Validation of the CoaguChek XS international normalised ratio point-of-care analyser in patients at Charlotte Maxeke Johannesburg Academic Hospital, South Africa

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Background. Measurement of the international normalised ratio (INR) is essential in the management of patients on long-term warfarin therapy. The CoaguChek XS portable coagulometer is a point-of-care test for INR measurement. It offers the advantage of improved patient accessibility, particularly in peripheral clinics.

Objectives. To evaluate the clinical utility of the CoaguChek XS for monitoring of patients on standard warfarin therapy (INR 2 - 3) as well as those with mechanical heart valve replacements (INR 2.5 - 3.5).

Methods. We compared the performance of the CoaguChek XS device with that of the STAGO laboratory analyser with regard to accuracy and precision in 304 patients referred for routine testing.

Results. The mean INR value of the CoaguChek XS of 2.75 (standard deviation (SD) 1.18) was comparable to that of the STAGO (2.65 (SD 1.04)). The Bland-Altman difference plot revealed good agreement. Bias between the two methods was small, and the imprecision was within acceptable limits. Within the target range (2.0 - 3.5), 93.9% of the CoaguChek XS INR readings were within 0.5 units of the standard laboratory method result. There was, however, an increase in the variability of the differences between the two test methods when the INR was >3.6.

Conclusion. The CoaguChek XS point-of-care device can be used to provide accurate and precise INR measurements over a wide range for monitoring of valvular and non-valvular patients on long-term warfarin therapy.


Point-of-care testing (POCT) is the fastest-growing segment of the diagnostic tests used by laboratories in the developed world. Laboratories have become increasingly involved in supporting testing at the bedside in order to improve turnaround time and reduce the cost of healthcare delivery.

Measurement of the international normalised ratio (INR) is essential in the management of patients on long-term warfarin therapy, and POCT has an important role to play in this setting. Warfarin has a narrow therapeutic range, and because it is subject to numerous drug and food interactions, frequent monitoring to maintain the target INR is vital. The target INR is 2.5 (range 2.0 - 3.0) for most indications, including venous thromboembolic disease, non-valvular cardiac conditions including atrial fibrillation, left ventricular systolic dysfunction and mural thrombus, and in the first 3 months following anterior myocardial infarction. The target INR is 3.0 (range 2.5 - 3.5) for most patients with mechanical prosthetic valves. However, a range of 2.0 - 3.0 is recommended for low-risk patients with bileaflet mechanical valves in the aortic position.

Predisposing factors for rheumatic fever persist in developing areas of southern Africa, leading to a high incidence of rheumatic valvular heart disease. An average of 1 500 patients attend the anticoagulation clinic at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), South Africa (SA), every month. Twenty-five percent of these are patients with mechanical valve replacements on lifelong anticoagulation therapy. In the developing world the question still remains whether it is safe to perform mechanical valve replacements in patients who will require lifelong anticoagulation therapy and have limited or no access to its monitoring. The introduction of POCT in peripheral clinics has the potential to solve this problem. There is also an opportunity for self-monitoring for patients who are able to test themselves at home and avoid taking time off from work to attend a clinic for INR testing.

POCT offers other distinct advantages, including improved turnaround time for dose adjustments in the clinic setting, a small sample volume required for testing and potential long-term cost savings. The volume required for analysis is very small (8 µL), making this technology particularly suitable for paediatric measurements, as blood sampling in this age group is often technically difficult.

Many POC devices are commercially available. The CoaguChek XS device (Roche Diagnostics, Switzerland) is a small bench-top instrument for INR analysis, suitable for use in anticoagulation clinics. This analyser measures the prothrombin time (PT) in seconds using an electrochemical method and shows good correlation with laboratory automated coagulation analysers up to INR values of 3.0.[1,2] However, correlation studies at INR values >3.0 are limited.[3-6]

Methods

Study design and population

The study was performed in the main haematology laboratory at the CMJAH National Health Laboratory Service (NHLS) over a 3-week period. Blood samples were obtained from 304 patients attending the anticoagulation clinic at CMJAH. Blood samples for INR analysis were obtained by fingerstick testing for measurement on the CoaguChek XS and by venepuncture using citrate tubes (Becton-Dickinson, UK) for measurement on the STAGO coagulation analysers in
the laboratory (Fig. 1). Citrate samples of adequate volume (>4 mL) received within 2 hours of collection were included. Samples (n=4) processed on the CoaguChek that yielded error results were excluded from the final analysis.

