

“I know my value”

A middle-aged man with short brown hair, wearing a light blue button-down shirt, is holding a white rectangular sign. The sign has the number "2.6" written on it in a dark blue, cursive-style font. He is looking directly at the camera with a neutral expression. The background is a blurred pharmacy or laboratory setting with shelves of bottles.

*Accuracy and precision in oral
anticoagulation monitoring*

Coagulation measurements can vary for different reasons

INR allows for direct comparison of measured values

There is a natural variation in the response of patients towards anticoagulation therapy with vitamin K antagonists (VKAs). One study has shown that biological variation of the International Normalized Ratio (INR) within patients treated with VKAs is between 9.1% and 10.9% (coefficient of variation [CV], in %).¹

In addition to this natural variation, which cannot be influenced, measurement deviations can also be caused by external factors. These can lead to differences between measurements from different laboratories or between measurements performed with the CoaguChek® system and the lab. These deviations may be due to different sensitivities of the reagents used, different pre-analytics methods, or variations in the calibration of laboratory reagents (determination and consideration of the deviation of a reagent/instrument to a reference).²

Figure 1 shows an example of differences in coagulation values obtained using different measurement methods.

CoaguChek XS	Innovin	Recom-biplastin	Thrombotest	Neoplastin plus	Hepato Quick	Thrombo-plastin C Plus	Min	Max	Diff (max-min)
2.1	2.40	2.33	1.99	2.25	2.25	2.40	1.99	2.40	0.42
2.5	3.02	2.78	2.91	2.68	3.00	2.89	2.50	3.02	0.52
3.0	3.56	3.00	2.76	3.18	3.09	3.25	2.76	3.56	0.80

Fig. 1: INR values obtained using different measurement methods (CoaguChek XS and different laboratory thromboplastins) within a defined INR range of 2.0–3.0. Source: Roche Diagnostics GmbH, CoaguChek XS Evaluation Study³

Theoretically, coagulation values can be reported as either % Quick, seconds or INR units.

The use of INR allows direct comparison of measured values, because the reagents used for measuring the prothrombin time (PT) are calibrated by a well-defined procedure and designated with a specific index called the International Sensitivity Index (ISI).⁴ The ISI value indicates the degree of compliance to World Health Organization (WHO) reference thromboplastin, whereby an ISI of 1.0 means that the reagent has the same sensitivity as reference thromboplastin.⁴

Due to the lack of standardisation, % Quick values measured with different reagents cannot be compared. Societal guidelines, such as those issued by the American College of Chest Physicians (ACCP),⁵ provide recommendations based upon INR values. Patients are provided with a target INR range by their physician, and ideally their measured INR should stay within this therapeutic range for as long as possible in order to reduce the risk of vascular events and major hemorrhage. However, coagulation values measured in INR units are still susceptible to measurement deviations caused by external factors.

The use of INR allows direct comparison of measured values because reagents are calibrated by a well-defined procedure and designated with an ISI value that indicates the degree of compliance to WHO reference thromboplastin⁴



Three external factors can contribute to measurement deviations

Reagent sensitivity, pre-analytcs, and calibration

The causes of measurement deviations can generally be assigned to three categories: differences in the sensitivities of the reagents; pre-analytcs errors; and calibration errors.²

I) Reagent sensitivity

A high degree of comparability between INR values is achieved through calibration and standardisation to ISI. However, the reagents have different sensitivities to the activities of the clotting factors that are influenced by VKAs. Experience has shown that reagent sensitivity is heavily dependent on various factors:

- The source of thromboplastin used (e.g. rabbit, bovine or human)⁶
- Phospholipids contained in the thromboplastin (e.g. natural mixture or synthetically produced)⁷
- The reagent composition (e.g. with/without stabilisers and/or glycine; an aqueous or dry chemical substance)⁶
- The sample (e.g. whole blood or plasma, undiluted or diluted)⁸

Each reagent is unique – there are no two reagents with absolutely the same properties. Even two WHO reference thromboplastins show a certain degree of deviation, which is larger for higher INR values (Figure 2).

