Performance evaluation of the new CoaguChek XS system compared with the established CoaguChek system by patients experienced in INR-self management

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Summary
The aim of the study was to analyze the concordance of INR values obtained by educated lay users with those obtained by professionals and to determine the imprecision of the new system. The new CoaguChek® XS system was tested in a user study over six weeks at four study centres in Austria, Denmark and Germany. Seventy-five patients receiving oral anticoagulant therapy were enrolled in the study. The INR results in capillary whole blood taken by professionals and by patients using the CoaguChek XS system were similar, and the mean relative bias was < 1 %. The imprecision of the CoaguChek XS system calculated from duplicate testing is low (< 6 %) and slightly better than for the established CoaguChek S system. The INR results measured during the home testing phase correlated quite well between patients receiving oral anticoagulant therapy and thenew CoaguChek XS system with a mean bias of 0.14 INR. This is a remarkably low bias taking into consideration that more than 30 different test strip lots were applied. A questionnaire was filled out by all patients to assess their personal impression. It revealed that patients were very satisfied with the new system and found it easy to operate. The results demonstrate that the agreement between professional and patient INR results for the new CoaguChek XS system was excellent and that INR values can be determined by lay users as well as by professionals. The instrument is very well accepted by the patients and their satisfaction even increased after four weeks practice at home.

Keywords
Patients education, clinical trials, oral anticoagulants, home monitoring, INR-self management

Introduction
In 1993, the capillary blood prothrombin time (PT) monitoring system CoaguChek was introduced and analytically evaluated (1). Since then more than 150,000 patients receiving oral anticoagulant therapy have been trained in using this system and they successfully perform self-testing or self-management (2–6). Patients are provided with their own portable instruments so that they can frequently measure their INR and manage their oral anticoagulation. Several reports demonstrate that patients self-management is safe and can improve the quality of monitoring the anticoagulation therapy (7–9). Since 1993 several changes have been performed with the CoaguChek system, but the test principle has remained unchanged for 12 years. The test strip of the new CoaguChek XS system has been completely redesigned using a human recombinant thromboplastin with an ISI of 1.01 and amperometric detection of the thrombin effect in the blood sample. An integrated quality control function can detect misused test strips and thus check in combination with all other integrated failsafe features the reliability of the system.

The aims of this study were i) to investigate whether patients experienced in self monitoring can easily operate the new system and generate identical INR values with professional operators, ii) to compare INR-results from the new CoaguChek XS PT with the present CoaguChek PT test strips based on rabbit brain thromboplastin (CoaguChek test strip), iii) to assess the imprecision from capillary blood testing for the new test strip, iv) to as-
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assess patient’s handling of the CoaguChek XS, and v) to assess patient’s satisfaction with the new system using a questionnaire.

Materials and methods

The study was conducted at sites in Germany (Deutsches Herzzentrum München und Klinik am See, Rüdersdorf), Austria (Allgemeines Krankenhaus der Stadt Wien) and Denmark (Aarhus University Hospital) within a narrow time frame of four weeks at each of the four sites between April and May 2005. Seventy-five patients receiving oral anticoagulant therapy were enrolled in the study. No selection criteria except age above 18 and experience in INR-self-testing for at least one month before starting the study were applied. Pregnant women or women during the lactation period were excluded from the study.

Protocol

The study consisted of three sections: a start session, a one-month self-monitoring phase and a final session. In the start session the study protocol and the use of the new device was explained by the coworkers of the manufacturer. All patients had to bring with them was their own CoaguChek S system and their CoaguChek PT test strips. At the beginning of the first session all systems were checked using a liquid control material. A finger puncture device (Softclix®) was used to produce a drop of capillary whole blood. The first fingerprick was performed by a skilled assistant, who applied the first drop of blood for the determination of the PT on the patient’s monitor with the current test strip and the second on the new system. A second and third fingerprick had to be performed by the patient on its own. Both times INRs were determined on the established and the new device out of one fingerprick. The same procedure was done during the final session at the end of the study. The purpose of duplicate testing during the start and the final session was to determine the imprecision of the whole blood capillary PT. At the end of the session the patients had to fill in a questionnaire concerning their first impression of the new device.

The CoaguChek system and its successor the CoaguChek S system were used by the patients. To facilitate the reading this is only named as CoaguChek S system.

During the self-monitoring phase the patients had to measure eight INRs in four weeks at home. The first puncture had to be applied on their regular PT test strip, a second one using another finger on the new CoaguChek XS PT test strip.

