# Performance Evaluation of the Coag-Sense® Prothrombin Time PT/INR Monitoring System

## Introduction

Oral anticoagulant therapy (OAT) using warfarin (Coumadin®) has surged in recent years due to an increased number of indications and its demonstrated effectiveness.[1] The primary means of monitoring the response to warfarin is the Prothrombin Time (PT) test, which is measured in seconds.[2,3] The increased use of OAT has led to the development of point-of-care (POC) portable monitoring devices designed to use a capillary sample of whole blood for PT determination.[1]

PT test results can vary widely depending on the method of clot detection and the thromboplastin reagent used.[2] For that reason the World Health Organization (WHO), in conjunction with the International Committee for Standardization in Haematology and the International Committee on Thrombosis and Haemostasis (ICSH/ICTH), developed a measure of coagulation called the International Normalized Ratio (INR).[3] The INR is a mathematical calculation that corrects for the variable sensitivities of thromboplastin reagents.

The Coag-Sense® Prothrombin Time (PT)/INR Monitoring System (Coag-Sense® PT/INR System) is a novel in vitro diagnostic device that provides quantitative PT results, reported in PT seconds and INR units. It is the first portable monitoring device capable of directly detecting a clot using fresh capillary whole blood obtained from a fingerstick or recalcified plasma. All other currently marketed POC devices utilize a secondary means of clot detection, such as detecting changes in current across the sample or pressure as the sample moves through a restricted capillary. Direct clot detection reduces the possibility of interference from blood constituents not involved in clot formation including changes in hemoglobin and hematocrit levels. This is particularly important in the high INR range when the clot is reduced and its characteristics change.

The purpose of this study was to compare INR values obtained using the Coag-Sense® PT/INR System with those obtained using the WHO tilt-tube reference method, which is the recognized “gold standard,”[4] as well as traditional plasma-based core laboratory systems, in a population of patients on long-term anticoagulation.

## Materials and methods

The study was conducted by Haemostasis Reference Laboratory, Inc. (HRL) in Ontario, Canada. Study participants were receiving long-term OAT with target INR values between 2 and 4. Non-anticoagulated subjects were also included in the study to verify the calculation of the INR values.[3]

Venous samples to be used for analysis were collected in two separate tubes after a discard tube. The first was a plastic tube containing no anticoagulant. Whole blood from this tube was immediately applied to two different Coag-Sense® PT/INR System to obtain duplicate INR results. The second tube contained 3.2% trisodium citrate dehydrate and was centrifuged to produce platelet-poor plasma for subsequent testing on the reference method and the laboratory systems. Samples were tested in duplicate on the laboratory systems and in singlet for the reference tilt-tube method. CLSI guidelines were followed for collection and processing of all subject samples.[5]

The laboratory systems used in this study were the BCS® XP System (Siemens), the Sysmex® CA 1500 (Siemens), and the STA Compact® (Diagnostica Stago). All utilized a single lot of Siemens Dade® Innovin® as the PT reagent. To ensure proper function of each system, two levels of quality control samples were tested each testing day using the reference method, the Coag-Sense® PT/INR System, and the laboratory systems. All laboratory systems employed secondary means of clot detection (i.e., photometric and movement cessation of a steel ball in a magnetic field).

The tilt-tube reference method was performed by an HRL technician trained to follow the WHO recommended methodology for use of International Reference Preparations (IRPs). The IRP used in this study was recombinant human tissue factor coded RTF/95.

The statistical methodology for comparing the INR results obtained with the different systems included orthogonal regression analyses and a plot of the average value of a pair of measurements versus their difference, applying the Bland-Altman method.[6] There were 127 reportable results for all systems that covered a range from 0.9 to 6.8 INR. All evaluable data points were used in the analysis. (Note that in the few cases where duplicate measurements were not

available, the available single datum points were used.) For the Coag-Sense® PT/INR System and laboratory systems, the duplicate results were averaged for analysis. For the Coag-Sense® PT/INR System an estimate of imprecision was calculated from the duplicate analyses and simple least squares linear regression analysis.

## Factors to consider for system comparability

For most coagulation assays the concept of a true value is not applicable.[7] The INR system is very useful; however, clinically important discrepancies are often observed among laboratory-based PT test systems as well as POC systems.

