

# A National Field Study of Quality Assessment of CoaguChek Point-of-Care Testing Prothrombin Time Monitors

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## Abstract

*A system for quality assessment (QA) of the CoaguChek (Roche Diagnostics, Mannheim, Germany) point-of-care testing prothrombin time monitor has been developed by the European Concerted Action on Anticoagulation. Hitherto there has not been an adequate rapid method for CoaguChek QA.*

*Sets of 5 certified international normalized ratio (INR) plasma samples were tested on 539 CoaguChek monitors by experienced staff at 9 Netherlands Thrombosis Centers and results compared with certified INR. A 15% or more deviation has been classified as significant deviation.*

*Overall mean and certified INR values were similar, but 20.3% of participants showed a 15% or more deviation from the certified INR on at least 1 of the 5 QA plasma samples. Statistically significant differences in results with different lots of CoaguChek test strips were found. There is need for large scale QA of CoaguChek monitors. The importance of the 5 CoaguChek certified INR QA plasma samples being tested on a single occasion is demonstrated.*

Demands for warfarin anticoagulation have increased greatly in recent years. Worldwide, centers are being overwhelmed by requests for international normalized ratio (INR) monitoring, and many patients may not be receiving this treatment because of limited monitoring facilities.<sup>1</sup> Therefore, innovative point-of-care procedures have been developed for INR testing that need less technical expertise because they use unmeasured whole blood samples and may be used by patients for self-testing.

The principal point-of-care monitor, the CoaguChek (Roche Diagnostics, Mannheim, Germany), has been introduced successfully internationally with promotion to the medical profession and direct to the public. In Germany alone, as many as 400,000 patients are stated to be involved.<sup>2</sup> It also is widely used in the Netherlands and on an increasing scale in the United Kingdom and in North America. A meta-analysis published in the *Lancet* in 2006 claimed improved quality of oral anticoagulation by self-testing with the CoaguChek compared with standard testing.<sup>3</sup>

The INR must be reliable with any prothrombin time (PT) system because thrombotic events increase disproportionately at an INR less than 2.0 and bleeding complications at an INR greater than 4.5.<sup>4</sup> Quality assessment (QA) is the only reasonable check on individual CoaguChek monitors for INR because local International Sensitivity Index (ISI) calibration is not feasible; it requires manual parallel PT testing on plasma samples from the same blood samples from 60 anticoagulated patients and 20 healthy subjects. It would not be practical for the huge numbers of CoaguChek monitors to be enrolled in national or regional QA, and such schemes have not developed a specific method for the CoaguChek. Hitherto there has been no satisfactory QA procedure for this monitor.

Therefore, the European Concerted Action on Anticoagulation (ECAA) Technology Implementation Plan<sup>5</sup> developed a European Community (EC)-approved system, based on the experience of collaborative studies at European centers.<sup>6-8</sup>

The practicality of the large-scale application of the ECAA QA procedure for CoaguChek monitors currently in use for oral anticoagulant control has been assessed. The European Action on Anticoagulation (EAA), formerly the ECAA, invited the collaboration of European Concerted Action on Thrombosis (ECAT), which provides an international external QA program for hemostatic tests. Nine clinics in the Netherlands Thrombosis Service invited their patients to bring the CoaguChek monitors used to regulate their doses to be assessed by experienced staff of the centers.

The EC-approved ECAA procedure specifies that a set of 5 QA plasma samples with certified INR values based on the CoaguChek monitor should be provided for a single QA exercise. A deviation of 1 of the QA plasma samples from the set of 5 by 15% or more from the certified CoaguChek INR is considered significant deviation, and the test should be repeated. If the error persists, the advice of the manufacturer should be sought because the monitor-displayed INR cannot be changed by the user.

## Materials and Methods

Nine clinics in the Netherlands Thrombosis Service at Amsterdam, Amersfoort, Enschede, Lichtenvoorde, Koog a/d Zaan, Groningen, Etten-Leur, Leeuwarden, and Leiden participated in the study.