The study was approved by the University of the Witwatersrand Human Research Ethics Committee (M130468), and informed consent was obtained from the patients.

**Study protocol**

This validation was performed in accordance with the International Council for Standardisation in Haematology 1993, and using the method comparison from the Clinical and Laboratory Standards Institute (CLSI EP9-A2, USA). For the method comparison study, a prospective, side-by-side comparative study of the CoaguChek XS against the STAGO (Roche Diagnostics, Switzerland) automated coagulation analyser was performed. INR measurement was done on 304 adult patient samples. The samples were analysed sequentially by a dedicated phlebotomist on the CoaguChek XS and by a technologist on the STAGO coagulation analyser using the respective instruments’ standard operating procedures including adequate performance of internal quality control material (Fig. 1).

For the analysis, whole blood collected by capillary sampling was placed on a CoaguChek XS specific test strip. The strips contain recombinant human thromboplastin with an international sensitivity index (ISI) of 1.0. The PT was converted to an INR using the ISI value. A result is obtained within a minute and requires a sample volume of only 8 μL.

Within-run precision evaluation was performed with the normal reference control material analysed 20 times. Acceptable imprecision limits were determined from the manufacturer’s within-run precision data.

**Warfarin dosage and INR measurements**

Clinical utility was assessed by two methods. Firstly, clinical agreement was measured by discrepant INR measurements resulting in different warfarin dosage adjustments in accordance with the SA guidelines.[7] Warfarin dosage adjustments were made by dedicated nursing sisters at the anti-coagulation clinic based on the venous plasma laboratory INR method.

Secondly, published criteria for ‘expanded’ and ‘narrow’ clinical agreement were also assessed.[2] ‘Expanded’ agreement was achieved if the CoaguChek XS and laboratory INR results both fell within one of the three different INR ranges, namely within, above or below the target range, or the difference between the CoaguChek XS and laboratory INR when one of the pair was within the target range and the other outside it was no more than 0.5 INR units.

‘Narrow’ agreement was considered as both readings being between 2 and 3, or below the target range and within 0.4 INR units of each other, or above the target range and within 0.8 INR units of each other. If one reading was within the target range and the other within 0.5 INR units, this was also considered to be in ‘narrow’ agreement.[1,5]

**Statistical analysis**

The results were collated on an Excel spreadsheet, tabulated and graphically summarised using standard statistical methods. Agreement between results obtained on the different analysers was evaluated using standard difference plots.

**Results**

**Study population**

Three hundred and four patients participated in the study. In four cases the CoaguChek XS device failed to produce an INR reading, and these samples were excluded from the analysis (Fig. 1). Patient indications for anticoagulation are listed in Table 1.

**Method comparison analysis**

The limit of agreement between the two methods is demonstrated in the Bland-Altman difference plot (Fig. 2), which revealed good agreement. On the logarithmic scale, the mean of the differences was 0.09 (–0.61, 0.79). Sixteen data points were outside the 95% limits of agreement. The mean INR values of the CoaguChek XS and STAGO were 2.75 (standard deviation (SD) 1.18) and 2.65 (SD 1.04), respectively, representing an overestimation of INR values by the CoaguChek XS (Table 2). Below the target range (<1.9), 100% of the CoaguChek XS INR readings were within 0.5 units of the standard laboratory method result. Within the target range (2.0 – 3.5), 93.9% of the CoaguChek XS INR readings were within 0.5 units of the standard laboratory method result. There was, however, an increase in the variability of the differences between the two test methods at INR readings above the target range (>3.6).

**Precision analysis**

The intra-assay coefficients of variation were within allowable limits of performance in the within-target range (0%).