- In a study of laboratory-based PT systems, a 20% INR non-agreement was noted among 12 different reagent/instrument combinations, which represent only a fraction of the 300+ possible reagent/instrument combinations.[8]
- A survey of 115 labs in North America revealed up to 17% variability in INR results among labs.[9]
- Extensive INR variability has also been reported among POC systems.[10]
- Many factors, including pre-analytical and analytical variability, can contribute to the discrepancy in INR determinations among systems.[2]

System differences are typically not an issue when one system is used to monitor the patient over time. However, when replacing one method with another or when a patient is monitored using more than one system, any clinically relevant differences should be known. There is no universal agreement on acceptable differences or those differences that should not affect patient care. The literature suggests in a method comparison, 95% of differences should be within of 0.4 to 0.5 INR.[11]
A correlation coefficient (r) of 0.90 is considered acceptable.[12]

## Results and discussion

### Accuracy with Venous Samples

*Comparison of Coag-Sense® PT/INR System with reference method and laboratory systems*

Orthogonal regression analyses for the correlation between the Coag-Sense® PT/INR System and the reference tilt-tube method, as well as the laboratory systems, is shown in Table 1 and Figure 1A-D. “r” values are greater than 0.90.

| Coag-Sense® vs. Instrument | Correlation “r” | Slope | Slope Lower CL | Slope Upper CL | y-intercept |
|---|---|---|---|---|---|
| Tilt-tube method (RTF/95) | 0.9813 | 0.9430 | 0.9108 | 0.9763 | 0.0482 |
| Siemens BCS® | 0.9608 | 0.8344 | 0.7926 | 0.8783 | 0.2120 |
| Siemens Sysmex CA 1500® | 0.9614 | 0.8974 | 0.8528 | 0.9442 | 0.1622 |
| Stago STA Compact® | 0.9574 | 0.8014 | 0.7595 | 0.8456 | 0.2835 |

**Table 1.** Orthogonal regression analysis of Coag-Sense® PT/INR System average INR results compared with INR results from the reference tilt-tube method with RTF/95 IRP thromboplastin and the average INR results from the Siemens BCS®, Siemens Sysmex® CA1500, and Stago STA Compact® core laboratory systems. All laboratory systems used the same lot of Dade® Innovin® thromboplastin reagent. CL = confidence limit.

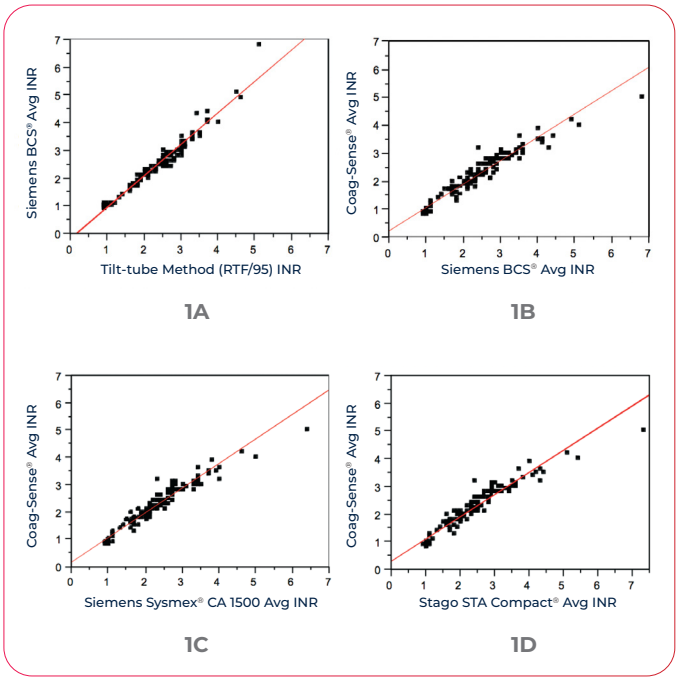


**Figure 1.** Orthogonal regression analyses of Coag-Sense® PT/INR System average INR results compared with A) the INR results of the reference tilt-tube method with RTF/95 IRP thromboplastin and the average INR results of the B) Siemens BCS®, C) Siemens Sysmex® CA 1500, and C) Stago STA Compact® laboratory systems.

