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Reliability of Point-of-Care International Normalized Ratio Measurements in Various Patient Populations

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Purpose: The aim of this study was to determine if the Coagsense point-of-care (POC) instrument provides more reliable international normalized ratio (INR) measurements than Coagucheck XS POC in comparison to the Stago laboratory instrument in different disease states.

Methods: This was a prospective study of outpatient warfarin patients comparing venous Stago INR to fingerstick INR on the Coagsense and Coagucheck XS POC meters. Patients were invited to study if they had an of INR 2.0 to 5.0 and had a medical history of antiphospholipid syndrome, hypercoagulable disorder, autoimmune condition, peripheral vascular disease, mechanical heart valve, atrial fibrillation, or deep vein thrombosis/pulmonary embolism/cerebrovascular accident history.

Results: Seventy-seven patients were enrolled. Coagsense correlated well (92% of INRs within 20% of Stago, 64% of INRs within 0.2 of Stago, overall INR bias of 0.1 or 4%). Six patients had greater than 20% POC INR bias, which could have resulted in 4 warfarin dosing errors.

Coagucheck XS INRs correlated poorly (49% within 20% of Stago, 10% of INRs were within 0.2 of Stago, overall INR bias of 0.66 or 25.7%). Forty-one patients had greater than 20% POC INR bias in all diseases, which could have resulted in 28 warfarin dosing errors.

The average Coagucheck XS INR bias (0.46–1.3 INR) increased with each 0.5 increase in laboratory INR, whereas Coagsense bias remained stable (0.1–0.25) as INR increased up to 4.3. Two patients correlated well on Coagucheck XS but not Coagsense.

Conclusion: Coagsense correlated better than Coagucheck XS and did not show increasing bias as INR increased. Both POC instruments had higher INR variability in 4 disease states (antiphospholipid syndrome, autoimmune, peripheral vascular disease, and hypercoagulable). Patient-specific laboratory correlations may be needed on each POC device.

Key Words: anticoagulation, international normalized ratio reliability, point-of-care, Coagsense, Coagucheck XS, Stago, warfarin, antiphospholipid syndrome, Hypercoagulable disorders

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Warfarin is an oral anticoagulant drug with a narrow therapeutic window and dosing is based on periodic monitoring of the patient's international normalized ratio (INR) blood test. The typical INR range of 2.0 to 3.5 provides adequate anticoagulation while minimizing bleeding risk.

The most reliable INR is measured by a referenced laboratory analyzer requiring a venipuncture to spin down venous blood to test platelet poor plasma. Testing plasma eliminates interactions that may occur with high or low hematocrit or platelet levels. Laboratory INR results are not immediately available and may delay appropriate warfarin dose adjustments by a couple days in some cases.[1]

A more convenient method of outpatient INR monitoring is a fingerstick capillary whole blood sample on a point-of-care (POC) INR instrument for immediate INR reporting and warfarin dose adjustment. This can be done in a clinic or home setting with a Clinical Laboratory Improvement Amendments waived device.[2,3] In recent years, more insurance companies are paying for POC INR instruments for home use, but little is generally known about reliable accuracy of POC instruments and medical conditions that may affect POC INR measurements. Variable or inaccurate POC INR measurements result in more frequent INR monitoring, increased health care costs, and potential incorrect dosage changes, which may increase the risk of bleeding or clotting, resulting in increased morbidity or disability.

Testing for POC INR has many benefits, providing instant INR results to address drug or food interactions with immediate dose adjustment and patient education. However, there are disadvantages to POC INR testing that must be recognized and considered. According to POC manufacturer package inserts, the following factors can interfere and alter POC INR measurements: severe anemia, polycythemia depletion of vitamin K–dependent factors, coadministration with direct thrombin or XA inhibitors, low-molecular-weight heparin, and presence of antiphospholipid antibodies (aPLs) such as lupus anticoagulant (LA) found in antiphospholipid syndrome (APS).[4,5] The use of whole blood with different hematocrits can change the ratio of plasma to thromboplastin on the POC test cartridge, affecting the INR, and high platelet counts can potentially activate coagulation or consume factors before the test reaction, falsely increasing the INR.[1] The manufacturer of Coagsense also mentions the lack of studies using POC INR meters on patients with Scleroderma, Raynaud disease, severe liver disease, cancer, anemia or in pediatric patients.[4] An additional challenge is evaluating POC INRs greater than 3.0 when a POC instrument has poor correlations as the INR increases.[6]

