INR is not available. However, to minimize clinical problems arising from implementation of this technology, collaboration between manufacturers, pathology laboratories, and general practice and adherence to a recognized external quality assurance scheme is essential.

## Conclusion

CoaguChek XS Pro shows an excellent agreement with Sysmex CS2000i for INR results. The minimal positive bias of POC-INR is evident in the therapeutic and supratherapeutic range which could affect the dosing decision and therefore needs to be confirmed with the laboratory INR measurement.

### Authors' Note

Data can be provided by corresponding author on request.

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### Declaration of Conflicting Interests

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