Bias plots illustrate how well systems agree and can also indicate where in the INR range a bias may be occurring.[6] A bias plot of the Coag-Sense® PT/INR System INR results relative to INR results with the reference tilt-tube method revealed an average bias of -0.08 INR across the entire INR range (Figure 2).

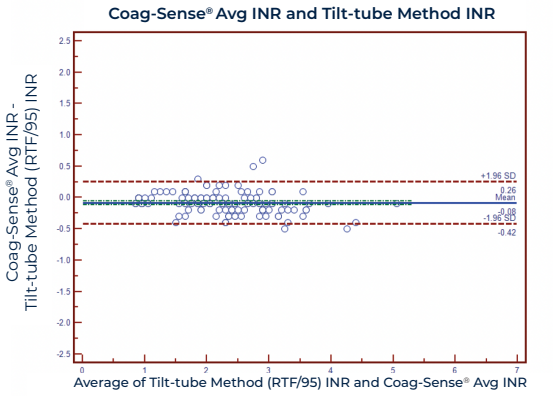


**Figure 2.** Bland-Altman method comparison bias plot of Coag-Sense® PT/INR System average INR results compared with the INR results of the reference tilt-tube method with RTF/95 IRP thromboplastin. Avg = average.

Bland-Altman method comparison bias plots comparing the Coag-Sense® System INR results with the INR results from the three laboratory systems showed an average bias of -0.07 to -0.19 INR to approximately 4.0 INR (Figure 3A-C). Beyond 4.0 INR, however, bias plots revealed that all three laboratory systems produced INR results that were up to 1.5 and 2.3 INR higher than those obtained with the Coag-Sense® PT/INR System and the reference tilt-tube method (Figure 4A-C). It should be noted that some laboratory system manufacturers do not guarantee performance beyond 4.0 INR.

Bland-Altman method comparison bias plots demonstrated that for values beyond 4.0 INR, INR results with the laboratory systems were consistently higher than INR results with the reference tilt-tube method (Figure 4A-C). These results demonstrate that when considering adding a new POC system to your facility, consider including testing with the reference “gold standard” tilt-tube method when comparing data beyond 4.0 INR.

