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Overview

Quality Assessment of CoaguChek Point-of-Care Prothrombin Time Monitors: Comparison of the European Community–Approved Procedure and Conventional External Quality Assessment

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Background: **There is a need for dependable quality assessment (QA) of the widely used CoaguChek point-of-care testing prothrombin time monitor. By use of the prescribed set of 5 CoaguChek certified international normalized ratio (INR) QA plasmas, we compared the reliability of the immediate QA of individual monitors described in the European Community–recommended Technology Implementation Plan with conventional external QA analysis.**

Methods: **Experienced staff tested CoaguChek point-of-care monitors in routine use for controlling oral anticoagulant dosage at 9 Netherlands Thrombosis Service Centres. Testing was performed with both the certified CoaguChek INR for a set of 5 QA individual plasmas from the Eur Con Action on Anticoag (ECAA) and conventional external QA analysis.**

Results: **Patients brought 523 CoaguChek monitors to our service centers for assessment. The proportion with unsatisfactory performance indicated by a 15% deviation from the ECAA set was compared with 15% deviation from overall median INR of all CoaguChek monitors in the survey, as in conventional QA analysis. The results were similar (20.3% and 18.5%, respectively). Interlot differences of CoaguChek test strips were detected, but the incidence of unsatisfactory performance was similar with both analyses, from 6.5% to 37.5% with the certified INR method and from 5.9% to 33.3% with the overall median analysis.**

Conclusions: **The results validate the use of the European Action on Anticoagulation rapid single-instrument QA-specific procedure for CoaguChek users compared with the nonspecific conventional QA analysis that relies on deviation from the overall median INR.**

CoaguChek point-of-care testing is used widely for prothrombin time (PT)[6] testing in Germany and in The Netherlands and on an increasing scale in the United Kingdom, other European countries, and North America.

CoaguChek monitors must give reliable displayed international normalized ratios (INR) within the 2.0–4.5 interval, because there is a dramatic increase in the risk of thrombotic and bleeding complications, respectively, at INR <2.0 and >4.5 *(1)*. Recent reports have reiterated the need for reliable quality assessment (QA) of CoaguChek monitors *(2, 3)*. Hitherto, no readily available system has

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[6] Nonstandard abbreviations: PT, prothrombin time; INR, international normalized ratio; QA, quality assessment; ISI, international sensitivity index; ECAA, European Concerted Action on Anticoagulation (now known as the European Action on Anticoagulation); EC, European Community.

existed for the local QA of CoaguChek monitors. Local QA is essential because International Sensitivity Index (ISI) calibration of individual monitors by the WHO ISI method *(4)* is not feasible. This is because of the need in ISI calibration for parallel conventional manual PT testing with the local PT test system (instrument/thromboplastin combination) and an international reference thromboplastin on plasma from the same whole blood samples used in tests on the CoaguChek.

We report here on a joint study by the European Concerted Action on Thrombosis and the European Concerted Action on Anticoagulation (ECAA; now known as the European Action on Anticoagulation). The goal of this study was to assess the reliability of the European Community (EC)-approved QA method and compare it with conventional QA analysis.

The ECAA *(5)* developed a simple method, approved by the EC for the local QA of the CoaguChek. This method uses a selected set of 5 lyophilized QA plasmas with assigned CoaguChek INR *(6, 7)*. The certified CoaguChek INR values are provided by a group of experienced laboratories. In the ECAA QA, deviations of individual QA plasmas from certified INR are determined. A 15% difference from the assigned value with 1 or more of the set of 5 is classified as significant deviation and provides an immediate on-the-spot assessment of performance of individual CoaguChek monitors.

Conventional national and regional QA schemes use a different approach. In these schemes, an immediate assessment of performance of an individual monitor is not possible. Analysis is based on deviation of the monitor from the overall performance of all participants involved in an exercise, usually expressed as percentage difference from the median INR (or mean INR). Data are collected and analyzed centrally. The production of overall and individual center reports therefore takes a considerable time, and given the ECAA findings that a minimum of 5 QA plasmas is required to characterize the performance of individual CoaguChek monitors, it may take many months to achieve.

Conventional QA analysis based on deviation from median INR is also not specific for the CoaguChek monitor, and the same procedure is applied to other PT methods. None of the previous QA programs for the PT have incorporated a dedicated set of samples certified in terms of an individual test system (thromboplastin/instrument combination) as in the ECAA scheme for the QA of the CoaguChek.