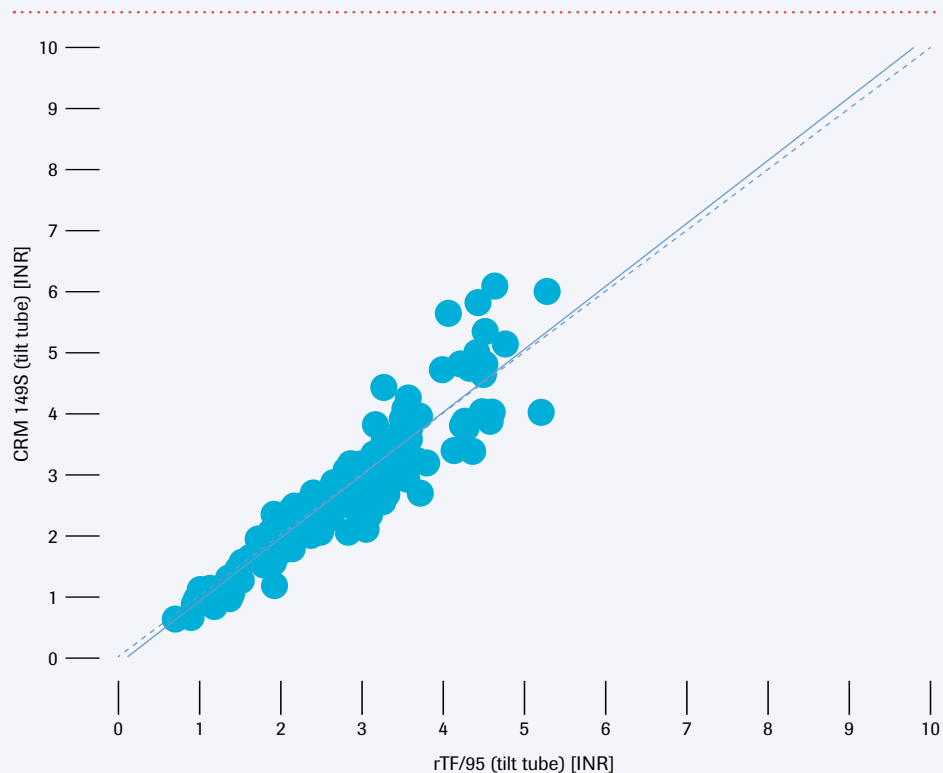


Fig. 2: Comparison of two reference thromboplastins (rTF/95 and CRM 149S).
Source: Roche Diagnostics GmbH, CoaguChek XS Evaluation Study;³ n = 273



II) Errors in pre-analytics

Pre-analytics includes all steps that are performed prior to measurement using a point-of-care (POC) system (e.g. CoaguChek) or in the laboratory. Several sources of error can affect measurement results at these steps.

Experience has shown that when measuring with the CoaguChek system, attention must be paid to the following:

- The puncture site should be sufficiently dried if it had been disinfected with alcohol
- Hands should be sufficiently dried after washing and dried if sweaty (e.g. due to fear of pricking)
- The time elapsed between pricking and sampling should not be too long
- If an additional measurement is required, blood should be taken from a different puncture site
- The finger should not be excessively squeezed around the puncture site. This increases the risk of contamination and false results due to thromboplastin from the tissue

Venous blood samples to be used in laboratory tests also show a number of potential error sources:⁹

- Secondary venous access (e.g. back of hand). Blood sampling from the back of the hands or feet is generally more difficult than obtaining a fingerprick blood sample and can lead to coagulation activation, for example if repeated pricking occurs
- Wrong needle size. If the needle diameter is too small, this can lead to activation of coagulation, especially in case of rapid withdrawal of the sample
- Venous stasis due to blocking of blood circulation for too long
- Incorrect sampling tubes, wrong sequence of blood collection
- Wrong blood volume leading to false citrate/blood ratio (tubes must be at least 80% full)
- Insufficient mixing of sample
- Too high proportion of platelets due to inappropriate centrifugation
- Impairment of sample stability, improper storage (activation of factor VIIa)
- Hemolytic, lipemic or coagulated samples
- Evaporation of the sample caused by long queuing in the automated analyser

III) Errors in the calibration of laboratory reagents

Manufacturers of laboratory reagents provide an ISI for their reagent lots, which is based on a specific reagent-analyser combination. Most users have no way to check the specified ISI or to determine it for their system. At both levels – manufacturer or user calibration – experience has shown that there are several potential sources of error.