Anticoagulation management services and providers should be aware of these risks and develop policies and procedures to ensure that a POC instrument provides adequate INR measurements for warfarin dosage adjustments. A 2016 Food and Drug Administration workshop on POC INR meters recommended 95% of POC INR samples should read within 20% of the reference laboratory method for INRs up to 4.5, but the Food and Drug Administration has not formally adopted this device standard.[6,7] Our anticoagulation clinic service identifies patients with certain medical conditions who have demonstrated POC INR variability or a history of erratic INR readings for no apparent reason such as dosing error, drug, or food interaction and conducts POC to laboratory

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INR comparison studies over 3 or 4 clinic visits. Our clinic sets the acceptable difference or bias between a POC and laboratory INR at a maximum average of 20% bias (normally 0.5 INR bias, slightly higher for INR >3.0) when laboratory INR is 1.8 to 4.5. Isolated high POC INRs may result in an automatic failure of the comparison study in some high-risk patients based on the variable nature of disease states like APS and lupus. Polycythemia patients are only monitored by laboratory INR at our clinic due to POC package insert warning and demonstrated poor laboratory-to-POC correlations with sudden blood count changes. We explain to patients that a laboratory INR is more reliable and should be used when POC INR is significantly out of range for no apparent reason.

Since 2016, the number of patients with erratic INR readings on the Coagucheck XS requiring monitoring by laboratory INR tripled to roughly 10% of our clinic patients. Data from our 2017–2018 clinic comparison studies of INR variability between Coagucheck XS POC and Stago laboratory INR showed the following: (1) There is very low or negligible variability when INR is less than 2.0 so we do not include INRs less than 1.8 in our comparison studies. (2) When variability is detected, the Coagucheck XS POC INR is always higher (positive bias) than the Stago laboratory INR. (3) There is greater bias or larger differences between Coagucheck XS and Stago INR once the INR is greater than 3.0, and there is little correlation once the INR is greater than 4.0. In September 2018, a product safety bulletin was released by Coagucheck XS recommending any INR greater than 4.5 on the Coagucheck XS POC be verified with a laboratory INR owing to more variability in test strips manufactured in 2018 using a new World Health Organization International Sensitivity Index (ISI) thromboplastin rating. On October 31, 2018, several lots of Coagucheck XS test strips were recalled because of higher INRs with the new ISI thromboplastin rating.[8–10] However, our correlations over a 2-year period had high INR variability with strips not involved in the recall.

Several published studies have compared POC devices to the laboratory INR,[11–17] but the purpose of this study was to evaluate the bias between 2 POC instruments using different methods of clot detection. The Coagucheck XS uses electrochemical impulse for clot detection, whereas a newer POC instrument, Coagsense, uses photo mechanical clot detection using a spinning wheel in the cartridge. In addition, this study evaluated how well each POC meter measured INRs in patients with specific medical conditions, including APS, other hypercoagulable disorders, mechanical heart valves (MHVs), peripheral vascular disease (PVD), autoimmune conditions, atrial fibrillation with no history of clots, and patients with history of pulmonary embolism (PE), deep vein thrombosis (DVT), or ischemic stroke with no history in other categories. This study aimed to identify which patients should be prioritized for POC-to-laboratory comparison testing.

MATERIALS AND METHODS

This study was a prospective, single-center cohort conducted in patients managed by Parkview Medical Center Anticoagulation Clinic from January to February 2019. Patients were identified by their warfarin indications and medical history significant for APS, autoimmune disorder (lupus without APS, rheumatoid arthritis, scleroderma, or Raynaud syndrome), hypercoagulopathy (factor V Leiden, protein C or S deficiency), peripheral vascular or arterial disease, MHV, atrial fibrillation, venous thromboembolism, or stroke. Patients were recruited by the investigators, and signed written informed consent was collected before testing. This study was approved by the Parkview Medical Center Institutional Review Board.

Study Population

Patients were included if they were at least 18 years of age, had taken warfarin for at least 6 months before the study date with no known drug interactions affecting the INR at the time, have had an INR of 2.0 to 5.0, and had a hematocrit of 25% to 55% on file within the past year to be eligible for POC INR monitoring per clinic policy. Patients excluded were pregnant patients, pediatric and incarcerated patients, patients on low-molecular-weight-heparin, and those who could not understand and sign the informed consent. Baseline patient demographics were collected, including age, sex, indication for anticoagulation, INR goal range, and presence of one of the studies disease states.