The relative reliability of the 2 different methods of analysis has therefore been compared in this multicenter study, which supplements a separate report demonstrating the feasibility of the ECAA Technology Implementation Plan (5) to provide a reliable large-scale QA of the CoaguChek monitor with a dedicated set of 5 ECAA plasmas (unpublished data).

Materials and Methods

TEST SYSTEM

CoaguChek point-of-care testing PT monitors and CoaguChek test strips in routine use for anticoagulant treatment monitoring were manufactured by Roche.

PROCEDURE

Nine centers in The Netherlands Thrombosis Service participated, in Amsterdam, Amersfoort, Enschede, Lichtenvoorde, Koog a/d Zaan, Groningen, Etten-Leur, Leeuwarden, and Leiden. Patients were invited to bring their CoaguChek monitor to their local clinic. QA was performed according to ECAA recommendations *(7)* and the EC-approved Technology Implementation Plan *(5)*. Results are also presented as in conventional QA analysis as deviation from overall median INR.

CERTIFIED COAGUCHEK INR VALUES

The certified CoaguChek INR were not the displayed CoaguChek INR but INR derived from the combination of instrument-displayed PT, local mean normal PT, and the ISI obtained from a full multicenter calibration according to the method described by Tripodi et al. *(8)*. This was performed on each of the monitors at 3 reference centers, Leiden (Hemostasis and Thrombosis Research Center), Manchester (ECAA Central Facility), and Milan (A. Bianchi Bonomi). Informed consent was obtained from all donors. The study was approved by the local ethics committees at the 3 centers. The 3 certifying centers were all experienced in ISI calibration with the manual PT technique, having been the prime organizers and having taken part in the series of published official WHO ISI calibrations. The mean normal PTs on 20 healthy participants with the 3 CoaguChek monitors at the 3 certifying centers were 12.08 (Leiden), 12.22 (Manchester), and 12.52 (Milan). The certified INR of each test plasma was the mean result from the 3 centers. ISI were obtained at each certifying center from 20 healthy participants and 60 coumarin-treated patients tested as plasma samples with the ECAA rabbit reference thromboplastin by the manual PT technique and as whole blood from the same patient on the local CoaguChek monitor. The same batch of CoaguChek test strips (lot 726) was used at all 3 centers.

The 5 QA plasmas were selected to give certified INR over the 1.8–4.5 interval in duplicate testing. The mean normal PT for the CoaguChek system at each center was used with the mean ISI from the 3-center ISI calibration to calculate the certified CoaguChek INR according to the guidelines (WHO Expert Committee, 1983; $INR = [PT/\text{mean normal } PT]^{ISI}$) *(4)*.

PERFORMANCE CRITERIA

Deviation from certified INR. According to the ECAA Technology Implementation Plan *(5)*, a ≥15% deviation from the mean assigned INR with a single certified QA plasma from the set of 5 is classified as "significant deviation".

Results 15% from median INR. Results that show ≥15% deviation from the overall median INR of all participants in the exercise on a single ECAA QA plasma from the set of 5 are classified as unsatisfactory performance. This is the same criterion used in United Kingdom National External Quality Assessment Scheme surveys and termed outwith consensus. This term also applies to other PT methods and coagulation tests and was used also in a recent Italian CoaguChek study *(4)*.

The number of monitors in both these categories were assessed with each of the 5 individual QA plasmas and for the whole group of monitors, different lots of CoaguChek test strips, and the different operators at the clinics. Test strips were donated by The Netherlands Thrombosis Service Clinics from their own routine supplies.

TEST PROCEDURE

A single batch of sets of ECAA QA plasmas was used in the study. At the 9 participant centers in The Netherlands Thrombosis Service, the procedure was as follows.

Before reconstitution, the plasmas stored at 2–8 °C were left for 15–30 min at room temperature before reconstitution. Distilled water (0.5 mL) was added to each vial, and the cap was replaced; after a minimum of 10 min at room temperature but within 2 h, the plasmas were tested on individual monitors by the trained staff of the Thrombosis Service Centre as follows: To 0.1 mL plasma in a plastic tube, 0.1 mL of 17 mmol/L calcium chloride was added and gently mixed without shaking or inversion. Within 10–15 s after recalcification, test plasma was added to the CoaguChek test strip; the observed INR value was recorded. The procedure was repeated for each of the 5 QA samples.