### The CoaguChek

The CoaguChek system consists of the meter, specific lots of numbered CoaguChek test strips incorporating thromboplastin, and a code chip containing calibration information relevant to the specific lot such as mean normal PT, ISI, lot number, and expiration date. The test strip, which contains iron oxide particles and thromboplastin, is inserted into the monitor and warmed to 37°C. An unmeasured drop of the reconstituted test plasma sample is applied to the strip. The test sample then is transported to the reaction area by capillary forces, and the coagulation process is triggered by contact with the thromboplastin. There are 2 magnets below the test strip, a permanent magnet and an electromagnet; the former causes the iron particles on the test strip to align horizontally, and the latter forces these particles into the vertical plane within a set frequency, giving rise to a regular pulsation pattern. A photo-detector above the test strip registers the changes in reflected light caused by this pulsation pattern. As soon as a clot begins to form, movement of the iron particles slows until they stop. This results in a decrease in reflection interpreted as the onset of coagulation. An algorithm programmed into the specific code chip converts this result into the PT and INR.

### Certified CoaguChek INR Values

The certified INR values were obtained from an ISI calibration of each of the 3 individual monitors at the 3 certifying centers in Leiden (Haemostasis and Thrombosis Research Center), Manchester (EAA Central Facility), and Milan (A Bianchi Bonomi Hemophilia & Thrombosis Centre). The CoaguChek ISI values were obtained from results of blood samples from 20 healthy subjects and 60 warfarin-treated patients tested as plasma samples with the ECAA rabbit reference thromboplastin using the manual PT technique and with whole blood from the same samples on the CoaguChek monitors.<sup>9</sup>

A previous ECAA report indicated that a minimum of 5 certified plasma samples tested on the same occasion is required to characterize the performance of individual CoaguChek monitors.<sup>10</sup> A single lot of CoaguChek test strips (lot No. 726) was used at all 3 centers for the certifications.

The certified CoaguChek INR of each of the 5 external QA plasma samples was the mean from the 3 EAA centers using a single CoaguChek monitor at each center. The 5 QA plasma samples were certified by duplicate testing on 3 days. The mean normal PT for the 20 healthy subjects for the CoaguChek system at each center was used with the mean ISI from the 3-center ISI calibration to calculate the INR of each plasma sample according to World Health Organization guidelines.<sup>11</sup>

### Performance Criteria

In conventional PT testing, an INR deviation of 10% is regarded as a clinically relevant difference,<sup>12</sup> but CoaguChek monitors have been shown to give less precision than conventional PT test systems.<sup>6,13,14</sup> A 15% or more deviation from the certified INR on a single certified plasma sample, therefore, was adopted by the ECAA as the limit of acceptable performance. Monitors giving this degree of deviation from the certified CoaguChek INR with 1 or more from the set of 5 ECAA QA plasma samples are described as showing significant INR deviation.

According to the EC-approved recommendation in which a CoaguChek monitor shows significant INR deviation with a single ECAA test plasma sample from the set of 5, the test should be repeated, and, if the deviation persists, the monitor should be checked. Repeated tests were not possible in this study because each plasma sample was tested without the users being aware of its certified value.

The effect on QA of the different operators and different numbered lots of CoaguChek test strips also were assessed.

### Test Procedure

A single batch of sets of 5 certified ECAA plasma samples was used in the study. At the 9 clinics in the Netherlands Thrombosis Service, the procedure was as follows: The plasma samples stored at 2°C to 8°C were left for 15 to 30

minutes at room temperature before reconstitution. Distilled water (0.5 mL) was added to each vial and the cap replaced; after a minimum of 10 minutes at room temperature but within 2 hours, the plasma samples were tested on individual monitors by the trained staff of the Thrombosis Service Centre as follows: To 0.1 mL of plasma in a plastic tube, 0.1 mL of 17 mmol/L calcium chloride was added and mixed well. Within 10 to 15 seconds 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. Lyophilized plasma samples were provided for the study so there was potential for reconstitution error by users, although only experienced staff at the 9 centers were allowed to take part. The study was completed during a 3-month period in late 2005.

## Results

A total of 539 CoaguChek monitors were brought by patients to 1 of 9 Thrombosis Centers. Results from 16 were incomplete and were excluded.

