



ELSEVIER

THROMBOSIS
RESEARCH

intl.elsevierhealth.com/journals/thre

REGULAR ARTICLE

Results of the performance verification of the CoaguChek XS system

W. Plesch^a, T. Wolf^a, N. Breitenbeck^b, L.D. Dikkeschei^c, A. Cervero^d,
P.L. Perez^d, A.M.H.P. van den Besselaar^{e,*}

^a Roche Diagnostics, Mannheim, Germany

^b NB Research, Indianapolis, USA

^c Isala Klinieken, Zwolle, The Netherlands

^d Hospital General, University of Valencia, Spain

^e Department of Thrombosis and Haemostasis, Leiden University Medical Centre, P.O. Box 9600, 2300 RC Leiden, The Netherlands

Received 4 December 2007; received in revised form 14 April 2008; accepted 24 April 2008

KEYWORDS

CoaguChek;
Oral Anticoagulation
Monitoring;
ISO 17593:2007 standard;
Performance Verification;
Self-Testing and
Self-Management

Abstract

Background: This is the first paper reporting a performance verification study of a point-of-care (POC) monitor for prothrombin time (PT) testing according to the requirements given in chapter 8 of the International Organization for Standardization (ISO) 17593:2007 standard "Clinical laboratory testing and in vitro medical devices — Requirements for in vitro monitoring systems for self-testing of oral anticoagulant therapy". The monitor under investigation was the new CoaguChek XS system which is designed for use in patient self testing. Its detection principle is based on the amperometric measurement of the thrombin activity generated by starting the coagulation cascade using a recombinant human thromboplastin.

Methods: The system performance verification study was performed at four study centers using venous and capillary blood samples on two test strip lots. Laboratory testing was performed from corresponding frozen plasma samples with six commercial thromboplastins. Samples from 73 normal donors and 297 patients on oral anticoagulation therapy were collected. Results were assessed using a refined data set of 260 subjects according to the ISO 17593:2007 standard.

Results: Each of the two test strip lots met the acceptance criteria of ISO 17593:2007 versus all thromboplastins (bias -0.19 to 0.18 INR; $>97\%$ of data within accuracy limits). The coefficient of variation for imprecision of the PT determinations in INR ranged from 2.0% to 3.2% in venous, and from 2.9% to 4.0% in capillary blood testing. Capillary versus

* Corresponding author. Tel.: +31 71 5261894; fax: +31 71 5266755.

E-mail address: a.m.h.p.van_den_besselaar@lumc.nl (A.M.H.P. van den Besselaar).

venous INR data showed agreement of results with regression lines equal to the line of identity.

Conclusion: The new system demonstrated a high level of trueness and accuracy, and low imprecision in INR testing. It can be concluded that the CoaguChek XS system complies with the requirements in chapter 8 of the ISO standard 17593:2007.

© 2008 Elsevier Ltd. All rights reserved.

Introduction

Vitamin K antagonists (VKA) such as warfarin, phenprocoumon and acenocoumarol represent the state-of-the-art drugs in long-term oral anticoagulant therapy (OAT) to prevent thrombosis. Laboratory monitoring of the international normalized ratio (INR) is mandatory to ensure efficacy and safety of VKA in OAT. Ideally a patient should spend the entire time of treatment within the recommended therapeutic target range because the risk of thrombotic or bleeding events increases dramatically when the level of anticoagulation is below or above the INR target range. The benefits of self-testing and self-management in OAT using point-of-care (POC) monitors have been evaluated in a recent meta-analysis which reviewed the available study data in the literature [1]. In nine out of the 14 relevant randomized trials comparing self-monitoring with routine anticoagulation the CoaguChek/CoaguChek S system (Roche Diagnostics, Mannheim, Germany) was used as the POC monitor for patient self-testing [2,3]. Meanwhile these systems are used by more than 200,000 patients worldwide.

The new CoaguChek XS system is the successor of the CoaguChek S system [4–6]. It is designed for use in patient self-testing. The test strips contain a recombinant human thromboplastin with an ISI of 1.0, and the INR scale has been calibrated versus the mean INR of the international reference thromboplastins rTF/95 (human recombinant) and AD149 (rabbit plain) [4]. As part of the system performance verification study, the calibration concept of the system was validated and the reliability of the resulting INR values was confirmed in comparison to the international reference thromboplastins rTF/95 and AD149 at one study center [5]. Moreover a validation of the new system in the hands of lay-users was successfully performed in comparison to the CoaguChek S system [6].

Recently, a new International Standard has been published by the International Organization for Standardization (ISO) entitled: "Clinical laboratory testing and *in vitro* medical devices-Requirements for *in vitro* monitoring systems for self-testing of oral anticoagulant therapy" [7]. This document is concerned with several different aspects of *in vitro*

measuring systems for self-monitoring of VKA therapy, including performance, quality assurance, user training, and procedures for the verification of performance by the intended users under actual and simulated conditions of use.