This resulted in at least eight paired INR-results per patient. Patients had to fill in a case record form detailing the date of measurement, which finger they had punctured, the way they switched on the new monitor (by pressing the power-button or by inserting the test strip), how the drop of blood was applied (on top of the application field or from the side), the INR results and the oral anticoagulant dose until the next measurement. Patients were instructed to repeat the blood test only if an improper technique, as defined in the manual and package insert, was used and to explain the reason for the repeated test. Moreover, they were instructed that they had to take only the INR values of their own CoaguChek S system for therapeutic decisions into consideration. They were also instructed to document any observations about the test strips or instruments in the comment area of the case record form. Unlike the separately sealed test strips used for the older CoaguChek S system the new strips are stored in a container with 24 strips. Therefore it is important to avoid the test strips from being exposed to humidity. At the final session the patients had to repeat the two INR determinations on their own and in addition one by a professional using both systems. Furthermore, they had to fill in a questionnaire to assess their satisfaction with the new system, general aspects of the operator convenience, the handling and the new test strips. Most questions had to be rated on a five point scale, e.g. the weight of the new coagulation monitoring system is: 1=light; 2=rather light; 3=neither nor; 4=heavy; 5=too heavy.

All patients gave written informed consent at the beginning of the first session. The study was conducted under the regulations of the In Vitro Diagnostics Directive (IVDD) as well as the International Conference of Harmonization (ICH) Good Clinical Practice (GCP), and has been approved by the local Ethics Committee (Bayerische Landesärztekammer).

Statistical analysis

We examined the agreement of both systems and of the patient and professional data, using the methods described by Passing and Bablok (10) as well as Bland and Altman (11). The mean absolute relative deviation (MRD) of INR results was calculated according to the following formula:

\[
\text{MRD} = 100 \times \frac{1}{n} \sum_{i=1}^{n} \left| \frac{\text{test} - \text{reference}}{\text{reference}} \right|
\]

‘Test’ in the MRD formula is the system which should be tested – in our case the CoaguChek XS system and ‘reference’ the system against which it is compared to – i.e. the CoaguChek S or CoaguChek system.

Results

Patient characteristics

Seventy-five patients agreed to participate in the study (Table 1), 33% were female. The mean patient age was 56 years (range 26–76

Table 1: Patient demographics.

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Mean (Min – Max)</th>
<th>56 (26 – 76)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral anticoagulant therapy (OAT)</td>
<td>Phenprocoumon 80%</td>
<td>Warfarin 19%</td>
</tr>
<tr>
<td></td>
<td>Acenocoumarol 1%</td>
<td></td>
</tr>
<tr>
<td>Indication for OAT Mechanical heart valve 48%</td>
<td>Atrial fibrillation 20%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>DVT 16%</td>
<td>others 16%</td>
</tr>
<tr>
<td>Therapeutic range (INR) 2.0 – 3.0 64%</td>
<td>2.5 – 3.5 31%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3.0 – 4.0 5%</td>
<td></td>
</tr>
<tr>
<td>Duration of self-monitoring (years) Mean (Min – Max) 3.5 (0.4–12.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Instrument for self-monitoring CoaguChek 21%</td>
<td>CoaguChek S 79%</td>
<td></td>
</tr>
</tbody>
</table>

OAT=oral anticoagulant therapy; DVT=deep venous thrombosis; INR=international normalised ratio.
years). Eighty percent of the patients took phenprocoumon, 19% warfarin and 1% acenocoumarol. The indication for anticoagulation therapy was a mechanical heart valve in 48%, atrial fibrillation in 20%, deep venous thrombosis in 16% and other indications in 16%. Sixty-four percent of the patients had a target range of the INR of 2–3 and 31% of 2.5–3.5. The mean duration of self-monitoring their anticoagulation prior to this study was 3.5 years (range 0.4–12.5 years). Most patients (79%) had been using the CoaguChek S monitor, the remainder used the precursor model CoaguChek system (both monitors use the same test principle).

### Agreement between INR values obtained by patients and professionals

The slopes of the regression line and the intercept in both sessions were all approximately the same (slope: 1.00 vs. 1.03; intercept: 0.00 vs. −0.08). The mean absolute bias was virtually zero, the mean relative bias <1% and the Pearson’s r was close to 1 (Table 2).

