Point-of-Care Testing of Coagulation in Patients Treated With Non–Vitamin K Antagonist Oral Anticoagulants

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Background and Purpose—Specific coagulation assays for non–vitamin K antagonist oral anticoagulants (NOAC) are relatively slow and often lack availability. Although specific point-of-care tests (POCT) are currently not available, NOAC are known to affect established coagulation POCT. This study aimed at determining the diagnostic accuracy of the CoaguChek POCT to rule out relevant concentrations of rivaroxaban, apixaban, and dabigatran in real-life patients.

Methods—We consecutively enrolled 60 ischemic stroke patients newly started on NOAC treatment and obtained blood samples at 6 prespecified time points. Samples were tested using the CoaguChek POCT, laboratory-based coagulation assays (prothrombin time and activated partial thromboplastin time, anti-Xa test and Hemoclot), and liquid chromatography–tandem mass spectrometry for direct determination of NOAC concentrations.

Results—Three hundred fifty-six blood samples were collected. The CoaguChek POCT strongly correlated (r=0.82 P<0.001) with rivaroxaban concentrations but did not accurately detect dabigatran or apixaban. If used to estimate the presence of low rivaroxaban concentrations, POCT was superior to predictions based on normal prothrombin time and activated partial thromboplastin time values even if sensitive reagents were used. POCT-results ≤1.0 predicted rivaroxaban concentrations <32 and <100 ng/mL with a specificity of 90% and 96%, respectively.

Conclusions—If anti-Xa test is not available, we propose the use of the CoaguChek POCT to guide thrombolysis decisions after individual risk assessment in rivaroxaban-treated patients having acute ischemic stroke.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT02371044. (Stroke. 2015;46:2741-2747. DOI: 10.1161/STROKEAHA.115.010148.)

Key Words: apixaban ■ dabigatran ■ rivaroxaban ■ stroke ■ thrombolytic therapy

Non–vitamin K antagonist oral anticoagulants (NOAC) inhibiting factor Xa or thrombin provide an effective alternative to vitamin K antagonists (VKA) for patients requiring long-term anticoagulation. Although efficacy and safety of NOAC have been established in large randomized controlled trials, concerns about feasibility of thrombolysis in acute ischemic stroke during NOAC therapy exist.2

Rapid assessment of coagulation status in NOAC-treated patients is problematic. Specific laboratory assays—calibrated anti-Xa test for rivaroxaban/apixaban and ecarin clotting or diluted thrombin time for dabigatran—show excellent correlation to NOAC concentrations. However, these tests are currently not sufficiently available.3 Routine coagulation assays like prothrombin time (PT) and activated partial thromboplastin time (aPTT) provide qualitative rather than quantitative information about the presence of NOAC.4 Both routine and NOAC-specific assays are usually conducted in central laboratories, and therefore results are inevitably delayed by sample transportation and preparation.

For VKA, several point-of-care tests (POCT) provide instantaneous information on the PT. Use of the CoaguChek (Roche, Switzerland), a popular PT-POCT, has shown to be reliable and accelerate time to thrombolysis by 28 minutes in VKA-treated patients.5

POCT specific to NOAC are currently unavailable, but influences of NOAC on established coagulation POCT have been reported.6–10 Data based on artificially spiked blood samples from healthy volunteers suggest a high correlation for the

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Hemochron POCT and dabigatran, as well as the CoaguChek POCT and rivaroxaban. Studies using samples from real-life patients found a correlation between test results obtained with different POCT and therapeutic dabigatran or rivaroxaban concentrations. However, the authors encountered a significant overlap between test results of samples with low NOAC concentrations and samples from healthy volunteers containing no NOAC at all.

To date, little attention has been paid to the diagnostic value of POCT with regard to thrombolysis. This study aimed at determining the diagnostic accuracy of the CoaguChek POCT in ruling out relevant concentrations of rivaroxaban, apixaban, and dabigatran in real-life patients.

Methods

Study Design
The study was a single-center, prospective observational trial with partially blinded outcome assessment. Clinical Trial Registration Information unique identifier is NCT02371044. Institutional Review Board approval was obtained from the ethics committee of Tübingen University (protocol-no 259/2013BO1). Written informed consent was obtained from all patients before enrollment.