**Clinical utility**

Clinical agreement was demonstrated by 93.0% of the values when assessed using

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**Table 1. Indications for anticoagulation of study patients**

<table>
<thead>
<tr>
<th>Indication for anticoagulation</th>
<th>n (%)</th>
</tr>
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<tbody>
<tr>
<td>Thromboembolic events</td>
<td>110 (36.2)</td>
</tr>
<tr>
<td>Deep-vein thrombosis</td>
<td>54 (17.8)</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>32 (10.5)</td>
</tr>
<tr>
<td>Deep-vein thrombosis and pulmonary embolism</td>
<td>13 (4.3)</td>
</tr>
<tr>
<td>Upper limb thrombosis</td>
<td>5 (1.6)</td>
</tr>
<tr>
<td>Left ventricular thrombus</td>
<td>5 (1.6)</td>
</tr>
<tr>
<td>Dural venous sinus thrombosis</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td>59 (19.4)</td>
</tr>
<tr>
<td>Non-valvular heart disease</td>
<td>87 (28.6)</td>
</tr>
<tr>
<td>Dilated cardiomyopathy</td>
<td>5 (1.6)</td>
</tr>
<tr>
<td>Congestive cardiac failure</td>
<td>4 (1.3)</td>
</tr>
<tr>
<td>Ischaemic heart disease</td>
<td>4 (1.3)</td>
</tr>
<tr>
<td>Stroke</td>
<td>3 (0.9)</td>
</tr>
<tr>
<td>Congenital cardiac disease</td>
<td>2 (0.7)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>69 (22.7)</td>
</tr>
<tr>
<td>Other/not stated</td>
<td>48 (15.8)</td>
</tr>
</tbody>
</table>

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**Fig. 1. Flow diagram of patient sample collection. (PI clinic = anticoagulation clinic.)**
Discussion
In this prospective study, we demonstrated the analytical and clinical performance of the CoaguChek XS point-of-care device for the monitoring of warfarin therapy across a wide range of INR values. The CoaguChek XS is a portable coagulometer that was introduced into the clinical setting in October 2005. Previous studies on point-of-care devices have shown increased variability at supratherapeutic INR levels. A recent study performed on the CoaguChek XS, however, demonstrated improved accuracy even at higher INR values.

We demonstrated excellent agreement between the CoaguChek XS and laboratory measurement with the STAGO analyser. INR values were overestimated on the coagulometer. Ninety-four percent of the values had a clinically significant difference of <0.5 units in the target range, making this an acceptable alternative method for monitoring stable patients on long-term warfarin therapy with INRs within the therapeutic range of 2 - 3. Using narrow agreement criteria, the point-of-care device also performed well in the INR ranges of <2 and 2 - 3.5. However, in the above-target range of >3.6, 64.4% were in agreement. These findings are consistent with the study by Ryan et al., in which 162 patients had dual measurements performed using the CoaguChek XS and standard laboratory methods. For laboratory INR values of <1.9, 2 - 3.5 and >3.6, 97.8%, 89.3% and 67% of readings, respectively, were within 0.5 INR units. In the SA setting, where there is a high prevalence of rheumatic heart disease and patients with mechanical heart valves, the CoaguChek XS point-of-care device could be implemented as a method for monitoring these patients, but clinical correlation would be advised at levels >3.6 units with more frequent monitoring and formal laboratory testing.

Several research groups have demonstrated the advantages of having a simple and reliable POCT for INR monitoring, e.g. small sample volumes and improved turnaround time. However, POCT has limitations including preanalytical (e.g. staff competency) and biological (e.g. temperature variations, heparin contamination, extremes of haematocrit, fibrinogen levels and presence of antiphospholipid antibodies) variables.

In SA, the CoaguChek XS point-of-care device could be implemented in the peripheral clinics as a screening tool for patients on long-term warfarin therapy in an attempt to reduce the workload of central anticoagulation clinics. The capacity and infrastructure of peripheral clinics would have to be assessed before installation of the devices. It is imperative that implementation of POCT be accompanied by a robust quality control system with satisfactory performance in internal and external quality assessment programmes. In specific settings, formal laboratory INR analysis will still be required when INR values >3.6 are obtained using this device and there is a history of bleeding events.

Conclusion
In this cohort, the CoaguChek XS provided accurate and precise INR measurements for a wide range (2 - 3.5 units) of INR...
measurements and would be an accurate and reliable method for warfarin therapy monitoring.

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References

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