- The mean normal value, in seconds, which is used by the laboratory to calculate the INR, may change or may have been determined incorrectly
- Deviations may occur when laboratory reagents need to be recalibrated, thereby changing the ISI
- Deviations can be caused by different calibration methods

In general, INR differences between POC devices such as CoaguChek® systems and laboratory systems are of the same order of magnitude as those observed between various laboratory systems¹⁰

Experience has shown that measurement deviations are generally observed between different coagulation measurement systems, independently of whether POC or laboratory



INR differences between CoaguChek and the laboratory are normal

Between-laboratory measurement differences are of similar magnitude



In general, INR differences between POC devices such as CoaguChek systems and laboratory systems are of the same order of magnitude as those observed between various laboratory systems.¹⁰ There are no specific measurement differences between the CoaguChek system and the laboratory. Measurement deviations are generally observed between different coagulation measurement systems, independently of whether POC or laboratory.

The following points generally apply to measurement deviations:

- Deviations are more common in patients with unstable anticoagulation, in whom coagulation factors are even more variable. In addition, the likelihood of measurement differences is increased further by different reagents sensitivities
- In general, the higher the INR, the greater the possible deviations may be:¹¹
 - INR below 2.5: possible deviation 0.1 – 0.3 INR
 - INR 2.5 – 4.5: possible deviation 0.5 – 1.0 INR
 - INR above 4.5: possible deviation 1.0 – 2.0 INR
- In cases of differences between values obtained using laboratory systems and CoaguChek devices, check whether a systematic offset exists between the CoaguChek device and the specific laboratory. A systematic measurement offset against one laboratory method does not mean that the measured value offset will exist against other laboratory methods
- It should be noted that for patients taking VKAs with previously stable therapeutic INRs who present with a single out-of-range INR of ≤ 0.5 below or above therapeutic, recent guidelines suggest continuing the current dose and testing the INR within 1 to 2 weeks¹²
- In case of unclear readings, it is advisable to not change between systems

What to do if therapeutically relevant differences occur

A simple decision algorithm

In situations where a therapeutically relevant difference in INR values is obtained between a CoaguChek® device and the laboratory, the suggested Roche algorithm below (Figure 3) can help physicians to determine the possible error source(s).

