

External quality assessment (EQA) for CoaguChek monitors

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Summary

Anticoagulant control facilities are being overwhelmed by requests for monitoring and large numbers of patients are not therefore receiving treatment. Procedures designed for point-of-care testing have therefore been developed, the most popular being the CoaguChek. The need for external quality assessment (EQA) of monitors used by patients in self-management has been stressed in a European Commission (EC) Directive. It would not however be feasible for all CoaguChek monitors to be enrolled in national or regional EQA schemes which take time to organise and analyse. The European Concerted Action on Anticoagulation (ECAA) has therefore evolved a simpler system. Its value has been assessed in collaboration with the European Concerted Action on Thrombosis (ECAT). 523 monitors were tested at nine clinics which asked patients to bring their CoaguChek instruments to be assessed with the ECAA/ECAT procedure

based on a set of 5 plasma samples with certified international normalised ratios (INR). 15% or more deviation from the certified INR on a single certified plasma sample from the set was defined by the ECAA as the limit of acceptable performance. One hundred and six (20.3%) of the monitors tested showed significant deviation and higher than average incidence of significant INR deviations reported with one specific numbered lot of test strips. Recent ECAA/ECAT, Danish and Italian studies report regular EQA of CoaguChek monitors is essential. There is general agreement that this should be performed at reasonably frequent intervals, at six months or whenever there is a change of the manufacturer's test strips.

Keywords

Oral anticoagulation, external quality assessment, point-of-care monitors, INR deviation, accuracy, precision

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Introduction

Greater worldwide recognition of the value of oral anticoagulation in a widening range of clinical disorders including atrial fibrillation (AF), has led to increasing demands for control, putting a great strain on facilities in hospitals and community clinics.

Anticoagulation, to be safe and effective, must conform to defined therapeutic targets expressed as international normalised ratios (INR). INR less than 2.0 are generally ineffective in prevention of thrombosis whereas INR greater than 4.5 dramatically increase the risk of bleeding (1). Anticoagulant control centres are being overwhelmed by requests for INR monitoring and a large number of patients are not therefore receiving this treatment because of limited laboratory facilities.

One result of the increased demand has been increased application of innovative point-of-care procedures developed for INR testing which need less technical expertise because they employ unmeasured whole blood samples and therefore can be used also

by patients themselves for self-testing, INR determination and, in a select group, self-dosage.

A range of elegant, hand-held, easy-to-use, prothrombin time (PT) monitors has therefore been developed (2). By far the most popular and widely used is the CoaguChek (Roche Diagnostics, Mannheim, Germany). This was introduced in Germany with promotion to the medical profession and directly to the general public. It has also been employed widely on an increasing scale in the Netherlands, United Kingdom, North America and elsewhere. As many as 400,000 instruments are stated to be engaged in Germany alone in patient self-monitoring and 150,000 in patient self-testing/self-dosage. It is essential therefore that CoaguChek instruments provide accurate INR. The earlier models, CoaguChek and CoaguChek S, have been in clinical employ for several years and have also been the subject of clinical trials of patients' self-testing/self-management. They are now being replaced by the lower International Sensitivity Index (ISI) CoaguChek XS containing a more responsive human recombinant thromboplastin replacement for

rabbit reagent dependent on a different principle of end-point detection.

The need for external quality assessment

INR results must be reliable. Although Tripodi et al. (3) devised an elegant method for ISI calibration of “point-of-care” PT monitors to accord with the WHO system of PT standardisation. This is too demanding for routine CoaguChek users. It requires multicentre calibration and parallel testing on 60 patients and 20 healthy subjects together with conventional PT testing with the appropriate WHO reference thromboplastin (4).

Validation of “point-of-care” testing must depend therefore on external quality assessment (EQA). EQA is the only reasonable check on individual CoaguChek monitors. In assuring the quality of examination procedures the International Standards Organisation (ISO) states that participation in an EQA shall be required where available (5).