Enrollment was targeted to include at least 10 patients in 7 different disease states to determine if certain medical conditions led to more INR variability on POC instruments. Based on our observations of higher INR variability or bias on our previous Coagucheck XS POC instrument, 5 medical conditions were considered as high-risk groups:

1) Diagnosis of APS or presence of LA antibodies
2) Autoimmune conditions group: lupus patients not diagnosed with APS, significant rheumatoid arthritis, scleroderma, and calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia (CREST) syndrome
3) Hypercoagulopathy group: factor V Leiden, protein C deficiency, protein S deficiency, and undefined coagulopathy in their medical history but not APS or other autoimmune condition
4) Peripheral vascular or arterial disease but none of the other conditions
5) MHV. If an MHV patient also had APS or autoimmune condition, those patients were listed in the APS or autoimmune group. All patients were categorized in only 1 group based on highest risk condition.

Two groups of patients considered low risk were included who did not have any of the above medical conditions or history of erratic INR as a comparison of typical INR variability that may take place with POC instruments. The low-risk patient groups included:

6) Atrial fibrillation with no history of clotting or conditions listed above
7) Routine clot patients with history of a "clot" such as DVT, PE, or stroke but none of the conditions listed in 1 to 6

Study Procedures

During the routine INR monitoring visit at the anticoagulation clinic, the patient's standard of care INR was evaluated utilizing either a laboratory INR or Coagsense INR (as deemed appropriate by institution policy and procedure before study initiation). If the standard of care INR was 2.0 to 5.0, additional blood samples were drawn, including a venous citrated sample to run on the Stago laboratory benchtop instrument, and 2 capillary blood finger sticks were to run on the 2 POC INR meters, the Coagsense and Coagucheck XS. Appendix A lists all reagent lots and ISI values.

Venous and capillary samples were drawn at the same time, or within 1 hour prior. Dosing adjustments were made based on the patient's standard of care INR. However, if the warfarin dosing was based on the Coagsense INR for that patient and later the laboratory INR was reported and varied more than 0.4, the pharmacist was notified of the discrepancy to determine if a dosing adjustment was warranted. The INR results for all 3 methods were recorded and deidentified data were entered into an electronic spreadsheet for data tracking and statistical analysis.

Statistical Analysis

All INR data were compared in the EP Evaluator software using linear regression analysis for Alternate (Quantitative) Method Comparison assessing each POC instrument INR to the reference Stago laboratory INR. The software calculated the INR bias and percentage bias and identified which patients exceeded the allowed 20% bias on each POC instrument in comparison to the reference Stago laboratory INR. Scatterplots of each POC instrument INRs were plotted against the reference Stago laboratory INR by disease state for all patients in the study (Fig. 1).

Additional statistical analysis was completed using the Tukey honest significant difference post hoc test to compute a *P* value for each POC device average INR to the average laboratory INR for all patients, for each disease state group, and for all patients separated into INR range groups. Results were considered significant with a *P* value less than 0.05. Power analysis was not conducted owing to observational study with no anticipation of reaching statistical significance with our limited number of patients in each disease state.

RESULTS

Of the 77 patients enrolled (Table 1), the Coagsense correlated with 92% of all patient INRs within 20% of the STAGO laboratory INR, 64% of all INRs within ±0.2 of Stago INR, resulting in an overall INR bias of 0.1 or 4% bias. The Coagsense correlated well across all disease states with no patients outside the 20% bias in the atrial fib, routine clots, or MHV patient groups. Six patients did have INR readings outside the 20% allowed bias in the antiphospholipid (n = 2), autoimmune (n = 2), PVD (n = 1), and hypercoagulopathy groups (n = 1) groups, which could have led to incorrect warfarin dosing in 4 patients (Table 2).

In comparison, only 49% of Coagucheck INRs were within 20% of Stago and only 10% of all INRs were within 0.2 of Stago INR, resulting in an overall INR bias of 0.66 or 25.7% bias. The Coagucheck correlated poorly across all disease state groups, with 11 of 13 (85%) patients in the hypercoagulopathy group and 50% to 65% of patients in the APS, autoimmune, PVD, and MHV groups outside the 20% acceptable bias. Because of the small sample size in each group, this was statistically significant ($P < 0.05$) only in all patients and the hypercoagulopathy and MHV groups, which had at least 12 patients. Even the low risk groups had nearly a 30% rate outside the acceptable 20% bias. These results could have led to incorrect warfarin dosing in 28 patients (Table 2).