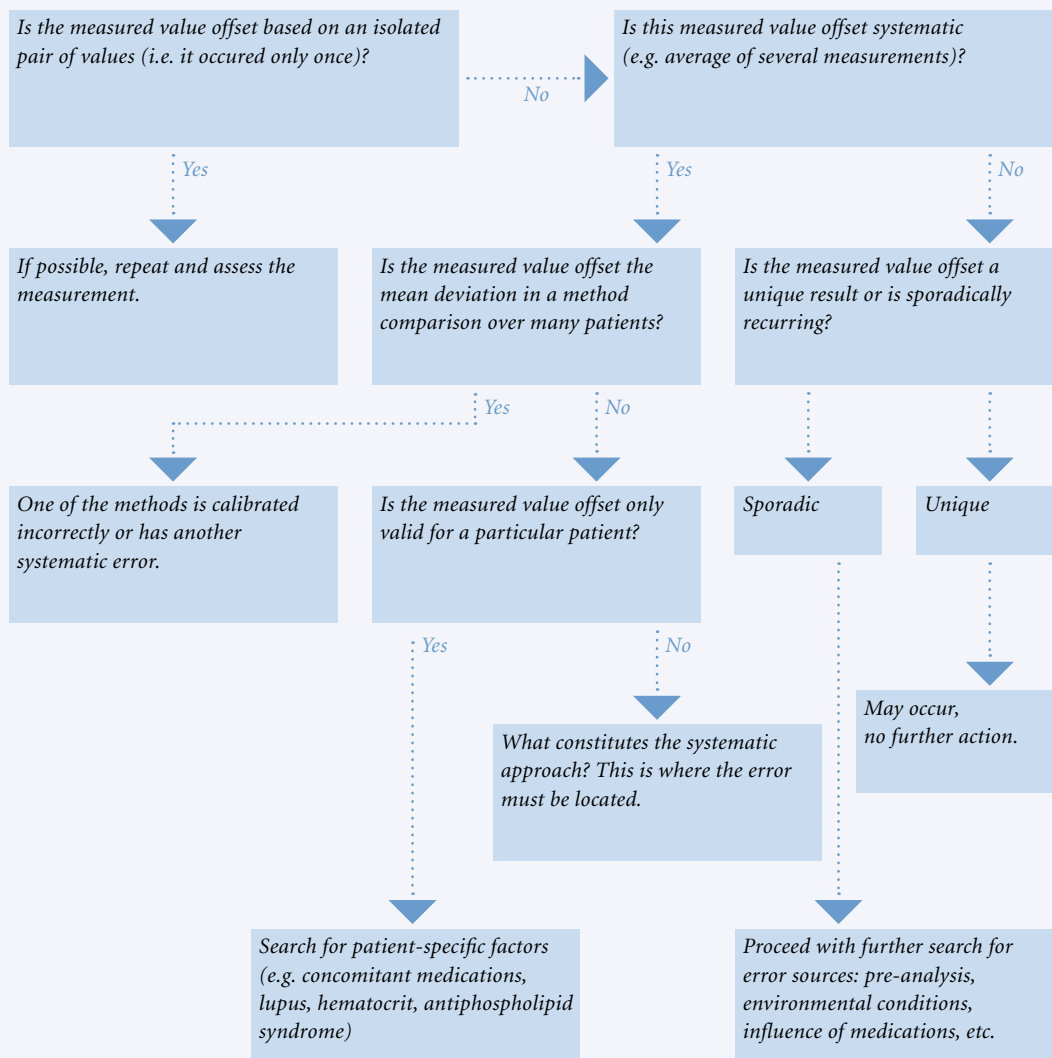


Fig. 3. Suggested Roche algorithm for determining the error source of a measured value offset; for example, a laboratory INR value of 2.3 and a CoaguChek INR value of 3.6.

When differences are observed between INR values measured using laboratory systems and CoaguChek devices, check whether a systematic offset exists between the CoaguChek device and the specific laboratory

A systematic measurement offset against one laboratory method does not mean that the measured value offset will exist against other laboratory methods



The CoaguChek[®] XS system

Providing patients and their physicians with quality, reliable results

Excellent performance: high correlation, high accuracy and high precision

The performance of the CoaguChek XS system has been verified in a study conducted at four study centres, using venous and capillary blood samples on two CoaguChek XS PT Test Strip lots.¹³ Laboratory testing was performed on frozen plasma samples with six commercial thromboplastins. Results were assessed using a refined data set of 260 subjects according to the International Organization for Standardization (ISO) 17593:2007 standard.¹⁴

- **High correlation.** For patient samples in the therapeutic range (INR 2.0 – 4.5), each of the two test strip lots met the ISO acceptance limits of ± 0.3 INR (bias -0.19 to 0.18 INR)
- **High accuracy.** For patient samples with an $\text{INR} \leq 4.5$, more than 97% of all INR differences to a reference thromboplastin were found within the combined ISO acceptance limits of ± 0.5 INR or $\pm 30\%$
- **High precision.** For patient samples with an $\text{INR} \leq 4.5$, the CV for INR imprecision ranged from 2.0% to 3.2% in venous blood testing, and from 2.9% to 4.0% in capillary blood testing (all upper confidence limits of the CVs were $< 4.5\%$)

In another study, a 4-year examination of External Quality Assessment (EQA) for INR tests using CoaguChek XS and CoaguChek XS Plus systems indicated that the quality of results as indicated by inter-site variability is similar among POC sites as for hospital laboratories.¹⁰

Calibrated to WHO guidelines for reliability

CoaguChek XS PT test strips are manufactured with a human recombinant tissue factor and have been assigned an ISI of 1.0¹⁵ according to the WHO guidelines for thromboplastins and plasmas used to control anticoagulant therapy.⁴ The validity of the CoaguChek XS calibration concept has been demonstrated¹⁶ and is explained in Figure 4.