## Coag-Sense Comparisons

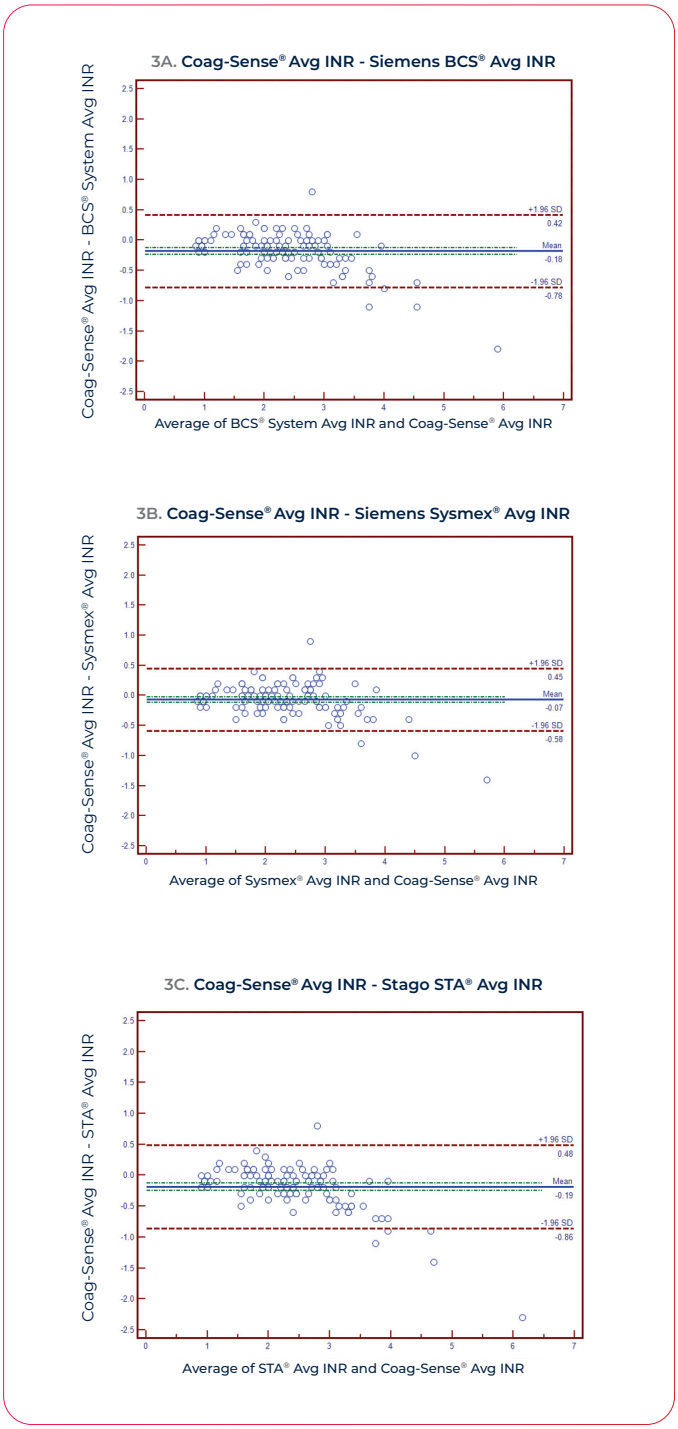


**Figure 3.** Bland-Altman method comparison bias plots of Coag-Sense® PT/INR System average INR results compared with the average INR results from the A) Siemens BCS®, B) Siemens Sysmex® CA 1500, and C) Stago STA Compact® laboratory systems. Avg = average.

## Tilt-tube Comparisons

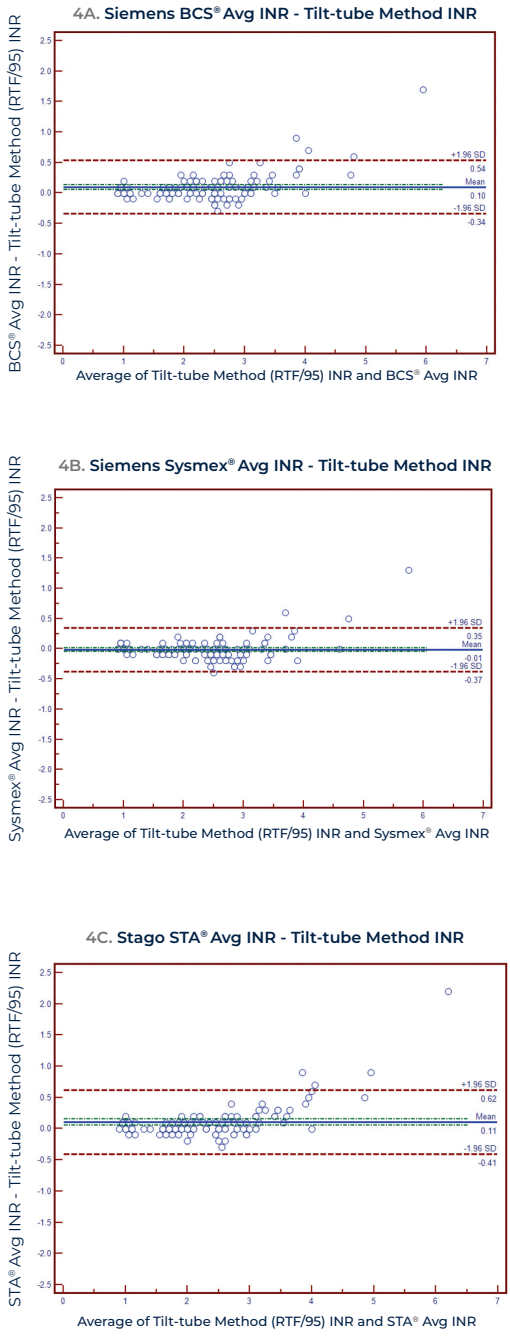


**Figure 4.** Bland-Altman method comparison bias plots of the average INR results of the A) Siemens BCS®, B) Siemens Sysmex® CA 1500, and C) Stago STA Compact® laboratory systems compared with the INR results of the reference tilt-tube method with RTF/95 IRP thromboplastin. Avg = average.