The goal of the present study was to report the verification of the analytical performance of the new CoaguChek XS system according to the requirements given in chapter 8 ("System performance verification") of the above-mentioned ISO document.

Materials and Methods

Study subjects

Four study sites participated in the study in the time frame from March to June 2005: The Leiden University Medical Center, Department of Thrombosis and Haemostasis, Leiden, The Netherlands (01), The University Hospital, Department of Medicine, Hematology Unit, Valencia, Spain (02), Isala klinieken, Department of Clinical Chemistry, Zwolle, The Netherlands (03), and NB Research, Indianapolis, USA (04). The study has been approved by the institutions' ethical committees. The study subjects received written information and informed consent was given by the study subjects. Subjects could withdraw at any time during the study, but none did. A total of 370 subjects including 73 normal donors and 297 patients on long-term oral anticoagulation therapy using warfarin, phenprocoumon or acenocoumarol were enrolled in the study. From this population a refined data set was generated to meet the requirements of the ISO standard (see below). The demographics of patients and normal donors at each study site for the ISO data set are given in Table 1.

Data set for assessment according to the ISO 17593:2007 standard

The ISO 17593:2007 standard requires a minimum of 200 subjects including 20 normal donors (=10% of the entire data set) [7]. A certain distribution across the INR range up to INR 6 is requested (Table 2). The data collected from the 370 subjects in the study did not meet the requirements of the standard because the fraction of normals exceeded the requested 10% (73 in 370 is ~20%). Therefore a data set of 260 subjects including 26 normal donors (=10% of the subjects) and 234 patients on OAT was prepared from the 370 subjects enrolled in the study in a stepwise procedure:

- 1st step: Exclude all subjects with incomplete data.
- 2nd step: Exclude all patients with INR above 6.
- 3rd step: Exclude normal donors exceeding a proportion of 10% of the remaining subjects.

Table 1 ISO data set: number of study subjects and their demographics

Site	Normal donors	Patients	Mean age (range)	Gender		Indication for anticoagulation ^a (fraction of patients)				
				Female	Male	MHV	AF	TE/Thr	MI	Other
01	7	57	60.7 (21–86)	22 (0.45)	42 (0.55)	4 (0.07)	18 (0.31)	13 (0.23)	9 (0.16)	13 (0.23)
02	5	27	65.1(21–85)	14 (0.44)	18 (0.56)	5 (0.18)	20 (0.74)	1 (0.04)	1 (0.04)	0
03	6	92	63.3(10–87)	30 (0.31)	68 (0.69)	7 (0.08)	46 (0.50)	16 (0.17)	0	23 (0.25)
04	8	58	68.2(24–89)	32 (0.48)	34 (0.52)	8 (0.14)	23 (0.39)	12 (0.21)	3 (0.05)	12 (0.21)
Total	26	234	64.1	98 (0.38)	162 (0.62)	24 (0.10)	107 (0.46)	42 (0.18)	13 (0.06)	48 (0.20)

^a MHV = Mechanical Heart Valve; AF = Atrial Fibrillation; TE/Thr = Thromboembolism / Thrombosis; MI = Myocardial Infarction.

- 4th step: Iteratively exclude subjects from bins in retrograde order until required data distribution across INR range is met. Consequently, this procedure mimics the ISO standard request to fill up bins until required numbers are achieved.

The number of observations (N) in these data is twice the number of samples (n) due to the testing in duplicate for each CoaguChek XS test strip lot.

With the actual data set of 260 subjects all assessments are based on an equal number of observations:

- Entire data set: 260 samples (N=520); 26 normals/234 patients
- All data up to INR 4.5: 236 samples (N=472); 26 normals/210 patients
- Therapeutic INR (2.0–4.5): 199 samples (N=398); 0 normals/199 patients
- Data below INR 2.0: 37 samples (N=74); 26 normals/11 patients

One sample had to be excluded for Neoplastin Plus due to an unexplained obvious outlier result in the laboratory data (site 03, patient nr. 53: INR 8.1; all other thromboplastins INR 2.1 to 2.6). Two samples were missing in the Thromboplastin C Plus data (site 04, patient nrs. 149 and 154).

POC System

The CoaguChek XS system consists of the CoaguChek XS monitor and the CoaguChek XS PT test strips. It uses an electrochemical detection method by applying alternating (AC) and direct current (DC) to the reaction pad of the test strip. The test strip contains a recombinant human thromboplastin and a peptide substrate. The system quantitatively determines the prothrombin time (PT) in INR, % Quick or Seconds using capillary blood from a fingertip or untreated venous whole blood. The required lot specific information is stored on a code chip which comes with each vial of test strips. The code chip must be inserted into the CoaguChek XS monitor.

Moreover the test strip contains an integrated functional control which picks up any mishandling of the test strips due to exposure to humidity and/or elevated temperature and/or light.

If a mishandling is detected the meter will display an "Error QC" message to the user, but no INR result.