The need for EQA of procedures used by patients in self-management has also been stressed in an European Commission (EC) Directive 98/79 (► Table 1) of the European Parliament and of the Council of October 27th 1998 on *in vitro*-diagnostic medical devices (6). This requires manufacturers of self-test kits to have their conformity to various essential requirements contained in the Directive independently assessed by a “notified body”. Thus, there is a clear need for a reliable mandatory EQA procedure for users of devices involved in “INR self-testing” to meet recommended safety demands of EU law. User control of devices for self-testing as required by the EC Directive can be achieved by EQA of the devices.

It would not be feasible for all the massive number of CoaguChek monitor users to be enrolled in national or regional EQA schemes. These surveys take a considerable time to organise and analyse and are not dedicated to a single type of monitor. Furthermore, in CoaguChek EQA so far, none of the EQA schemes have achieved the minimum total of five plasmas in a single exercise recommended by the European Concerted Action on Anti-coagulation (ECAA). Until recently there has therefore been no practical EQA procedure for these monitors.

The ECAA EQA procedure

The ECAA has evolved a simple system, based on collaborative studies at major European centres. This has been approved in principle by the EC in the ECAA Technology Implementation Plan (7).

Its value in large-scale application to CoaguChek monitors currently in use for oral anticoagulant control has been assessed by the ECAA in collaboration with the European Concerted Action on Thrombosis (ECAT) which provides an international external EQA program for haemostatic tests (8, 9).

Nine clinics in the Netherlands Thrombosis Service asked their patients to bring their CoaguChek monitors to them to be assessed by the experienced staff of the centre with the ECAA/ECAT procedure. This specifies that a set of five plasma samples with INR based on the specific type of CoaguChek monitor and certified by ECAA expert laboratories should be tested in a single exercise. A small but persistent certified INR difference was observed between the CoaguChek, CoaguChek S and CoaguChek XS instruments. A deviation with one of the five EQA test samples by 15% or more from the certified CoaguChek INR for the specific type of monitor is classified as significant deviation. In this case the tests should be repeated on a fresh set of five EQA plasmas. If the error persists, advice is to be sought because the monitor-displayed INR cannot be changed by the user.

ECAA/ECAT certified CoaguChek INR

The scheme for INR certification of the ECAA plasmas is described in ► Table 2. Certified INR values are obtained from results with each different type of monitor at a minimum of three certifying centres including Leiden (Haemostasis and Thrombosis Research Centre), Manchester (ECAA Central Facility), and Milan (A Bianchi Bonomi Hemophilia & Thrombosis Centre). CoaguChek ISI values are obtained from the mean values of the results at all of the certifying centres on blood samples from 20 healthy subjects and 60 warfarin-treated patients. These are 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, according to the method described by Tripodi et al. (3). One numbered lot of CoaguChek test strips is used at all centres in a single certification. The certified CoaguChek INR of each of the five external EQA plasma samples is the mean value from the ECAA certifying centres using a single CoaguChek monitor at each centre. The five EQA plasma samples are certified by duplicate testing on three different days and the overall mean in terms of PT (sec) and INR determined. According to WHO Revised

Table 1: Current European law contained in Council Directive 98/79 EC related to the safety of “in vitro diagnostic medical devices”. (OJ L 331, 7.12. 1998, p.19 and OJ L 331, 7.12. 1998 p. 16)

“Section B7.1. Devices for self-testing must be designed and manufactured in such a way as to: –ensure that the device is easy to use by the intended lay user at all stages of the procedure, and – reduce as far as practicable the risk of user error in the handling of the device and in the interruption of the results.”

“Section B7.2. Devices for self-testing must, where reasonably possible, include user control, i.e. a procedure by which the user can verify that, at the time of use, the product will perform as intended.”

“Section A4. The traceability of values assigned to calibrators and/or control materials must be assured through reference measurement procedures and/or available reference materials of higher order”.