## Comparison of laboratory systems with reference tilt-tube method

The laboratory systems were also compared with the reference tilt-tube method. Orthogonal regression analyses for the laboratory systems are shown below (Table 2 and Figure 5A-C) and all "r" values were above 0.9.

| Tilt-tube Method (RTF/95) vs. Laboratory Instrument | Correlation "r" | Slope | Slope Lower CL | Slope Upper CL | y-intercept |
|---|---|---|---|---|---|
| Siemens BCS® | 0.9796 | 1.1208 | 1.0808 | 1.1622 | -0.1898 |
| Siemens Sysmex® CA 1500 | 0.9803 | 1.0490 | 1.0122 | 1.0872 | -0.1242 |
| Stago STA Compact® | 0.9768 | 1.1715 | 1.1269 | 1.2178 | -0.2824 |

**Table 2.** Orthogonal regression analysis of the individual and combined laboratory systems average INR results compared with the reference tilt-tube method with RTF/95 IRP thromboplastin. All laboratory systems used the same lot of Dade® Innovin® PT reagent. CL = confidence limit.

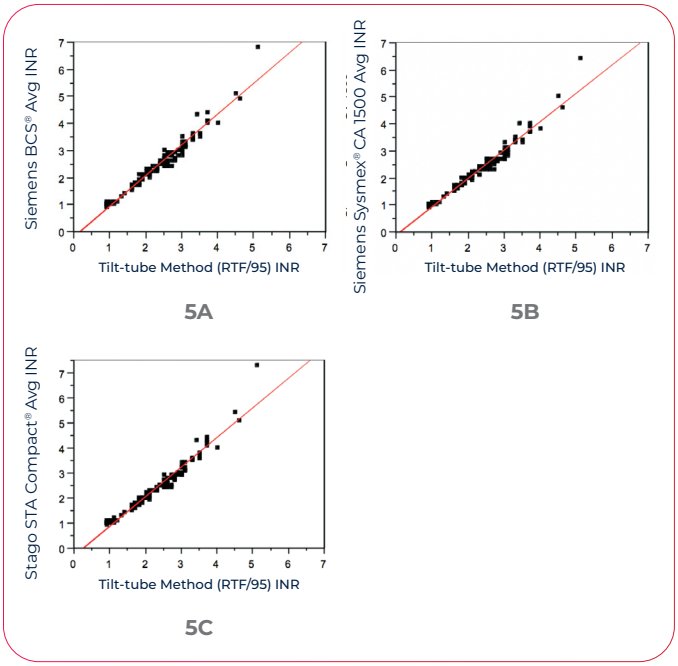


**Figure 5.** Orthogonal regression analyses of the INR results of the reference tilt-tube method with RTF/95 IRP thromboplastin compared with the average INR results for the A) Siemens BCS®, B) Siemens Sysmex® CA 1500, and C) Stago STA Compact® laboratory systems, all with the same lot of Dade® Innovin® thromboplastin reagent. INR = International Normalized Ratio.

## Precision of Coag-Sense® PT/INR System with Venous Samples

The precision of the Coag-Sense® PT/INR System was evaluated by comparing INR results from duplicate venous whole blood samples on two different Coag-Sense® PT/INR Systems. Linear regression analysis (Table 3 and Figure 6) shows the precision of the Coag-Sense® PT/INR System across the INR range. The correlation coefficient was 0.991 (Table 3).

A Bland-Altman method comparison bias plot (Figure 7) also demonstrated the precision of the Coag-Sense® PT/INR System across the INR range.

| Whole Blood Precision Results | |
|---|---|
| N | 123 |
| Mean (INR) | 2.08 |
| Range (INR) | 0.8 - 3.9 |
| Average CV's (%) | 2.40 |
| Correlation (r) | 0.991 |
| Intercept | 0.032 |
| Slope | 0.978 |
| Average SD | 0.046 |

**Table 3.** Linear regression analysis of INR results from duplicate venous whole blood samples on two different Coag-Sense® PT/INR Systems. CV = coefficient of variation, SD = standard deviation.