Two lots of the CoaguChek XS PT Test strips were used in the study: lot 020 (standard lot, exp. 31-Dec-2005) and lot 022 (2nd reproduction lot, exp. 31-Dec-2005). Both lots had been manufactured according to standard operation procedures and had been calibrated in terms of INR versus a master lot of test strips [4,5].

Each test strip lot was tested in duplicate on two monitors. Monitor sets were changed half-way through the study (sites 01, 03, 04) or day by day (site 02). Thus each strip lot was tested on four different monitors at each site, using a total of eight monitors per site.

In the entire study 32 CoaguChek XS monitors and approximately 3000 test strips were used.

Venous testing procedure

From a venipuncture approximately 10 mL of blood was drawn into a plastic syringe either directly or by means of a butterfly. Blood was transferred into two 4.5 mL Vacutainer tubes (silicized glass, lot 5006351; 105 mmol/L Citrate; Becton-Dickinson, Franklin Lakes, New Jersey, USA) for reference testing. The remaining blood in the syringe was used for dosing the test strips.

Capillary testing procedure

Within 15 minutes of the venipuncture the patients received two consecutive fingerpricks. From each fingerprick two test strips were dosed, one of each test strip lot. It was due to the operator's preference which mode of dosing to choose, either top- or side-dosing of the test strip.

Laboratory testing

At two sites (01 and 02) an additional EDTA tube was filled for haematocrit testing. At site 03 haematocrit determination was performed from citrate blood, at site 04 from capillary blood using the spun haematocrit.

The citrated blood in the Vacutainer tubes was processed to plasma according to the routine procedures of the laboratory. The

Table 2 Distribution of the 260 samples for assessment according to the ISO 17593:2007 standard (ISO data set)

INR range	Target	Achieved	No. of samples
<2.0	10–15%	14%	37 ^a
2.0–2.8	15–40%	30%	77
2.9–3.7	15–40%	31%	80
3.8–4.5	10–30%	16%	42
4.6–6.0	5–10%	9%	24

^a including 26 normal donors=10% of all subjects.

Table 3 Laboratory thromboplastins used for reference testing

Thromboplastin	Manufacturer	Lot no.	Analyzer	ISI	MNPT	ISI calibration
Innovin	Dade-Behring	526909	CA 1500	1.16	10.07 s	local vs rTF/95
Recombiplastin	Hemoliance	N0934137	MLA 1800	0.95	11.43 s	local vs rTF/95
Neoplastin Plus	Stago	655433	STA-R	1.30	13.27 s	manufacturer's
Hepato Quick	Stago	644311	STA-R	0.91	26.04 s	manufacturer's
Thrombotest	Axis Shield	10111491	KC 10	0.99	34.12 s	local vs OBT/79
Thromboplastin C Plus	Dade-Behring	527096	CA 1500	1.82	10.93 s	manufacturer's

remainders of each plasma were frozen in four cryo vials, and stored at or below -70°C . A set of two vials of each frozen sample was shipped to the Leiden lab for reference testing. The remaining two vials were shipped to Roche Diagnostics, Mannheim, saved as spare samples, and discarded after completion of the study.

The frozen plasma samples were analyzed in single determinations using six routinely used laboratory thromboplastins in the laboratory in Leiden. The traceability of the INR is indicated by the route of calibration (manufacturer's ISI, or local ISI assignment at the laboratory in Leiden versus international reference preparations, Table 3). All routes of calibration were performed according to WHO Guidelines [8]. The ISI for Innovin and Recombiplastin were determined locally by direct comparison to the International Standard for Thromboplastin, Human, Recombinant, Plain (coded rTF/95). The ISI for Thrombotest was determined locally by direct comparison to the International Reference Preparation, Bovine, Combined (coded OBT/79). For three other thromboplastins, the manufacturer's stated ISI were used.

Statistical Analysis

Imprecision of the CoaguChek XS test strips was calculated from the duplicate determinations for whole blood and is expressed as coefficient of variation (CV) including the upper confidence limit (ul) through the standard deviation according to paragraph 8.4.4.2 of the ISO standard 17593:2007 [7]:

$$sd_{t/r} = \sqrt{\frac{1}{2n} \sum_{i=1}^n (x_{1i} - x_{2i})^2}$$

(Calculation of the standard deviation [SD] from duplicates)

$$ul(\sigma_{t/r}^2) = \frac{n \cdot sd_{t/r}^2}{\chi_{n-2}^2}$$

$$ul(\sigma_{t/r}) = \sqrt{ul(\sigma_{t/r}^2)}$$

- CV = SD/grand mean (Grand mean is the arithmetic mean of all INR measurements)
- ul of CV = ul(σ)/grand mean

Trueness and accuracy in comparison to the reference thromboplastins were assessed according to the criteria fixed in the ISO 17593:2007 standard. Trueness means the closeness of agreement between the average value obtained from a large series of measurement results and an accepted reference value [7]. A measure of trueness is bias. The bias versus the reference method in the INR range 2.0–4.5 shall be ≤ 0.3 INR. Furthermore, the bias in the INR range 4.5–6.0 was calculated.