Table 2: Scheme for INR certification of ECAA plasmas.

| |
|---|
| At ECAA Central Facility 5 artificially depleted test plasmas selected to give a spectrum of INR across the 2.0–4.5 INR therapeutic interval with the WHO human thromboplastin IRP and WHO rabbit thromboplastin IRP. |
| ↓ |
| Sent to three ECAA certifying centres to be tested with manual prothrombin time (PT) technique using the two IRPs on three different days and the overall mean in terms of PT (secs) and INR determined. |
| ↓ |
| Results returned to ECAA Central Facility for analysis and certified INRs determined using mean values of the three ECAA certifying centres. |

Guidelines the mean normal PT for the 20 healthy subjects for the CoaguChek system at each centre is used with the mean ISI from a minimum three-centre ISI calibration to calculate the INR of each of the five ECAA plasmas (4).

Performance criteria

In conventional PT testing, an INR deviation of 10% is regarded as a clinically relevant difference (4), but CoaguChek monitors give less precision than conventional PT test systems (10–12). A 15% deviation from the certified INR on a single certified plasma sample was therefore adopted by the ECAA as the limit of acceptable performance. Monitors exceeding 15% deviation from the certified CoaguChek INR with one or more test plasmas from the set of five ECAA EQA samples are described as showing significant INR deviation. ► Figure 1 shows an example of INR results with one monitor plotted against the certified values with one result exceeding 15% deviation from the certified INR. Where a CoaguChek monitor shows significant INR deviation with one ECAA test

plasma sample from the set of five, the test should be repeated but if the deviation persists, the monitor should be checked.

The ECAA/ECAT collaborative EQA study

The practicality of the large-scale application of the ECAA EQA procedure for CoaguChek monitors was assessed by the ECAA/ECAT collaborative study (8). Nine clinics in the Netherlands Thrombosis Service invited their patients to bring the CoaguChek monitors used to regulate their dosage to participate in an EQA exercise by experienced staff of the centres (8, 9).

A single batch of sets of five certified ECAA plasma samples was used at the nine clinics but the INR values were not provided to the user.

With 539 CoaguChek monitors brought by patients, overall there was good agreement between the mean INR values from the 523 monitors included in the analysis and the mean of the certified INR values of the same five EQA plasma samples (mean difference, 1.6%) but 106 (20.3%) of the monitors tested showed significant (15% or more) INR deviation.

With six numbered lots of CoaguChek test strips each used on at least 16 monitors, the number of significant INR deviations varied between 6% and 38% at the different centres.

Inter-lot variation of CoaguChek test strips

Three operators at three centres each tested more than one lot of test strips. Results agreed on the higher than average incidence of significant INR deviation with one specific numbered lot of test strips. The chance of a monitor showing significant INR deviations was almost twice as high when using this specific lot (965) com-