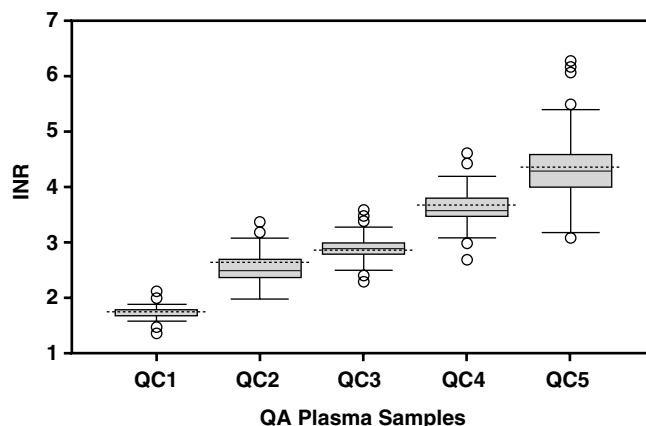
### Certified CoaguChek INR

The mean certified CoaguChek INR and the mean INR of all monitors tested with the 5 QA plasma samples are given in **Table 1**. The distribution of INR values is shown in **Figure 1**.

### CoaguChek Monitor Results

There was close agreement between the overall mean INR values from the 523 monitors and the mean of the certified INR values of the same 5 QA plasma samples (mean difference, 1.6%). The number of monitors tested and the percentage with each of the 5 QA plasma samples that showed significant (15% or more) INR deviation is given in Table 1.

**Table 2** shows that of the 523 monitors, the numbers tested at the 9 individual centers ranged from 6 to 126. Of the 523, 106 (20.3%) gave a 15% or more deviation from the certified CoaguChek INR with at least 1 plasma sample. Of these



**Figure 1** Distribution of international normalized ratio (INR) values of 5 quality assessment plasma samples showing mean certified INR and median INR (with interquartile ranges) and number of significant outliers. Dotted line, certified INR; solid line in box, median INR; box, interquartile range; circles, outliers. QA, quality assessment.

106 monitors, 81 (76.4%) showed significant deviation with 1 plasma sample, 19 (17.9%) with 2 QA plasma samples, and 5 (4.7%) with 3 of the 5 plasma samples. One monitor only gave unsatisfactory performance with 4 plasma samples.

Variance components analysis was carried out to determine whether the observed variation in INR values was due to the individual centers, the different operators, various test strip lots, or imprecision (random error). Approximately 52% of INR variation was found to be due to random error across the 5 QA plasma samples; 27.5% of INR variation was accounted for by the different lots of test strips, 18.9% by center differences, and 1.6% by operator. When results from the individual operators at the 9 centers who tested more than 10 monitors were considered, the rate of significant INR deviations ranged from 0% to 50% but this number also was affected by the use of different lots of test strips at the centers.

CoaguChek test strip lots are of limited size and have a stated expiration date. Differences in the performance of

**Table 1**  
Overall Performance With Individual Quality Assessment Plasma Samples

Plasma Sample	Certified CoaguChek INR (SD)	≥15% Deviation*	Mean (SD) INR for All Monitors
QC1	1.76 (0.12)	6 (1.1)	1.76 (0.13)
QC2	2.65 (0.12)	42 (8.0)	2.53 (0.23)
QC3	2.86 (0.21)	32 (6.1)	2.93 (0.31)
QC4	3.70 (0.38)	17 (3.3)	3.61 (0.25)
QC5	4.41 (0.21)	41 (7.8)	4.31 (0.44)
Total	—	138 (5.3)	3.03 (0.93)

INR, international normalized ratio.

\* Number (percentage) of plasma samples giving 15% or more deviations from the certified CoaguChek INR. Each of the 5 plasma samples was tested on 523 monitors, totaling 2,615 tests.

**Table 2**  
Monitors at Nine Centers Showing a 15% or More Deviation From the Certified CoaguChek INR\*

Center No.	No. of Monitors	≥15% Deviation
1	68	9 (13)
2	96	17 (18)
3	69	17 (25)
4	126	35 (27.8)
5	43	17 (40)
6	34	2 (6)
7	6	3 (50)
8	40	4 (10)
9	41	2 (5)
Total	523	106 (20.3)

INR, international normalized ratio.  
\* Data are given as number (percentage).