Setting and Eligibility Criteria
The study was conducted at the Department of Neurology and Stroke of Tübingen University Hospital, a tertiary care facility. We consecutively enrolled ischemic stroke patients receiving first dose of rivaroxaban, apixaban, or dabigatran for secondary prevention of thromboembolism. Subjects who had received VKA or NOAC within 14 days, low-molecular-weight heparin within 24 hours, or unfractionated heparin within 12 hours before first NOAC intake were excluded to rule out interference with measurements. Patients with either abnormal coagulation values at baseline (Quick <70% or aPTT >37 s) or history of coagulopathy were also excluded. Use of anti-platelet drugs was permitted.

Sample Collection
Six blood samples were collected from each subject via a venous catheter or by direct venipuncture to cover a wide spectrum of NOAC concentrations: before drug intake, 30 minutes, 1, 2, and 8 hours after intake, and immediately before intake of the second dose (12 hours for dabigatran/apixaban and 24 hours for rivaroxaban).

POCT and Laboratory-Based Coagulation Testing
Whole blood samples were tested immediately after collection using the CoaguChek XS Pro POCT (Roche, Switzerland; Figure 1), which uses a dry chemical PT assay containing recombinant thromboplastin and provides results <1 minute after device activation (specifications of assay precision and reproducibility, online-only Data Supplement). Further samples were collected in 3.2% sodium citrate tubes (Sarstedt, Germany), instantly transferred to the central laboratory, and centrifuged to acquire plasma. PT, aPTT, and anti-Xa activity were tested using the HemosIL APTT-SP (aPTT) and HemosIL RecombiPlasTin 2G (PT) reagents and the Chromogenix COAMATIC Heparin Test (anti-Xa) on an ACL TOP 700 (all by Instrumentation Laboratory, Germany). On the same analyzer, the anti-Xa assay was calibrated to determine rivaroxaban and apixaban concentrations using TECHNOVIEW calibrators (Technoclone, Austria). The lower limit of detection was 18 and 10 ng/mL. Other plasma aliquots were stored at −80°C until testing. The Hemoclot assay (Hyphen BioMed, France) provided measurements of dabigatran concentrations ≥50 ng/mL. Using the gold standard for measurements of NOAC, ultraperformance liquid chromatography–tandem mass spectrometry was performed (online-only Data Supplement).

Figure 1. The CoaguChek XS Pro (Roche, Switzerland).

All POCT and laboratory-based tests were performed according to manufacturers’ instructions by thoroughly trained investigators and technicians.

Blinding
All laboratory-based tests were conducted and interpreted by technicians blinded to POCT results.

Definition of Relevant NOAC Concentrations
One difficulty when assessing the clinical performance of coagulation tests for NOAC is that data to define relevant NOAC concentrations are currently limited. Therefore, we chose 2 concentration thresholds for our analyses (Table 1). First, median trough concentrations encountered in atrial fibrillation patients receiving therapeutic doses of NOAC15–17 because even urgent surgery is deemed safe at trough concentrations. Second, concentrations that may allow thrombolysis in ischemic stroke patients according to an expert recommendation.
Table 1. Investigated Concentration Thresholds

<table>
<thead>
<tr>
<th>NOAC</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Dabigatran</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median trough concentrations\textsuperscript{12–14}</td>
<td>32 ng/mL</td>
<td>103 ng/mL</td>
<td>91 ng/mL</td>
</tr>
<tr>
<td>NOAC concentrations that may permit thrombolysis (r-tPA) \textsuperscript{2}</td>
<td>100 ng/mL</td>
<td>10 ng/mL</td>
<td>50 ng/mL</td>
</tr>
</tbody>
</table>

NOAC indicates non–vitamin K antagonist oral anticoagulants; and r-tPA, recombinant tissue-type plasminogen activator.

and interquartile range. Areas under the ROC curve, sensitivity and specificity are given with 2-sided 95% confidence intervals.

Results

Patient Population

Sixty consecutive patients (20 for each NOAC) receiving NOAC for secondary prevention of ischemic stroke were enrolled between July 2013 and August 2014. Five patients had been previously treated with oral anticoagulants, but none had received VKA or NOAC within 3 weeks before study participation. For baseline characteristics and laboratory values, see Tables I and II in the online-only Data Supplement.

NOAC Concentrations

We collected 356 of 360 planned samples (S=118 rivaroxaban, S=118 apixaban, and S=120 dabigatran). Two samples could not be collected because 1 patient required emergency treatment for acute myocardial infarction, and 2 samples were missed because of a device malfunction.