<table>
<thead>
<tr>
<th>Phase</th>
<th>N</th>
<th>Bablok/Passing Regression</th>
<th>Mean abs. bias</th>
<th>Mean rel. Bias</th>
<th>Pearson’s r</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Intercept</td>
<td>Slope</td>
<td>(INR) (%)</td>
<td></td>
</tr>
<tr>
<td>Start</td>
<td>74</td>
<td>0.00</td>
<td>1.00</td>
<td>0.01</td>
<td>0.64</td>
</tr>
<tr>
<td>Final</td>
<td>75</td>
<td>−0.08</td>
<td>1.03</td>
<td>0.01</td>
<td>0.48</td>
</tr>
<tr>
<td>combined</td>
<td>149</td>
<td>0.00</td>
<td>1.00</td>
<td>0.01</td>
<td>0.56</td>
</tr>
</tbody>
</table>

**Table 2: Agreement between INR values obtained by patients (mean of duplicate measurements) and professionals of the CoaguChek XS system.**

**Agreement between INR values obtained by patients and professionals**

The slopes of the regression line and the intercept in both sessions were all approximately the same (slope: 1.00 vs. 1.03; intercept: 0.00 vs. −0.08). The mean absolute bias was virtually zero, the mean relative bias <1% and the Pearson’s r was close to 1 (Table 2).

**INR agreement between the new CoaguChek XS system and the present CoaguChek S system for patient data**

In total, 724 paired results of patients were obtained and analyzed using the Passing and Bablok method. The coefficient of correlation was $r = 0.835$ and the slope was 1.22 (Fig. 1). Method comparison using the Bland and Altman approach (Fig. 2) showed a mean difference of 0.14 INR units ($p<0.01$). There was a trend of greater differences in the INR range above 3.0. The mean relative bias was 5.71% and the MRD results were 12.1% for all results (Table 3).

**Imprecision from capillary blood testing for the new CoaguChek XS system**

The imprecision was calculated from 143 duplicates measured by the patients on the CoaguChek XS system at the start and final sessions. The slope of the regression line was 1.00 and the intercept 0.00. The mean absolute bias between the two measurements was 0.02 INR units for the CoaguChek XS system and the coefficient of variation (CV) was 5.92% at the start and 5.16% at the final session.

**Imprecision from capillary blood testing for the CoaguChek S system**

The imprecision of the CoaguChek S system was calculated from 144 measurements at the start and final session. The imprecision was slightly higher compared to the new CoaguChek XS system. The slopes of the regression lines were close to 1.0 and the intercept close to 0.00 in both sessions (slope: 0.98 vs. 1.00; intercept: 0.00 vs. 0.00). CV’s of the duplicate measurements were 6.07% at the start and 6.28% at the final session.

**Handling of the CoaguChek XS system**

During the start session 60% of the patients rated the handling as ‘easy’, 32% said ‘rather easy’ and 8% were ‘undetermined’.

### Figure 1: Agreement between CoaguChek system (x-axis) and CoaguChek XS system (y-axis) for patient data. Determination of the linear regression according to Passing and Bablok with no special assumptions regarding the distribution of the samples and the measurement errors ($n = 724$, $r = 0.835$, $Y = 1.22 X - 0.42$).

### Figure 2: Agreement between CoaguChek system and CoaguChek XS for patient data – Bland / Altman Plot ($n = 724$, mean difference = 0.142, standard deviation = 0.372)
The compliance of closing the test strip vial
The compliance of closing the test strip container during the self-monitoring phase was checked by determination of the residual humidity in the desiccant stopper of the used containers. The test strip containers were obviously opened only shortly and closed directly after taking out a test strip. The mean humidity in the desiccant stoppers were at the start of the study <4% and at the end of the study 5% (range 4%-6%). This finding showed a good compliance of appropriate closing of the test strip container during the self-monitoring phase.

Overall satisfaction with the CoaguChek XS system
At the start session, 92% of the patients answered that they liked the new system (31%) or liked it a lot (61%). This first positive impression was even better at the final session after four weeks experience at home when 97% answered that they liked it a lot. From those 81% answered that they liked it a lot and 16% that they liked it. The Danish participants showed the greatest improvement in their satisfaction from 35% who liked it a lot at the end of the start session to 90% at the final session of the study.

Discussion
The development of portable PT monitors has greatly facilitated the treatment with oral anticoagulants as timely controls can be performed safely by appropriately selected and trained patients (12). Due to the narrow therapeutic window of oral anticoagulants an optimal treatment monitoring is required through accurate INR measurement by portable monitors as well as by standard laboratory analyzers. Most evaluations of new analytical systems focus on the analytical performance, which is of course the basis of reliable results. However, instruments designed for patient self-measurement should also be evaluated with respect to how lay users manage to generate equally reliable results.