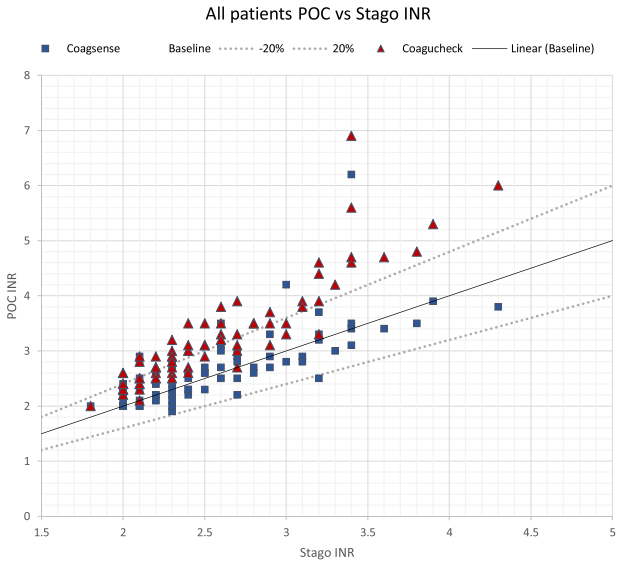

FIGURE 1. Scatterplot of POC INR vs Stago laboratory INR.

TABLE 1. Baseline Characteristics of the Study Population

Total number of patients	77
Number of patients in each medical condition group	10–13
Age	27–85 years Average: 62.3 years
Sex	Male: 51% (n = 39) Female: 49% (n = 38)
INR goal range	
2.0–3.0	65%
2.5–3.5	29%
Other between 2.0 and 3.7	6%

When all patient data were sorted by Stago laboratory INR range (Table 3), the Coagsense INR bias remained stable (within about 0.2 INR) across all laboratory INR ranges from 1.8 to 4.3. Conversely, the Coagucheck XS INR bias increased with each 0.5 increase in laboratory INR. The Coagucheck XS to laboratory INR bias was statistically significant across all INR ranges, except the group that had only 1 patient data point (Table 3).

DISCUSSION

The increasing INR bias, a known problem with Coagucheck XS as the INR increases to greater than 3.0 to 4.0, was not seen with Coagsense in this study (Table 3).[11–17] The average INR bias for Coagsense was consistent at 0.2 INR bias for INRs 1.8 to 4.3 and has been fairly consistent for patients that correlate well in our clinic for INRs even up to 6.4. As opposed to Coagucheck XS, there was a statistically significant increase in INR bias for each 0.5 increase in Stago INR range for INRs greater than 2.0. Two outpatient Anticoagulation Services have studied the issue of larger INR bias on POC INRs greater than 3.0.[15–17] Using comparison studies of POC INR with their standard reference laboratory INR, they created a correction factor to more reasonably estimate the INR when Coagucheck XS measures an INR greater than 3.0[6,15,16] or INR greater than 4.0[17] to guide warfarin dosing decision making.

In 2017, Vazquez et al[16] published a similar study comparing the same instruments, Coagucheck XS, Coagsense, and Stago, and observed a higher positive INR bias with INRs greater than 3.0 with both POC instruments. However, our results comparing the same instruments in 2019 did not measure a similar Coagsense INR bias drift for INRs greater than 3.0. This may be because of improved reagents and thromboplastin for Coagsense available in 2019 or differences in reagents used for all instruments in each study.[3,6,10,18] This encourages ongoing, periodic POC to laboratory comparison as thromboplastin reagents and ISI rating changes over time may alter POC INR reliability as demonstrated in the 2018 recall of Coagucheck XS test strips.[9,11]

The Coagsense outperformed the Coagucheck XS across all patients, all disease states studied, and INR ranges, with only 6 patients in 4 high-risk disease states outside the 20% acceptable limit (Table 2). Both POC instruments had patients with inaccurate INR measurements in the APS, autoimmune, PVD, and hypercoagulopathy diagnoses, demonstrating comparison of POC to laboratory INR in these patients may be warranted before fully relying on a POC INR meter for long-term warfarin dosing.

TABLE 2. Summary of INR Difference Between Stago Laboratory and Point-of-Care Instruments