No NOAC were found in baseline samples collected before first intake (S=60). Samples collected after drug intake had a median concentration of 102.1 ng/mL (interquartile range, 38.5–188.4, S=98) for rivaroxaban, 53.4 ng/mL (32.4–100.1, S=98) for apixaban, and 18.1 ng/mL (0–37.7, S=100) for dabigatran.

Correlation Between POCT and NOAC Concentrations

There were no differences in baseline CoaguChek POCT results between the 3 groups (P=0.279). Figures 2 and 3 show the individual POCT results related to NOAC concentrations and the time course of the mean POCT results and NOAC concentrations. Pearson’s correlation coefficient showed a strong overall correlation across sampling points for rivaroxaban (r=0.82; P<0.001), a weak correlation for apixaban (r=0.32; P<0.001), and no significant correlation for dabigatran (r=0.04; P=0.69). When additionally testing for correlation at each individual sampling point after drug intake, a significant correlation was detected at 4 of 5 sampling points (30 minutes, 1, 8, and 24 hours) in the rivaroxaban group but none in the dabigatran and apixaban groups. Further analyses were therefore conducted for rivaroxaban only.

Rivaroxaban Concentrations at Different POCT Results

When dichotomized at each of the 2 investigated thresholds, rivaroxaban concentration was <32 ng/mL in 42 of 118 samples and <100 ng/mL in 69 of 118 samples. Association of POCT results with rivaroxaban concentrations below both investigated thresholds was statistically significant (P<0.001 for both thresholds). The majority of samples containing rivaroxaban concentrations below the chosen thresholds yielded low POCT results (≤1.1). High results (≥1.3) almost excluded concentrations <100 ng/mL (Figure 4A).

Diagnostic Accuracy and Performance of POCT to Detect Relevant Rivaroxaban Concentrations

We used ROC analyses to further evaluate the performance of the CoaguChek POCT. The AUROC to detect 32 ng/mL was 0.90 (0.85–0.96) and to detect 100 ng/mL was 0.93 (0.88–0.98). Samples below the threshold of 32 ng/mL were accurately detected at POCT results ≤1.0. At this cutoff, 70% of the samples were picked up with 90% specificity (likelihood ratio, 6.8). If a POCT result of ≤1.1 was used as a cutoff for detection of samples <32 ng/mL, results became rather unspecific and misprediction was common (Table 2). For rivaroxaban concentrations <100 ng/mL, POCT results ≤1.0 had 96%
specificity and 52% sensitivity (likelihood ratio, 12.7). POCT results ≤1.1 yielded a specificity of 90% at increased sensitivity (83%; likelihood ratio, 8.1).

Performance of Laboratory-Based Coagulation Assays
Results of routine PT assays (HemosIL RecombiPlasTin 2G) correlated strongly with rivaroxaban concentrations (r=0.865; P<0.001). Only a weak correlation was found for the HemosIL APTT-SP assay (r=0.458; P<0.001).

Although a normal PT (Quick ≥70%) was significantly associated (P<0.001) with low rivaroxaban concentrations, specificity to predict concentrations <32 ng/mL was low (72%) and misprediction was frequent (28%) (Table 2; Figure 4B). A specificity of 92% and sensitivity of 84% were found for samples <100 ng/mL (likelihood ratio, 10.2). Almost identical results were obtained, if combination of normal PT and aPTT was used to predict rivaroxaban concentrations below the thresholds (Figure 4B; Table 2).

Performance of the Calibrated Anti-Xa Assay
The overall highest correlation to rivaroxaban concentrations was found for the calibrated anti-Xa assay (r=0.96; P<0.001). When performing ROC analyses at both thresholds, an almost maximal AUROC was found at 32 ng/mL (0.98) and at 100 ng/mL (0.99). The anti-Xa assay detected rivaroxaban concentrations <32 and <100 ng/mL with a specificity of 97% and 94%, respectively (Table 2; Figure 4C). Test sensitivity remained above 97% for both thresholds.

Discussion
Our study demonstrated that results of the CoaguChek POCT correlate well with rivaroxaban, to some extend with apixaban but not with dabigatran concentrations. Our results suggest that POCT results can be used to rule out relevant rivaroxaban concentrations, and that POCT-based predictions yield higher accuracy than predictions based on routine PT and aPTT assays.

Definition of Relevant NOAC Concentrations
Treatment with NOAC is based on a fixed dose scheme without regular monitoring of NOAC concentration. The lack of monitoring capability represents a pitfall in emergency situations. In addition, a widely accepted definition of relevant NOAC concentrations is currently nonexisting.