Although it seems to be self-evident that identical INR values will be generated by lay users and by professionals running the same instrument, it has to be demonstrated that it is true in reality. As generally known, the preanalytical phase is essential in coagulation testing (13). Critical factors in patient self-monitoring are the elaborateness of the fingerprick, the time required to apply the drop of blood and the correct storage and use of the test strips. Failure to comply with these items may lead to inaccurate results. The error rate with respect to problems with dosing the test strips was found to be 3.7%, which is well below an acceptable rate of 5%. Of particular importance is the integrity of the test strips. Unlike the separately sealed CoaguChek test strips for the first generation of CoaguChek S system, the new strips are stored in a container without additional wrapping. Therefore it is important to keep the test strips from deteriorating through exposure to external influences such as humidity. The compliance concerning closing the test strip was very high, so at least in our study group of patients that did not seem to have been forgotten. Test strips which would have been misused by humidity or longer exposure to daylight would have been detected by the automatic onboard quality control of the system.

Because the test principle of the new CoaguChek XS test strip, which is based on the electrochemical measurement of PT following activation of blood coagulation with human recombinant thromboplastin, differs substantially from the rabbit brain thromboplastin test strip used in the precursor systems, it is obvious that some disagreement among INR results is to be expected. Such discrepancies among most of the different PT reagents are well known from comparison studies (14, 15) and external quality control measurements (16) and are also reported in a multicentric evaluation of a PT reagent based on the same recombinant human tissue factor as is contained in the new test strips (17). The disagreement increases systematically towards longer PT times (18, 19). Thus, the higher proportion of differences between the new and the preceding system in the INR range above 3.0 is well in agreement with previous findings in the literature. It should be noted that the correlation between INR results measured during the home testing phase with the CoaguChek test strip and the new one is quite good when taking into consideration that over 30 different CoaguChek test strip lots were applied because patients used their own CoaguChek S instruments and test strips. Therefore, the mean bias of 0.14 INR units calculated with the Bland-Altman plot (Fig. 2), which is well within the range of the recommended analytical bias of ≤0.20 INR units (20), is remarkably low. Thus, the use of a

Table 3: Agreement between the CoaguChek S system and the CoaguChek XS system for all patient data.

<table>
<thead>
<tr>
<th>Phase</th>
<th>N</th>
<th>Intercept</th>
<th>Slope</th>
<th>INR bias</th>
<th>Pearson's r</th>
<th>MRD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Start</td>
<td>72</td>
<td>-0.50</td>
<td>1.23</td>
<td>0.10</td>
<td>0.845</td>
<td>11.5</td>
</tr>
<tr>
<td>Self-monitoring</td>
<td>577</td>
<td>-0.41*</td>
<td>1.22*</td>
<td>0.15</td>
<td>0.835</td>
<td>12.2</td>
</tr>
<tr>
<td>Final</td>
<td>75</td>
<td>-0.38</td>
<td>1.21*</td>
<td>0.16</td>
<td>0.835</td>
<td>12.0</td>
</tr>
<tr>
<td>combined</td>
<td>724</td>
<td>-0.42*</td>
<td>1.22*</td>
<td>0.14</td>
<td>0.835</td>
<td>12.1</td>
</tr>
</tbody>
</table>

human recombinant thromboplastin in the new test strip is a favourable approach to improve comparability. The agreement between the new CoaguChek XS and standard laboratory methods was evaluated in another study and will be published soon.

The results for the imprecision calculation from duplicate measurements show a very good reproducibility. The mean difference between the two measurements was 0.02 INR units for the CoaguChek XS system and −0.02 INR units for the CoaguChek S system. The imprecision was calculated from all duplicates measured on the CoaguChek XS system, the CV was 5.53% versus 6.18% for the CoaguChek S system. This is close to reported coefficients of variation in common coagulation analyzers (1–3% CV) and compares well to reproducibility data for the CoaguChek device (19, 21).

Patients evaluated the general handling of the new instrument as ‘favourable’. None judged it as ‘difficult’. The small size and light weight of the new instrument was appreciated by all patients. The positive impression even increased during the course of the evaluation.

In conclusion, this study showed that INR results obtained with the established system and the new CoaguChek XS system were highly comparable for both patients and professionals. The INR results measured during the home testing phase correlated well between the established CoaguChek S system and the new CoaguChek XS system. The handling was assessed by most of the patients as easy.

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We acknowledge the assistance of Ms. Karin Quantson, Marianne Maegaard, RN and Helle Korsgaard, Bioanalyst during the study. The study was initiated and financed by Roche Diagnostics GmbH as part of the evaluation of the new system. CoaguChek is a trademark of Roche.

Abbreviations
INR, international normalised ratio; PT, prothrombin time; MRD, mean relative deviation; CV, coefficient of variation; OAT, oral anticoagulant therapy; DVT, deep venous thrombosis.

References