CoaguChek test strips were evident. **Table 3** shows that with 6 numbered lots of CoaguChek test strips used on at least 16 monitors, the number of significant INR deviations varied from 6% to 38%. The overall mean INR for the 5 QA plasma samples with the various lots of test strips ranged from 2.96 to 3.21 (7.8% difference). Data for differences of lots of test strips are given in **Table 4**. Three operators, A, B, and C, at 3 centers each tested more than 1 lot of test strips. At centers 3 and 4, the same 2 lots of strips (019 and 965) were tested by 2 different operators. With lot 019, operators A and B had a much lower incidence of significant INR deviations than with lot 965. In contrast, operator B also tested an additional lot (996) on 24 monitors and had no significant INR deviations. Results from all 3 operators agreed on the higher than average incidence of significant INR deviation with lot 965. Operator C found results similar to those for lot 965 with an additional lot of strips (862).

When results with all other lots were combined, these totaled 234. These were compared with the 289 results (55.3%)

**Table 3**  
Results With Different Lots of CoaguChek Test Strips Showing More Than a 15% Deviation From the Certified CoaguChek INR and Overall Mean INR

Lot No. of Strips	No. of Monitors	≥15% Deviation*	Overall Mean INR of 5 Quality Control Plasma Samples
019	72	13 (18)	3.21
776	31	2 (6)	3.06
862	16	6 (38)	3.16
931	68	5 (7)	2.99
965	289	71 (24.6)	2.96
996	45	9 (20)	3.16
Other strips	2	0 (0)	—
Total	523	106 (20.3)	3.09

INR, international normalized ratio.  
\* Data are given as number (percentage).

with lot 965. **Figure 2** shows the means and distributions. Lot 965 showed a significantly lower mean INR across all 5 external QA plasma samples ( $P > .001$ ; 1-way analysis of variance). Of the 106 monitors with significant INR deviations, 71 (67.0%) used lot 965, but only 35 (33.0%) used other lots. This difference was significant at the 5% level ( $P = .007$ ; Pearson  $\chi^2$ ). The chance of a monitor showing significant INR deviations was almost twice as high when using lot 965 compared with other batches of strips combined (odds ratio, 1.9; 95% confidence interval, 1.2-2.9).

## Discussion

There is a widespread and growing demand for the provision of QA for the CoaguChek point-of-care testing PT monitor because of their large numbers and the absence of available procedures for their QA. The present report describes the largest QA survey of the monitor performed to date and confirms the

**Table 4**  
Interlot Comparisons\*

Center/Operator/Lot No.	No. of Monitors	≥15% Deviation <sup>†</sup>	Mean INR of 5 Quality Control Plasma Samples	P
Center 3, operator A				
965	28	11 (39)	2.76	<.01 ( <i>t</i> test)
019	19	0 (0)	3.17	
Center 4, operator B				
965	48	17 (35)	2.82	<.01 <sup>‡</sup> (ANOVA)
019	16	1 (6)	3.22	
996	24	0 (0)	3.14	
Center 5, operator C				
965	27	11 (41)	3.09	.66 ( <i>t</i> test)
862	16	6 (38)	3.16	

ANOVA, analysis of variance; INR, international normalized ratio.

\* Examples of results from 3 operators at 3 centers with different lots of CoaguChek test strips showing ≥15% deviation from the Certified CoaguChek INR.

<sup>†</sup> Data are given as number (percentage).

<sup>‡</sup> Differences in mean INR between lots 965 and 019 ( $P < .01$ ; *t* test) and lots 965 and 996 ( $P = .01$ ; *t* test) were statistically significant. Differences between lots 019 and 996 were not significant at the 5% level ( $P = 1.0$ ; *t* test).

feasibility of its large scale QA with the sets of 5 ECAA plasma samples. The extent of use and apparent popularity of the CoaguChek is demonstrated by the fact that more than 500 patients responded in a short time to the invitation to bring the monitors used for their dose control to the 9 Netherlands centers.