For OAT monitoring systems, accuracy is measured by the extent to which measurements of blood samples from different patients agree with INR values traceable to a thromboplastin International Reference Preparation [7]. More than 90% of the differences to the reference shall be within ± 0.5 INR in the INR range below 2 INR, or within $\pm 30\%$ in the INR range between 2.0 and 4.5 INR. Furthermore, the percentage of the differences within $\pm 20\%$ and $\pm 10\%$ were calculated.

Regression analysis between the CoaguChek XS PT test (y) and the reference thromboplastins (x) was performed after the method of Passing-Bablok [9] using the entire ISO data set including samples with INRs up to 6 as requested in the ISO standard (§8.5.8.3). Bland-Altman difference plots [10] were generated for the comparisons of CoaguChek XS PT test with a reference thromboplastin.

For comparison of data from capillary versus venous blood on the POC system the ISO standard requests a slope within 0.95 to 1.05 and an intercept between ± 0.1 INR in regression analysis.

Regression analysis was again performed after the method of Passing-Bablok [9], which gives an assessment of agreement of methods. The 95% confidence interval (CI) of the slope and the intercept, and the coefficient of correlation (r) were calculated. Deviation from the linearity was checked using the Cusum test [9,11]. Additionally Bland-Altman plots (BA) [10] were generated using the data of patients on oral anticoagulation only. The bias of the data in the BA plots is given in INR as a measure of trueness, and the solid lines show the lower and upper limits of agreement ($\pm 2SD$; LL and UL).

All statistical analysis was performed using the EASY-Software package, provided by Roche Diagnostics.

All error messages were recorded by the operators in this study, and evaluated in terms of user satisfaction and handling aspects. An error rate of less than 5% was deemed acceptable.

Table 4 Assessment of the trueness of CoaguChek XS INR results versus laboratory thromboplastins according to ISO 17593:2007

Trueness	Test strip lot	Thromboplastin					
		1	2	3	4	5	6
N (199 patients)(2.0–4.5 INR)		398	398	396	398	398	394
mean INR		3.24 INR	3.09 INR	2.90 INR	3.00 INR	3.12 INR	3.27 INR
bias (venous)	lot 020	−0.16 INR	−0.01 INR	0.18 INR	0.08 INR	−0.04 INR	−0.19 INR
	lot 022	−0.16 INR	−0.02 INR	0.18 INR	0.08 INR	−0.04 INR	−0.20 INR
bias (capillary)	lot 020	−0.19 INR	−0.04 INR	0.15 INR	0.05 INR	−0.07 INR	−0.22 INR
	lot 022	−0.18 INR	−0.03 INR	0.16 INR	0.06 INR	−0.06 INR	−0.21 INR

Valid for Tables 4 and 5: 1 = Innovin 2 = Recombiplastin 3 = Neoplastin Plus 4 = Hepato Quick 5 = Thrombotest 6 = Thromboplastin C Plus.

Table 5 Assessment of the accuracy of CoaguChek XS INR results versus laboratory thromboplastins according to ISO 17593:2007 (all data with INR \leq 4.5)

Accuracy	Test strip lot	Thromboplastin					
		1	2	3	4	5	6
N (26 normals/210 patients)(\leq 4.5 INR)		472	472	470	472	472	468
within \pm 30% or 0.5 INR (venous)	lot 020	100%	99.6%	98.1%	97.2%	98.7%	99.8%
	lot 022	100%	100%	98.7%	97.7%	98.9%	99.8%
within \pm 30% or 0.5 INR (capillary)	lot 020	99.8%	100%	98.1%	97.2%	98.9%	99.8%
	lot 022	99.6%	99.8%	98.5%	98.1%	99.2%	99.6%
within \pm 20% or 0.5 INR (venous)	lot 020	95.6%	97.2%	91.5%	93.9%	94.9%	95.3%
	lot 022	97.7%	99.4%	94.0%	94.9%	95.1%	97.4%
within \pm 20% or 0.5 INR (capillary)	lot 020	95.1%	97.9%	92.3%	93.2%	93.9%	95.1%
	lot 022	97.0%	98.3%	94.3%	93.3%	94.3%	95.5%
within \pm 10% or 0.3 INR (venous)	lot 020	70.8%	75.8%	72.1%	69.9%	68.4%	68.6%
	lot 022	73.5%	82.6%	72.8%	72.5%	72.0%	69.9%
within \pm 10% or 0.3 INR (capillary)	lot 020	66.1%	72.7%	73.8%	70.6%	69.7%	62.0%
	lot 022	70.3%	76.3%	73.2%	69.1%	67.6%	65.8%

Concerning the on board functional control of the test strips additional awareness was focused on the "Error QC" message. It was assumed that all test strips were handled according to given instructions and no "Error QC" should be expected. From these data the rate of falsely positive "Error QC" messages was calculated. A rate of equal or less than 4% was deemed acceptable.