Before urgent surgery, it is advised to delay the procedure for at least 12 hours or 1 half-life (=13 hours) in case of dabigatran and for 24 hours in case of rivaroxaban. For elective surgery with low bleeding risk, current guidelines recommend withholding NOAC for 24 hours. A period >48 hours is deemed safe for elective surgery with higher bleeding risk or thrombolysis in stroke patients. Steiner et al postulated explicit recommendations concerning NOAC concentrations that may permit thrombolysis in acute ischemic stroke after individual risk assessment. However, it should be kept in mind that these are not supported by data from a clinical trial.

Based on these recommendations, we investigated 2 concentration thresholds that might be considered relevant (Table 1): The median trough concentration which can be expected 12 hours (dabigatran and apixaban) or 24 hours (rivaroxaban) after NOAC intake, and which has been suggested as safe for urgent surgery and—in case of rivaroxaban—even elective surgery with low bleeding risk. The second threshold was chosen according to the concentrations that may permit thrombolysis.

Effects of NOAC on CoaguChek POCT
In accordance with a previous report, the results of the dry chemical PT assay used in the CoaguChek POCT correlated with factor Xa inhibitor concentrations, but not with the thrombin inhibitor dabigatran. The generally poor sensitivity of PT assays for dabigatran has been noted before. Interestingly, the effect of factor Xa inhibitors on CoaguChek POCT differed, with rivaroxaban showing a much stronger effect than apixaban. This finding corresponds with data obtained for laboratory-based PT assays. To our knowledge, no convincing explanation for this difference has been provided.
Sensitivity of POCT to NOAC varies largely between different reagents. Hence, our findings cannot be generalized to other POCT than the CoaguChek.

Coagulation Testing in Rivaroxaban-Treated Patients

Although liquid chromatography–tandem mass spectrometry remains the gold standard for measuring rivaroxaban concentrations, use of anti-Xa assays is seen as a more clinically practical method. Our findings support this approach because the anti-Xa assay provided the highest diagnostic accuracy at both evaluated thresholds. However, these assays are frequently not readily available.

In case an anti-Xa assay is not accessible, several authors have outlined alternative strategies to estimate the intensity of anticoagulation in rivaroxaban-treated patients based on routine coagulation testing. Although a normal PT does not rule out the presence of rivaroxaban, it has been suggested that intact hemostasis can be expected. Normal PT values measured with sensitive reagents are probably sufficient to expect acceptable coagulation in case of urgent surgery. Furthermore, thrombolysis for ischemic stroke may be considered in patients on rivaroxaban if PT and aPTT are normal after individual risk assessment. However, NOAC-specific sensitivity varies between test reagents, and general recommendations are therefore problematic. If doubts about anticoagulation status remain, thrombectomy without thrombolysis should be offered to patients with large artery occlusion.

To date, no trial has demonstrated convincing data regarding the use of POCT to rule out low but relevant rivaroxaban concentrations in emergency situations. A spiking study by Samama et al showed excellent correlation between the CoaguChek POCT and rivaroxaban concentrations, but allowed only limited predictions for low rivaroxaban concentrations because most samples contained high or supratherapeutic concentrations. Studies using samples from real-life patients found that the results of several coagulation POCT, including the CoaguChek, strongly correlated with rivaroxaban concentrations. Yet, CoaguChek POCT results at trough concentrations frequently fell into a reference range that had been established using samples from healthy volunteers. Hence, the authors concluded that POCT results cannot distinguish between normal results and trough concentrations.

**Table 2. Test Characteristics of All Investigated Coagulation Assays to Detect Rivaroxaban Concentrations Below the 2 Tested Thresholds**