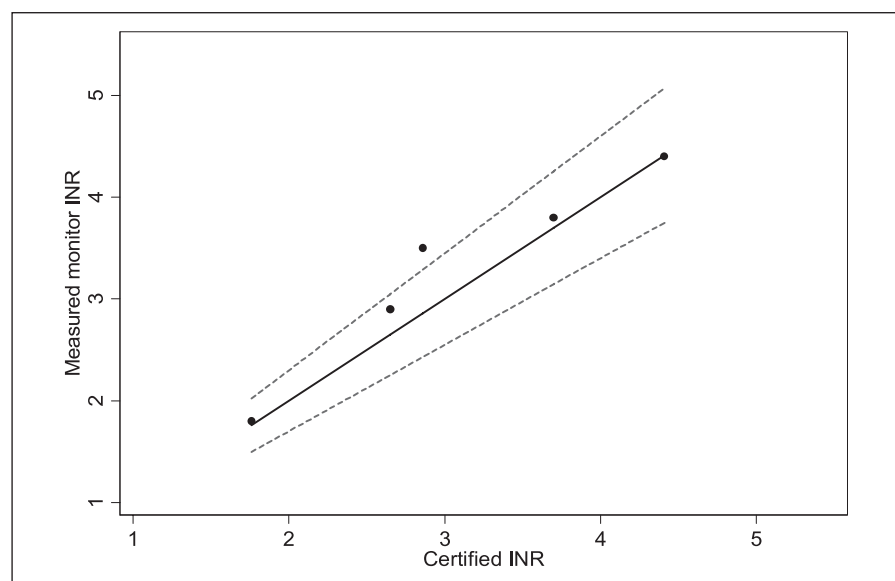


Figure 1: Example of results with five quality control plasmas from one monitor. The INR results are plotted against the certified INR. The solid line represents the 'true' line where the monitor results are the certified values. The broken lines indicate 15% deviation above and below the certified values.

pared with other batches of strips combined (odds ratio, 1.9; 95% confidence interval, 1.2–2.9).

A further report on the above study (9) showed that the 15% limit of deviation from the certified INR obtained with the set of five CoaguChek test plasmas by 20% of participants' monitors was closely comparable to 15% deviation from the median INR, the usual method for interpretation of results in UK national external quality assessment surveys. The EQA testing should be repeated at six-month intervals or whenever a change of test strips occurs. If one of the test results on a single plasma from the set of five falls outside the 15% deviation preferably the procedure should be repeated on a fresh set of five samples. If however the remaining four plasmas give a good linear relationship the repetition might be considered unnecessary and the four other test results be used for the orthogonal regression line.

A different method to avoid the need for repeat testing of the sets of the five ECAA/ECAT samples if one failed has recently been proposed (13). This analysis, however, can only be performed by an expert anticoagulant control centre as it requires determination of the slope, intercept and correlation coefficient of the regression line. Thus, the immediacy of the EQA and convenience to the patient of the ECAA procedure are lost.

Precision of CoaguChek XS

The precision of the CoaguChek XS system has been assessed in a four-centre study. The coefficient of variation for the imprecision of the INR ranged from 2.0% to 3.2% in venous samples, and from 2.9% to 4.0% in capillary blood samples (14).

The Danish study

A team of Danish investigators (15) recently reported a prospective study evaluating the accuracy and precision of a single CoaguChek S instrument and a single instrument of the newly introduced CoaguChek XS type, both tested in a group of patients on warfarin together with the local laboratory PT method. A total of 564 venous blood samples was obtained from 24 patients which were tested on the two different types of monitor weekly in parallel over a 42-day period as well as with the authors' conventional hospital prothrombin time method employing a low ISI rabbit thromboplastin (ISI 0.98–1.0) on a Stago coagulometer. The target INR was 2.0–3.0. The INR results on both types of CoaguChek instruments were considerably lower than with the hospital method (0.33 and 0.42 INR respectively for the CoaguChek S and CoaguChek XS). Unfortunately no ISI calibration of the local laboratory method was performed so the interpretation is debatable although the coagulometer was described as having been certified according to the ISTH Guidelines (International Society on Thrombosis and Haemostasis) but using certified calibration plasmas. The observations by the authors on accuracy are however most important as their results are similar to those of the joint EAA/ECAT

study. They concluded that EQA and perhaps ISI calibration of CoaguChek monitors seemed mandatory.

Italian EQA study

Comparative results of an EQA study in Italy using the ECAA/ECAT quality control plasmas were reported by Barcellona et al. (16). On a quarterly basis the performance of 95 CoaguChek S assigned to 99 anticoagulated patients at home was investigated. This was done by checking the monitors against a reference standard coagulometer in the laboratory at their Thrombosis Centre. The other aims were to carry out an EQA employing sets of INR certified ECAA plasmas and to assess the performance of different lots of strips.