Results

Trueness and accuracy according to the ISO 17593:2007 standard

Table 4 shows the bias between the CoaguChek XS INR measurement and the laboratory INR for each of the six different

thromboplastin reagents, for the 199 patients with INR within the therapeutic range (INR 2.0–4.5). The bias was calculated for two test strip lots and for both venous and capillary blood samples. All bias values were found within the ISO acceptance limits of \pm 0.3 INR. Bias values calculated for the 24 patients with INRs between 4.5 and 6.0, ranged from -0.57 INR to 0.91 INR. It should be noted that the ISO document does not list performance criteria for trueness and accuracy in the INR interval of 4.5 to 6.0.

Table 5 shows the accuracy of the CoaguChek XS INR expressed as the percentage of measurements for which the difference to a given reference thromboplastin was within the ISO limits of \pm 0.5 INR or \pm 30%. For venous and capillary blood samples more than 97% of all INR differences were found within these combined acceptance limits.

The ISO standard requests to give the percentage of observations for which the differences to a given reference throm-

Table 6 Results of the regression analysis of the CoaguChek XS PT test versus reference thromboplastins

Reference thromboplastin (x)	CoaguChek XS PT lot (y)	Blood sample on CoaguChek XS PT test	N	r	Slope	Intercept
Innovin	lot 020	venous	520	0.960	0.91	0.13
		capillary	520	0.956	0.88	0.16
	lot 022	venous	520	0.970	0.89	0.16
		capillary	520	0.961	0.88	0.17
Recombiplastin	lot 020	venous	520	0.959	1.05	-0.14
		capillary	520	0.956	1.04	-0.10
	lot 022	venous	520	0.969	1.04	-0.09
		capillary	520	0.960	1.03	-0.09
Neoplastin Plus	lot 020	venous	518	0.961	1.26	-0.50
		capillary	518	0.958	1.21	-0.42
	lot 022	venous	518	0.970	1.23	-0.42
		capillary	518	0.961	1.22	-0.42
Hepato Quick	lot 020	venous	520	0.941	1.19	-0.42
		capillary	520	0.940	1.15	-0.36
	lot 022	venous	520	0.950	1.15	-0.35
		capillary	520	0.940	1.15	-0.36
Thrombotest	lot 020	venous	520	0.946	1.08	-0.25
		capillary	520	0.944	1.05	-0.18
	lot 022	venous	520	0.951	1.05	-0.16
		capillary	520	0.942	1.04	-0.14
Thromboplastin C Plus	lot 020	venous	516	0.961	0.93	0.05
		capillary	516	0.956	0.90	0.10
	lot 022	venous	516	0.967	0.91	0.12
		capillary	516	0.958	0.90	0.11

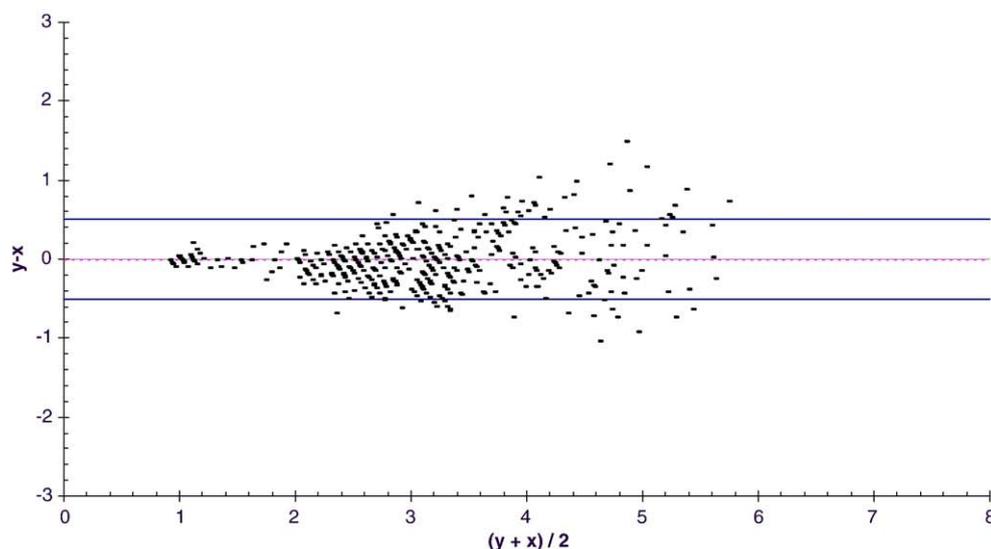


Figure 1 Method comparison of CoaguChek XS PT, lot 020, capillary blood (y) versus Recombiplastin (x) in INR (Bland Altman plot); ISO data set of 260 samples; N=520; bias=-0.02 INR (stippled horizontal line); solid horizontal lines represent +/-0.5 INR limits.

boplastin were within +/-20% limits. These percentages were at least 91.5% and 92.3% for the venous and capillary blood samples, respectively (Table 5).