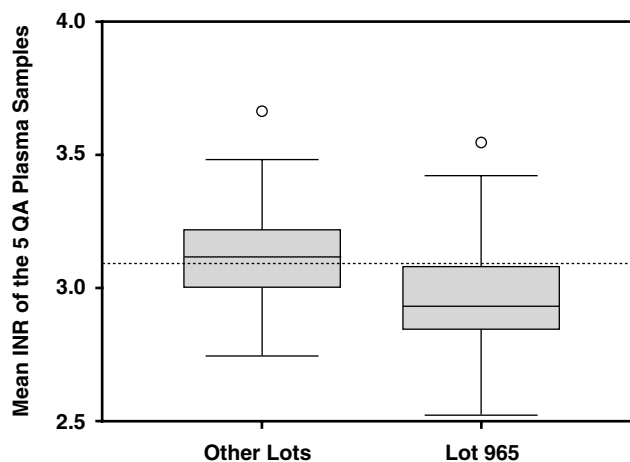
Other reports have stressed the need for QA of this monitor.<sup>2,15</sup> The EC-approved method performed in the study gives an immediate QA assessment without requiring parallel results from large numbers of other participants as demanded by conventional national and regional QA schemes and without the delays inherent in the central collection of the data and their analysis. The need for testing the mandatory minimum of 5 QA plasma samples on a single occasion cannot be accommodated easily in current QA schemes.

It is reassuring that the mean monitor INR closely approximated the mean certified values on all 5 QA plasma samples, indicating that there is not a fundamental fault in the manufacturer's INR certification of the monitors. Nevertheless, the fact that a fifth of the monitors tested gave significant deviations with at least 1 QA plasma sample must cause concern. The present report supplements previous ECAA findings on between-center variability in CoaguChek monitor-displayed INR values reported in a previous small study at 10 selected European centers.<sup>14</sup> The fact that all the INR discrepancies are not due simply to instrument variability but also are affected by other factors, including performance of individual CoaguChek test strips, is a problem that should be addressed.

This evidence of interlot differences of CoaguChek test strips is in accord with previous ECAA findings on ISI difference between lots of CoaguChek test strips detected by a modified full World Health Organization–type ISI calibration procedure.<sup>9</sup> It is of interest that the study also revealed that some individual operators at the 9 centers obtained significantly different INR values, although all were experienced staff, but this may be due in part or wholly to the fact that they were reconstituting lyophilized test plasma samples rather than using native whole blood samples, which would be the normal practice with this monitor.

Because CoaguChek monitors routinely use whole blood samples, it may be asked whether using plasma samples is valid for their QA. It has been shown, however, by ECAA collaborative studies that the formulation of lyophilized plasma and calcium chloride used in the ECAA procedure for the CoaguChek monitor characterizes performance sufficiently to provide dependable QA.<sup>5,10</sup>

It is important to appreciate that there are no comparable data on a similar number in a single exercise of any other PT test system (thromboplastin/coagulometer combination) based on a single dedicated set of PT system certified QA plasma samples, so no valid comparison with any other PT system can be made.



**Figure 2** Distribution of international normalized ratio (INR) values using CoaguChek strip lot 965 ( $n = 289$ ) compared with other lots combined ( $n = 234$ ). Dotted line, certified INR; solid line in box, median INR; box, interquartile range; circles, outliers. QA, quality assessment.

The ECAA Technology Implementation Plan instructs that repeated tests should be performed on any of the set of 5 QA plasma samples showing significant deviation. It was not possible in this survey; because of its design as a large-scale feasibility study, the certified values were withheld purposely from participants.

This large national survey in the Netherlands confirms the need for and feasibility of QA of individual CoaguChek monitors at the point of care, as recommended by the EC-approved technology implementation plan. It also confirms the recommendations of the previous ECAA study on the importance of the inclusion of 5 INR-certified ECAA plasma samples in a QA set to characterize the performance of the CoaguChek monitors. The inclusion of smaller numbers of QA PT plasma samples, not specifically dedicated to CoaguChek INR but for all PT methods, is the usual practice in national and regional QA testing. With the massive numbers of CoaguChek monitors in current use, it is essential that a simple, reliable system of QA giving a rapid screen for poor performance of an instrument or operator is widely available without delay. National or regional QA schemes have an important part but cannot substitute for this local QA. The EC-approved procedure based on ECAA plasma samples seems to be the answer to the problem.

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