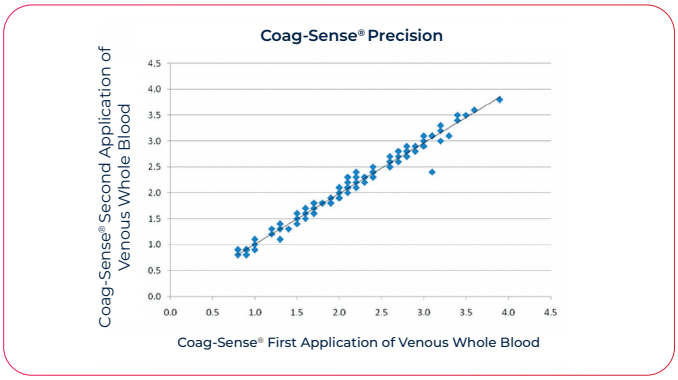


**Figure 6.** Linear regression analysis plot of INR results from duplicate whole venous blood samples on two different Coag-Sense® PT/INR Systems.

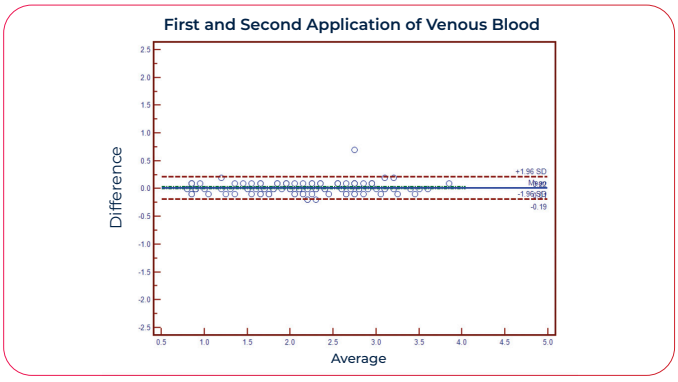


**Figure 7.** Bland-Altman method comparison bias plot of average INR results from duplicate venous whole blood samples on two different Coag-Sense® PT/INR Systems.

## Conclusion

The method comparisons for accuracy presented in this study demonstrated the strong performance of the Coag-Sense® PT/INR System relative to both the WHO gold standard reference tilt-tube method and three leading core laboratory systems.

Table 4 shows the mean difference between the Coag-Sense® PT/INR System and the tilt-tube reference method as well as the percentage of Coag-Sense® PT/INR System measurements within 0.5 INR units of the tilt-tube method measurement by average INR range. Overall, the mean difference was -0.08, and 99.21% of the Coag-Sense® PT/INR System measurements were within 0.5 INR units of the tilt-tube method measurements. As average INR result increased, the mean difference increased; however, the percentage of Coag-Sense® PT/INR System measurements within 0.5 INR units of the tilt-tube method measurements remained at 100%.

With an r value of 0.991, the precision comparisons demonstrated that the Coag-Sense® PT/INR System also compares well against itself when a duplicate venous sample is used. The Coag-Sense® PT/INR System offers a direct clot detection method (similar to that of the WHO reference tilt-tube method with no algorithms or look-up tables), rapid testing time, simplicity, and analytical results that correlate well with the leading methods of PT determination. The system is designed for use in both physician office laboratory and patient home testing settings.

| Average INR result | Mean Difference (INR units) | % within 0.5 INR units | No. of measurements |
|---|---|---|---|
| <2.0 | -0.03 | 100 | 46 |
| 2.0-3.0 | -0.08 | 98.41 | 63 |
| >3.0-4.0 | -0.17 | 100 | 15 |
| >4.0 | -0.33 | 100 | 3 |
| Overall | -0.08 | 99.21 | 127 |

**Table 4.** Agreement between Coag-Sense® PT/INR System and Tilt-tube INR measurements for increasing average INR result ranges.

## Important product usage and safety information

The Coag-Sense® Prothrombin Time (PT)/INR Monitoring System is intended for use by properly selected and trained patients or their caregivers on the order of the treating physician. Users should be stabilized on oral anticoagulation medications such as Coumadin® or warfarin prior to initiating self-testing with the system. Patients who have recently taken or are currently taking any type of Heparin or Low Molecular Weight Heparin anticoagulant should not use the system and should consult their doctor. The device is not to be used for screening purposes.

## References

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