Furthermore the ISO standard requests to give information on the +/-10% (or +/-0.3 INR below an INR of 2) differences from the reference thromboplastins. Within these limits between 60% and 80% of the observations were found (Table 5).

Table 6 shows the results of the regression analysis between the CoaguChek XS INR and the INR obtained with each one of the reference thromboplastins. The slopes of the regression lines ranged from 0.88 to 1.26 with intercepts between -0.50 to 0.17 and coefficients of correlation r from 0.940 (vs. Hepato Quick) to 0.970 (vs. Innovin and Neoplastin Plus).

Fig. 1 shows a plot of the differences in INR between the CoaguChek XS and Recombiplastin against the mean INR of the two measurements, for the entire data set of 520 observations. In this plot the observations with capillary blood with CoaguChek XS strip lot 020 were used. Up to a mean INR of 2.0 the differences were less than 0.3 INR, and up to a mean INR of 2.3 the differences were less than 0.5 INR. For the entire set of 520 observations the bias was only -0.02 INR.

The haematocrit values of the samples were in the range from 26% to 54% thus covering the range 35% to 50% required by the ISO standard. The specified haematocrit range for the CoaguChek XS system is given from 25% to 55% in the package insert.

Imprecision in venous and capillary blood testing

From the duplicate determinations on each sample with both lots of test strips imprecision CVs were calculated for venous and capillary blood testing. Since two different CoaguChek monitors were used for the determination of duplicate measurements, the CVs still include a monitor to monitor bias. From other studies it could be concluded that the monitor to monitor bias is negligible (between monitor CV ~0.3%; Roche internal data, not shown). The CVs were calculated for two data sets, i.e. for normal donors only, and for patients in the therapeutic range (INR 2.0–4.5). The CVs are shown in Table 7. The CVs from capillary blood in the therapeutic range of patients were 3.9% and 4.0% for strip lots 020 and 022 respectively. The CVs from venous blood in the therapeutic

range of patients were 2.5% and 2.0%, respectively. All upper confidence limits (ul) of the CVs were less than 4.5%.

Comparison of INR results from capillary blood with INR results from venous blood

Regression analysis of capillary versus venous blood INRs measured with the CoaguChek XS system was performed on the combined data of all study sites for the normal donors and the patients in the INR range up to 4.5. In this case patient data were selected based on the INRs determined with Recombiplastin, independently of the CoaguChek XS INR measurements. Table 8

Table 7 Imprecision coefficients of variation for venous and capillary blood testing

	CoaguChek XS			
	Lot 020		Lot 022	
	Normals	Therapeutic range	Normals	Therapeutic range
<i>Venous blood</i>				
n	73	204	73	204
SD	0.033	0.077	0.022	0.062
<i>ul of SD</i>	0.038	0.084	0.026	0.067
grand mean	1.02	3.11	1.03	3.10
CV	3.2%	2.5%	2.1%	2.0%
<i>ul of CV</i>	3.8%	2.7%	2.5%	2.2%
<i>Capillary blood</i>				
n	70	204	71	202
SD	0.029	0.120	0.030	0.123
<i>ul of SD</i>	0.034	0.131	0.036	0.134
grand mean	1.03	3.08	1.03	3.08
CV	2.9%	3.9%	3.0%	4.0%
<i>ul of CV</i>	3.3%	4.2%	3.5%	4.4%

Table 8 CoaguChek XS comparison of capillary versus venous blood INR results

Lot	N(INR <4.5 including normals)	r	Slope	Slope CI	Intercept	Intercept CI
020	640	0.991	1.000	1.000–1.000	0.000	0.000–0.000
022	641	0.992	1.000	1.000–1.000	0.000	0.000–0.000

shows the regression lines for both lots of test strips. Slopes and intercepts for both lots were 1.00 and 0.00, respectively, and correlation coefficients were greater than 0.99.

Figs. 2 and 3 show differences in INR between capillary and venous blood versus the mean INR, for strip lots 020 and 022, respectively. In these figures, data from all patients in the measuring range of the CoaguChek XS system up to INR 8.0 were used, excluding the normal donors. The bias (i.e. mean INR difference) was less than 0.05 for both strip lots.

Error rate in CoaguChek XS PT testing

No "ERROR QC" message was detected in the approximately 3000 determinations on the CoaguChek XS system in the course of this study.

The rate of other types of error was very low. Forty-five error messages were recorded in the data sheets, four in venous blood testing and 41 in capillary blood testing. The total error rate was 1.5%, in venous testing 0.3% and in capillary testing 2.7%. Mainly "ERROR 5" occurred in capillary blood testing ("not enough blood") at a rate of 2.2% (33 out of ~1500 determinations). "ERROR 6" ("test error") was observed in 8 cases (6 in capillary testing, 2 in venous testing). No instrument related error messages ("ERROR 8") were observed.