No difference in results between the PT INR obtained with the two systems was noted at the first quarterly check but a significant difference was found when the two systems were compared at the second and third quarterly checks. The Bland-Altman test showed increased disagreement between the first and the third occasion controls were tested. The percentage of INR values that showed a difference of more or less than 0.5 INR units in the PT values performed with both the systems was: 1.0% (first control), 7.5% (second control) and 11.5% (third control) (Chi-Square: 8.315, $p = 0.0156$). Lots with differences higher than 10% in terms of ± 0.5 INR units at the first, second and third controls were 16%, 20.8% and 61%, respectively. Seven monitors (7.3%) failed to test one or two of the INR certified plasmas of one set but performed well using a second set of plasmas. Three monitors (3.1%) failed to test two sets of plasmas but performed well using a different lot of strips. One monitor (1%) gave unsatisfactory results with different sets of plasmas and strips. All the other PT INR obtained with the monitors fell well within the different ranges of the INR certified plasmas.

Barcellona et al. (16) concluded that patients anticoagulated using self-testing or self-management should periodically bring their portable coagulometer to a reference Thrombosis Centre for EQA, especially when the lot of test strips is changed.

UK Health Technology Assessment

An evaluation of CoaguChek monitors was performed in a United Kingdom Health Technology Assessment in 2007 (17) which reported that in 16 selected randomised and eight non-randomised trials, patient self-monitoring of oral anticoagulation therapy was more effective than poor-quality usual care provided by family doctors and as effective as good-quality specialised anticoagulation clinics in maintaining the quality of anticoagulation therapy. There was, however, no significant reduction of major bleeding events between patient self-monitoring control and usual care. Pooled results showed that compared with primary care or anticoagulation control clinics, self-monitoring was associated with

significantly fewer thromboembolic events. The conclusion was that for selected, successfully trained patients, self-monitoring is effective and safe for long-term oral anticoagulation. In general, although patient self-management is unlikely to be more cost-effective than the current specialised anticoagulation clinics in the UK, more self-monitoring may enhance the quality of life for some patients who are frequently away from home, in employment or education, or who find it difficult to travel to clinics.

One of the important advantages of patient self-management is that anticoagulation control can be more frequent (every 1–2 weeks) than in usual care provided by family doctors or hospital clinics (every 2–4 weeks). Longer intervals in usual care up to 10 weeks are in fact regular practice in some hospitals and in practice outside of hospitals. The American College of Chest Physicians (ACCP) Guidelines (18) recommended a maximum four week interval between tests but this is acknowledged to be frequently exceeded in routine practice.

More frequent INR checks are easier with CoaguChek self-testing and generally improve the percentage of time in target INR range and presumably the clinical results.

Controlled trials were summarised in the UK Health Technology Assessment (17) stating that patient self-management is better than poor-quality anticoagulation control provided by family doctors, particularly in the prevention of inadequate anticoagulation (proportion of time INR spent below the target therapeutic range). This was on average 19% in patients using self-monitoring compared with 33% in patients managed by family doctors. Overall, CoaguChek patient self-management was as effective as the usual care of specialised anticoagulant clinics. They concluded that patient self-management is unlikely, however, to be more cost-effective than the current high-quality care provided by specialised anticoagulation clinics.

Plasma versus whole blood EQA

Use of plasma for the EQA in the ECAA method for EQA of CoaguChek monitors has been questioned. As well as the ECAA findings of the close correspondence of plasma and whole blood results, the UK National External Quality Assessment Service (UK NEQAS) (19) reported close agreement between them in UK National proficiency studies.

The ECAA in a 10-centre collaborative study showed that no correction for the use of whole blood and plasma in ISI calibrations was required with the CoaguChek whereas this was necessary with an alternative commercial point-of-care PT testing system (10, 21, 22). The reliability of plasma INR on the CoaguChek with the ECAA EQA closely depends on the calcium concentration in the test specimens and an optimum calcium concentration was therefore developed for the ECAA procedure.

CoaguChek S versus CoaguChek XS

The newly developed CoaguChek XS has a low ISI, stated to be 1.01 and incorporates a more responsive human thromboplastin reagent (22). The end-point is an electrochemical measurement of the PT. In their study at four centres Braun et al. (22) compared the new instrument with the established CoaguChek S. INR were similar, as was the correlation slope. There was however greater disagreement at higher INR.