Results

Of the 539 CoaguChek monitors brought by patients to the local Thrombosis Centres for checking, results from 523 were included in the analysis; results from the other 16 monitors were incomplete. The total number of monitors tested at the 9 individual centers ranged from 6 to 126.

CERTIFIED COAGUCHEK INR AND MEDIAN INR

Values for the certified CoaguChek INR on the set of 5 QA plasmas obtained at the 3 certifying centers and median INR from all 523 monitors are given in Table 1 and show close agreement between median and certified CoaguChek INR (mean difference, 2.9%). Table 1 gives results with monitors from all centers with the 5 individual QA plasmas according to the 2 methods of analysis. This shows the total numbers and percentages, with each plasma giving ≥15% INR deviation from the assigned CoaguChek INR and the number of monitors ≥15% from the median INR. The proportion showing ≥15% deviation on ≥1 plasma was similar with the 2 methods of analysis.

Table 2 presents the results from each of the 9 individual centers and shows that 106 of the 523 individual monitors (20.3%) showed ≥15% deviation from the certified CoaguChek INR on at least 1 QA plasma. Deviation from the overall median INR by ≥15% was shown by 97 (18.5%) of the monitors on at least 1 plasma.

Table 1. Incidence of 15% or more deviation from median INR and from certified CoaguChek INR with each of the 5 ECAA plasmas.[a]

Plasmas	Median INR	No. with ≥15% deviation, %	Certified CoaguChek INR	No. with ≥15% deviation, %
QC1	1.8	26 (5.0)	1.76	6 (1.1)
QC2	2.5	28 (5.4)	2.65	42 (8.0)
QC3	2.9	23 (4.4)	2.86	32 (6.1)
QC4	3.6	11 (2.1)	3.70	17 (3.3)
QC5	4.3	42 (8.0)	4.41	41 (7.8)
	Total	130 (5.0)	Total	138 (5.2)

[a] Number of monitors tested = 523.

Where monitors used by different operators were in sufficient numbers, both systems of analysis showed differences in performance by some of the experienced operators, although the number of monitors with unsatisfactory performance by the 2 methods of analysis was not significantly different (Table 2 shows Fisher exact test).

Six different lots of individual CoaguChek test strips were used on 16 or more monitors. Table 3 shows the percentage of results ≥15% from the median value with the different numbered lots of test strips. These were from 5.9% to 33.3% at the 9 centers. The numbers of monitors that gave ≥15% deviation from the certified CoaguChek INR were from 6.5% to 37.5%. There were no significant differences in unsatisfactory performance with the 2 QA methods with the different lots (Fisher exact tests). Significant interlot differences of performance were found with analysis based on deviation from the certified INR. In particular, lot 965, the largest single lot of strips, had a

Table 2. Number of monitors tested at the 9 centers and incidence of ≥1 plasmas with ≥15% deviation from median INR and certified INR (corresponding percentages in parentheses) at the 9 centers.[a]

		Number of monitors (%)		
Center	No. of monitors	≥15% deviation from median INR, %	≥15% deviation from certified INR, %	Fisher exact test, *P*
1	68	6 (8.8)	9 (13.2)	0.59
2	96	15 (15.6)	17 (17.7)	0.85
3	69	16 (23.2)	17 (24.6)	1.00
4	126	35 (27.8)	35 (27.8)	1.00
5	43	13 (30.2)	17 (39.5)	0.50
6	34	2 (5.9)	2 (5.9)	1.00
7	6	3 (50.0)	3 (50)	1.00
8	40	3 (7.5)	4 (10)	0.32
9	41	4 (9.8)	2 (4.9)	0.68
Total	523	97 (18.5)	106 (20.3)	0.53

[a] Fisher exact test for difference in numbers of unsatisfactory performance between the 2 methods is also shown.