<table>
<thead>
<tr>
<th>Coagulation Assay</th>
<th>Threshold, ng/mL</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>LR</th>
<th>MP, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>CoaguChek ≤1.0</td>
<td>&lt;32</td>
<td>71% (55–84)</td>
<td>90% (80–95)</td>
<td>6.8</td>
<td>10.5</td>
</tr>
<tr>
<td></td>
<td>&lt;100</td>
<td>52% (40–64)</td>
<td>96% (85–99)</td>
<td>12.7</td>
<td>4.1</td>
</tr>
<tr>
<td>CoaguChek ≤1.1</td>
<td>&lt;32</td>
<td>98% (86–100)</td>
<td>72% (61–82)</td>
<td>3.5</td>
<td>27.6</td>
</tr>
<tr>
<td></td>
<td>&lt;100</td>
<td>98% (86–100)</td>
<td>72% (61–82)</td>
<td>2.6</td>
<td>27.6</td>
</tr>
<tr>
<td>PT normal</td>
<td>&lt;32</td>
<td>98% (86–100)</td>
<td>72% (61–82)</td>
<td>2.6</td>
<td>27.6</td>
</tr>
<tr>
<td></td>
<td>&lt;100</td>
<td>95% (82–99)</td>
<td>72% (61–82)</td>
<td>2.5</td>
<td>27.6</td>
</tr>
<tr>
<td>PT and aPTT normal</td>
<td>&lt;32</td>
<td>95% (82–99)</td>
<td>72% (61–82)</td>
<td>2.5</td>
<td>27.6</td>
</tr>
<tr>
<td></td>
<td>&lt;100</td>
<td>97% (89–99)</td>
<td>94% (82–98)</td>
<td>15.9</td>
<td>6.1</td>
</tr>
</tbody>
</table>

Samples=118. aPTT indicates activated thromboplastin time; LR, likelihood ratio; MP, misprediction rate; and PT, prothrombin time.
Comparison of CoaguChek POCT to Routine Coagulation Assays

As sensitivity of different PT and aPTT reagents to NOAC varies, knowledge of the locally used reagents is necessary for test interpretation. We used the HemosIL RecombiPlasTin 2G for PT testing, which has repeatedly been identified as one of the most responsive reagents to rivaroxaban. aPTT assays generally show low response to rivaroxaban, a finding consistent for different reagents including the HemosIL APTT-SP used in this study. We therefore assume that our routine coagulation tests should provide above average accuracy for the detection of samples with relevant rivaroxaban concentrations.

Nevertheless, CoaguChek POCT yielded superior diagnostic accuracy compared with a normal routine coagulation screen (PT and aPTT both within the normal range) if a POCT result ≤1.0 was used to rule out relevant rivaroxaban concentrations. The fact that POCT uses dry chemistry may contribute to this superiority because blood samples in routine coagulation assays are diluted with sodium citrate and liquid test reagents.

Strengths and Limitations

Our study adds relevant insight to previous reports. For the first time, we focused on the diagnostic accuracy of POCT to rule out low but clinically relevant NOAC concentrations. We investigated all 3 currently approved NOAC using the CoaguChek, a widely available POCT. To our knowledge, apixaban has never been tested with this device. Different to previous studies, all coagulation testing (including baseline measurements) was conducted using real-life patient samples. This is, in our opinion, the most reliable method to gather relevant data for clinical decision-making. Finally, because of sample acquisition during treatment initiation rather than steady state, our study contains an especially large number of samples with minimal or very low NOAC concentrations and is therefore more suitable to assess the effects of low NOAC concentrations on POCT than previous investigations.

Our data are based on a single-center experience and need to be validated in a larger trial. It cannot be ruled out that sample collection during treatment initiation rather than steady state influenced our results. However, this approach helped to obtain a high number of samples with low NOAC concentrations while avoiding the use of spiked samples or a mix of samples from real-life patients and healthy volunteers. Out of practical reasons, 6 samples were collected from each of the 20 patients per NOAC group. Hence, a bias because of repeated measurements in individual patients cannot be excluded.

Conclusions

In conclusion, our results suggest that coagulation POCT with the CoaguChek can qualitatively rule out low concentrations of rivaroxaban but not of dabigatran or apixaban. Anti-Xa assays most accurately detect low rivaroxaban levels and should be used if available. However, we demonstrated that the diagnostic accuracy of CoaguChek POCT results ≤1.0 is superior to predictions based on normal PT and aPTT values even if sensitive reagents are used. If a specific anti-Xa test is not available, the CoaguChek POCT could therefore be a valuable tool to guide emergency decisions in patients on rivaroxaban having acute ischemic stroke. The growing number of rivaroxaban-treated patients warrants a larger study that investigates if the results are replicable in the situation of acute stroke and correlate with clinical outcome after thrombolysis.

Disclosures

Dr Poli received speaker’s honoraria and reimbursement for congress traveling and accommodation from Bayer and Boehringer-Ingelheim. Drs Ebner, Wolf, and Russo received reimbursement for congress traveling and accommodation from Bayer. Dr Birschmann received speaker’s honoraria and reimbursement for congress traveling from Bristol-Myers Squibb and CSL Behring. Dr Ziemann received speaker’s honoraria and reimbursement for congress traveling and accommodation from Biogen Idec and Medtronic. The other authors report no conflicts.

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