No "ERROR 7" message occurred meaning that all patient samples gave clotting times within the detection phase for clotting of the CoaguChek XS system. As long as the system detects a clot the INR > 8 message will be displayed when the result is above the measuring range. If a patient has a very high INR (INR > 10) no clotting will be detected by the meter, and an "ERROR 7" message displayed. In this case the user manual advises the patient to contact a doctor to receive a laboratory PT test to verify the high INR.

Discussion

This paper is limited to one, albeit important aspect of the ISO 17593:2007 standard, i.e. the system performance verification of a POC monitor for PT testing. Our paper is the first to report an analysis of performance of the CoaguChek XS system according to the criteria given in chapter 8 of the ISO 17593:2007 standard.

The CoaguChek XS system contains a recombinant human tissue factor reagent to trigger thrombin generation. In general, agreement between measurement systems is better if they are more similar with regard to the reagent composition. In the like-versus-like comparisons of the CoaguChek XS system with the recombinant human thromboplastins Innovin and Recombiplastin all criteria were met, since the bias (as a measure of trueness) was in the range from -0.19 INR to -0.01 INR (Table 4), and the accuracy was highly acceptable because more than 99% of the differences were within the ± 0.5 INR or $\pm 30\%$ limits (for the INR range below 2.0, and for the range between 2.0 and 4.5, respectively; see Table 5). Even when applying the more stringent $\pm 20\%$ limits (INR range between 2.0 and 4.5 INR) more than 95% of the differences were observed within these limits. Also in comparison with

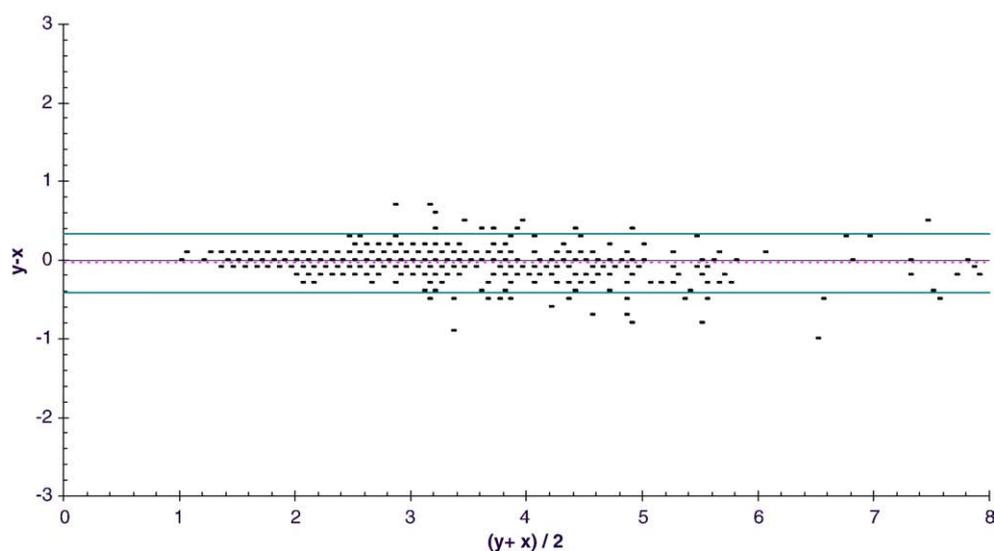


Figure 2 Method comparison of capillary versus venous blood for CoaguChek XS lot 020 (Bland Altman plot); y: capillary blood [INR]; x: venous blood [INR]; all patients without normal donors; N=568; bias=-0.04 INR (stippled horizontal line); horizontal solid lines indicate lower and upper limits of agreement (LL and UL, respectively); LL=-0.42 INR; UL=0.33 INR.