Table 3. Number of monitors tested using different lots of strips and incidence of ≥1 plasmas with ≥15% deviation from median INR and certified INR (corresponding percentages in parentheses) across different lots of strips.[a]

		Number of monitors, %		
Strip lot	No. of monitors	≥15% deviation from median INR, %	≥15% deviation from certified INR, %	Fisher exact test, *P*
019	72	18 (25.0)	13 (18.1)	0.42
776	31	2 (6.5)	2 (6.5)	1.00
862	16	4 (25.0)	6 (37.5)	0.70
931	68	4 (5.9)	5 (7.4)	1.00
965	289	54 (18.7)	71 (24.6)	0.11
996	45	15 (33.3)	9 (20.0)	0.23
Other strips	2	0 (0.0)	0 (0.0)	
Total	523	97 (18.5)	106 (20.3)	0.53

[a] Fisher exact test for difference in numbers of unsatisfactory performance between the 2 methods is also shown.

greater incidence of unsatisfactory performances (71 of the 289 monitors tested) compared with all the other lots of strips combined (35 of the 234 monitors tested) as shown in Table 4 ($P = 0.007$).

We also saw interlot differences in the analysis of results based on ≥15% deviation from median INR, although these differences were less evident. The number of results showing deviation similar to that of lot 965 (54 of 289 monitors) was, with this analysis, not significantly different from other lots of strips combined (43 of 234 monitors) ($P = 0.92$).

Discussion

This study shows that 2 different types of QA analysis (i.e., ≥15% deviation from certified INR according to the EC-recommended ECAA procedure and the conventional ≥15% INR deviation from median INR) reveal a similar proportion of unsatisfactory performances on the 523 CoaguChek monitors with the sets of 5 certified ECAA QA plasmas. The similar findings with the 2 types of QA analysis appear important because the simpler ECAA QA procedure was designed specifically for a rapid assessment of performance on a single user's CoaguChek monitor. The selection of the ECAA plasmas was based on previous collaborative studies in ISI calibration and QA of this monitor *(6, 9–12)*. The ECAA procedure has thus allowed over 500 monitors to be evaluated within a short time with the dedicated PT-specific set of ECAA plasmas. Conventional analysis based on percentage deviation from the overall median INR requires a large number of other participants to achieve the comparable level of QA, with inevitable delays.

Table 4. Number of monitors with 15% or more deviation from median INR and certified INR comparing incidence between strip lot 965 and all other strip lots combined.

A. Deviations from median INR.[a]

	Number of monitors, %		
Strip lot	≥15% deviation	<15% deviation	Total
965	54	235	289
Other lots combined	43	191	234
Total	97	426	523

B. Deviations from certified CoaguChek INR.[b]

	Number of monitors, %		Total
Strip lot	≥15% deviation	<15% deviation	
965	71	218	289
Other lots combined	35	199	234
Total	106	417	523

[a] Pearson χ^2 test: $P = 0.92$.
[b] Pearson χ^2 test: $P = 0.007$.

Furthermore, it has been shown previously that a minimum of 5 certified QA plasmas are required to characterize the performance of individual CoaguChek monitors *(7)*. This would require a series of national or regional QA exercises over an extended period, and it would have to be assumed that the performance of the monitors or of their test strips would be constant over this period.

The number of operators at the 9 centers totaled 24, and the number at individual centers varied between 1 and 4. In the present report, with both analyses it has been possible to observe interlot differences of different batches of CoaguChek test strips with no significant difference between the 2 methods of analysis. Differences in ISI with full WHO-type calibrations according to the method of Tripodi et al. *(8)* with different lots of CoaguChek test strips have been reported previously by the ECAA *(9)*.

The results of the present study indicate that with both analyses, the overall performance of the CoaguChek monitor in the hands of experienced users is reasonably satisfactory, although individual monitors are shown to require QA. Based on the present evidence, however, we cannot state that the overall performance with the CoaguChek is superior or inferior to conventional PT test systems (thromboplastin/instrument combinations), because results with a dedicated, independently validated set of test plasmas with certified INR have not been reported with other individual PT test systems. The great advantage of the EC-approved method is that it provides an immediate result for CoaguChek users compared with the relatively lengthy process involved in traditional external QA procedures.

Our study shows that a proportion of CoaguChek monitors in current everyday use for dosage control give unsatisfactory results by both methods of analysis, a problem that needs to be addressed. Whatever the quality of results with the CoaguChek ultimately is shown to be compared with the performance of conventional PT test systems (instrument/thromboplastin combination), the problems with QA of individual monitors and the ob-

served variability of the lots of CoaguChek test strips are real challenges.

The value and safety of this otherwise attractive approach to oral anticoagulant control by CoaguChek point-of-care testing could be greatly improved by combining it with the ECAA-recommended procedure for QA.

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