Unpublished data from a multicentre certification of the ECAA/ECAT EQA sets at the ECAA certifying laboratories indicated significantly greater precision of the INR with the CoaguChek XS compared with the CoaguChek S on four of the five test samples in the ECAA test set.

In a four-centre study, the CoaguChek XS' measuring range between INR 0.8 and INR 8.0 was calibrated against the mean INR of rTF/95 and rabbit thromboplastin (AD149) using polynomial regression. The relative bias between INRs calculated with the assigned ISI for the CoaguChek XS and INRs derived from polynomial regression was -0.5% at INR 2.0 and increased to -7% at INR 4.5. Overall the relative bias in the therapeutic range was less than $\pm 10\%$ which is regarded as clinically acceptable (23).

Conventional national and regional EQA schemes for CoaguChek users

These are based on different approaches. Unlike the ECAA/ECAT procedure which provides an immediate assessment of performance of an individual monitor this is not possible with conventional schemes and it may take days or weeks to obtain a report. Analysis is based on deviation of the monitor from the overall performance of all participants involved in an exercise after central analysis and is usually expressed as percentage difference from the median INR (or mean INR). Data are collected and analysed centrally. The production of overall and individual centre reports therefore takes a considerable time, and given the ECAA findings that a minimum of five EQA plasmas is required to characterise the performance of individual CoaguChek monitors, it may take months or even years to achieve. Conventional centralised EQA analysis based on deviation from median INR is also not specific for the CoaguChek monitor. The same procedure is applied to other PT methods. None of these EQA 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 EQA of the CoaguChek.

The relative reliability of these two different methods of analysis was therefore compared with the findings. This supplemented a separate report demonstrating the feasibility of the ECAA Technology Implementation Plan (7) in providing a reliable large-scale EQA of the CoaguChek monitor based on the dedicated set of five ECAA plasmas (9). This study shows that the two different criteria for unsatisfactory performance of EQA (i.e. over 15% deviation from certified INR according to the EC-recommended ECAA/

ECAT procedure and the conventional $\pm 15\%$ INR deviation from median INR) gave a similar proportion of unsatisfactory results on the 523 CoaguChek monitors in the ECAA/ECAT study using the sets of five certified ECAA EQA plasmas. The similar findings with the two types of EQA analysis appear important because the simpler ECAA EQA procedure was designed 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 EQA of the CoaguChek monitor. The ECAA procedure thus allowed over 500 monitors to be evaluated on site within a short time with the dedicated PT-specific set of ECAA plasmas (8). Conventional EQA analysis based on percentage deviation from the overall median INR requires a large number of other participant results to determine the comparable level of EQA with inevitable delays. Furthermore, it had been shown previously that results from a minimum of five certified EQA plasmas are required to characterise the performance of individual CoaguChek monitors (22). This would entail a series of conventional national or regional EQA exercises over an extended period in which it would have to be assumed over this period that the performance of the monitors or of their test strips would be constant.

The number of operators at the nine centres in The Netherlands ECAA/ECAT study (9) totalled 24, and the number at individual centres in the exercise varied between one and four. With both types of analyses it has been possible to observe inter-lot differences of different batches of CoaguChek test strips with no significant difference between the ECAA method of analysis and the delayed type of analysis of national proficiency studies.

Differences in ISI with full WHO-type calibrations according to the method of Tripodi et al. (3) with different lots of CoaguChek test strips have been reported previously by the ECAA. The results of the above study indicate that with both analyses ECAA and national/regional proficiency studies, the overall performance of the different models of the CoaguChek monitor in the hands of experienced users is reasonably satisfactory.

As reported elsewhere (2) by the recent ECAA/ECAT (8, 9), the Danish (14) and Italian (16) studies, regular EQA of CoaguChek monitors is essential. There is general agreement that this should be performed at reasonably frequent intervals, six months being suggested or whenever there is a change of the manufacturer's test strips.

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