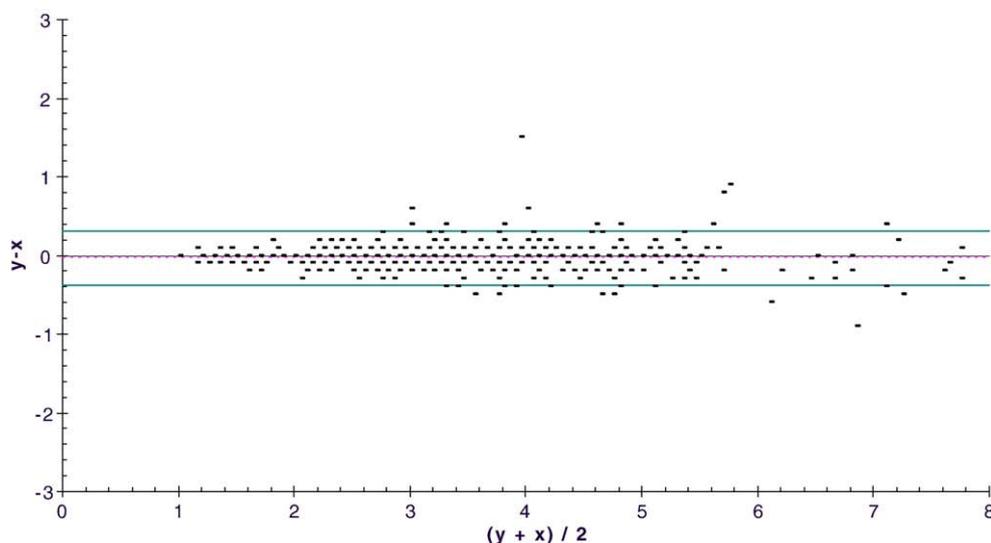


Figure 3 Method comparison of capillary versus venous blood for CoaguChek XS lot 022 (Bland Altman plot); y: capillary blood [INR]; x: venous blood [INR]; all patients without normal donors; N=575; bias=-0.03 INR (stippled horizontal line); horizontal solid lines indicate lower and upper limits of agreement (LL and UL, respectively); LL=-0.38 INR; UL=0.32 INR.

the other four non-human laboratory thromboplastins the ISO 17593:2007 criteria were met, since bias between the CoaguChek XS PT test and these four thromboplastins was observed from -0.22 INR to 0.18 INR, and more than 97% of the differences were within the ± 0.5 INR or $\pm 30\%$ limits. Duplicate testing showed very low imprecision with CV below 4.5% in capillary blood and below 3.5% in venous blood (Table 7). The imprecision of the CoaguChek XS appears to be slightly lower than that of the CoaguChek S as reported previously [6,12].

There was no significant deviation between results from capillary with those from the corresponding venous blood samples on the CoaguChek XS system. The regression lines were found equal to the line of identity. These findings demonstrate the equivalence of venous and capillary blood according to the criteria of the ISO 17593:2007 standard.

The error rate in this investigation was rather low (overall 1.5%). The system proved to be reliable and robust. The on-board control worked well by not giving false "Error QC" messages in properly stored and handled test strips.

We conclude that the CoaguChek XS system appears to be a major step forward concerning performance, on-board functional control and reliability in point-of-care coagulation testing to monitor oral anticoagulation therapy, especially when considering its use in patient self-testing. It complies with the requirements of chapter 8 in the ISO 17593:2007 standard.

Conflict of interest disclosure

Winfried Plesch and Tanja Wolf are employees of Roche Diagnostics GmbH, Mannheim, Germany, which is the manufacturer of the CoaguChek XS system.

This study was sponsored by Roche Diagnostics GmbH, Mannheim.

COAGUCHEK is a trademark of Roche.

Acknowledgements

Martha Hoekstra and Evelina Witteveen for performing the laboratory reference testing.

References

- [1] Heneghan C, Alonso-Coello P, Garcia-Alamino JM, Perera R, Meats E, Glasziou P. Self-monitoring of oral anticoagulation: a systematic review and meta-analysis. *Lancet* 2006;**367**: 404–11.
- [2] van den Besselaar AMHP, Breddin K, Lutze G, Parker-Williams J, Taborski U, Vogel G, et al. Multicenter evaluation of a new capillary blood prothrombin time monitoring system. *Blood Coagul Fibrinol* 1995;**6**:726–32.
- [3] Plesch W, Klimpel P. Performance evaluation of the CoaguChek S system. *Haematologica* 2002;**87**:557–9.
- [4] Leichsenring I, Plesch W, Unkrig V, Kitchen S, Kitchen DP, Maclean R, et al. Multicentre ISI assignment and calibration of the INR measuring range of a new point-of-care system designed for home monitoring of oral anticoagulation therapy. *Thromb Haemost* 2007;**97**:856–61.
- [5] Plesch W, van den Besselaar AMHP: Validation of the international normalized ratio (INR) in a new point-of-care system designed for home monitoring of oral anticoagulation therapy. *INT J Lab Haematol* in press.

- [6] Braun S, Watzke H, Hasenkam M, Schwab M, Wolf T, Dovifat C, et al. Performance evaluation of the new CoaguChek XS system compared with the established CoaguChek system by patients experienced in INR-self management. *Thromb Haemost* 2007;**97**:310–4.
- [7] ISO 17593:2007 standard, 1st edition, 2007-04-15: Clinical laboratory testing and in vitro medical devices-Requirements for in vitro monitoring systems for self-testing of oral anticoagulation therapy.
- [8] World Health Organization Expert Committee on Biological Standardization. Guidelines for thromboplastins and plasma used to control oral anticoagulant therapy. *WHO Technical Report Series* 1999;**889**:64–93.
- [9] Passing H, Bablok W. A new biometrical procedure for testing the equality of measurements from different analytical methods, Part I. *J Clin Chem Clin Biochem* 1983;**21**:709.
- [10] Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986;**1**:307–10.
- [11] Page ES. Control charts with warning lines. *Biometrika* 1955;**42**:243.
- [12] Attermann J, Andersen NT, Korsgaard H, Maegaard M, Hasenkam JM. Precision of INR measured with a patient operated whole blood coagulometer. *Thromb Res* 2003;**110**: 65–8.