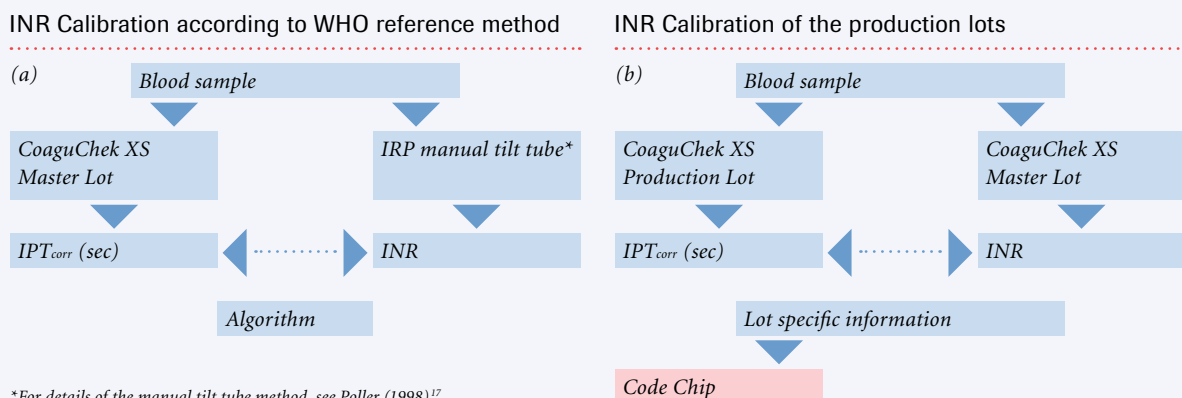


Fig. 4: (a). A master lot of test strips is directly calibrated by comparison with international reference preparations (IRP) and represents the manufacturer's working standard. (b). Further calibration in routine manufacturing of test strips is performed versus this master lot using whole blood samples from patients on oral anticoagulation and from normal donors.¹⁸ INR: International Normalized Ratio; IPT_{corr}: instrument PT (clotting time measured by the system corrected for hematocrit)

Equivalent performance across all CoaguChek XS systems

Equivalence has been demonstrated between INR results determined using the CoaguChek XS system and INR results determined using the CoaguChek XS Plus system.¹⁹ For three test strip lots, the maximum mean bias between the CoaguChek XS system and the CoaguChek XS Plus was 0.03 INR for samples below an INR of 2.0, and 0.07 INR for samples in the therapeutic range of oral anticoagulation therapy (INR 2.0 – 4.5).¹⁹

The equivalence of the CoaguChek XS Pro and CoaguChek XS Plus systems has also been demonstrated over the whole hematocrit range, meeting the acceptance criteria for all blood samples.²⁰

Additional quality features

The CoaguChek XS system also has the following additional features to ensure outstanding quality:

- **Integrated Quality Control system.** A separate chemical pathway detects deterioration of the strip chemistry due to exposure to humidity, heat, or light.¹⁸ As a result, no liquid quality control is needed in a CLIA-waived environment
- **Hematocrit correction.** INR results are corrected for hematocrit within the range of 25 – 55 %, allowing a broad range of patients to be measured with one device¹⁸
- **Hemolysis insensitivity.** INR results are insensitive to hemolysis up to 1,000 mg/dL²¹
- **Heparin insensitivity.** Test strips include an anti-heparin agent that has been added to neutralise the effects of heparin found in blood samples applied to the test strip. INR results are unaffected by unfractionated heparin up to 1 U/mL and LMW heparin up to 2 U/mL¹⁸

In summary, the CoaguChek XS system from Roche provides patients and their physicians with accurate and precise INR testing through careful calibration to international standards, ensuring quality, reliable results every time.



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