	All Patients	APS	Hypercoagulopathy	MHV	PVD	Autoimmune	Routine Clot	Atrial Fibrillation
Patients	77	11	13	12	10	10	10	11
POC INR compared with Stago INR								
Stago average INR	2.56	2.63	2.54	2.55	2.83	2.67	2.4	2.27
Coagsense average INR	2.66	2.86	2.72	2.66	2.71	2.91	2.42	2.3
p-value	0.669	0.878	0.725	0.877	0.929	0.730	0.996	0.986
Coagucheck XS average INR	3.22	3.46	3.36	3.13	3.64	3.27	2.92	2.64
p-value	<0.0001	0.180	0.004	0.038	0.086	0.158	1.04	0.144
Average INR bias to Stago								
Coagsense	0.1	0.24	0.18	0.11	−0.14	0.24	0.02	0.03
Coagucheck XS	0.66	0.84	0.82	0.58	0.85	0.6	0.52	0.36
Average % INR bias to Stago								
Coagsense	4.00%	9.00%	7.30%	4.25%	−4.80%	9.00%	0.80%	1.20%
Coagucheck	25.70%	31.80%	32.40%	22.90%	29.40%	22.47%	21.70%	16.00%
INR within 0.2 of Stago								
Coagsense, no. (%) patients	50 (65)	6 (55)	8 (62)	8 (67)	4 (40)	6 (60)	6 (60)	11 (100)
Coagucheck, no. (%) patients	8 (10)	1 (9)	0 (0)	0 (0)	2 (20)	2 (20)	0 (0)	3 (27)
INR 20% or more different than Stago								
Coagsense, no. (%) patients	6 (8)	2 (18)	1 (8)	0 (0)	1 (10)	2 (20)	0 (0)	0 (0)
Coagucheck, no. (%) patients	41 (51)	6 (54)	11 (85)	6 (50)	6 (60)	6 (60)	3 (30)	3 (27)
Warfarin dosage error possible with POC INR								
Coagsense	4	1	1	0	0	2	0	0
Coagucheck	28	4	8	4	6	3	2	1

Because this study was small in power with a limited number of patients available and eligible in each of the 7 disease states, we did not expect to reach statistical significance in individual disease states. The Coagucheck XS INR bias was statistically significant for all patients and the hypercoagulopathy and MHV groups, which had at least 12 patients.

Interestingly, 2 of the 6 patients with greater INR bias on Coagsense actually correlated well with Coagucheck XS, whereas the opposite was true for 38 patients correlating well on Coagsense, but not Coagucheck XS. There may be patient-specific variables, possibly reduced clotting factors, fibrinogen levels, and elevated antibodies interacting with a specific thromboplastin affecting the reliability of that specific instrument in that patient. This shows that POC to laboratory comparisons may be needed on each different POC device in high-risk patients and not to make assumptions of reliability between different POC devices.[3,6,10]

Medical Conditions Studied for POC INR Variability

Antiphospholipid syndrome is a systemic autoimmune disease often associated with fetal loss and a hypercoagulable state. The presence of aPLs, specifically LA but also anticardiolipin antibody, anti-beta 2 glycoprotein 1, and antithrombin, is documented in POC INR instrument package inserts as a potential interaction falsely prolonging the prothrombin time (PT), resulting in a higher INR.[4,5,19–28] Even laboratory analyzers may measure a falsely prolonged PT and elevated INR with aPLs interacting with specific thromboplastin reagents.[19,20] Antibody levels may also increase or decrease over time, further complicating INR measurements in this patient population. Numerous studies have evaluated LA effect on INR, with inconsistent results. There seems to be a subset of patients with falsely elevated POC INRs that should only be monitored by laboratory

TABLE 3. POC INR Variation by Laboratory INR Range

			Coagsense = CS			Coagucheck XS		
Laboratory INR	No. Patients	Stago Laboratory INR Avg	CS Avg INR	CS Bias Avg	CS *P*	CC Avg INR	CC Bias Avg	CC *P*
1.8–4.3	77	2.56	2.66	0.10	0.297	3.22	0.66	<0.0001
>2.0	1	1.8	2.0	0.20	n too small	2.00	0.20	n too small
2.0–2.4	40	2.175	2.277	0.103	0.032	2.632	0.457	<0.0001
2.5–2.9	19	2.674	2.768	0.095	0.245	3.31	0.637	<0.0001
3.0–3.5	13	3.223	3.431	0.208	0.440	4.361	1.138	0.0004
3.6–4.3	4	3.900	3.650	−0.250	0.235	5.200	1.300	0.008

CC = Coagucheck XS bias increases as INR increases.

CS = Coagsense bias consistent across all INR ranges up to 4.3.

Avg = Average (mean).

INR. In addition, a smaller group of APS patients with falsely elevated PT in the laboratory may need evaluation of chromogenic Factor X levels in comparison with laboratory INR to identify an INR range providing 20% to 40% Factor X range for adequate anticoagulation.[19,20,25,26]

Unfortunately, many known and unknown APS patients are monitored on POC instruments at home, in physician offices, and other anticoagulation clinics despite package insert and the APS Foundation of America warning against the use of fingerstick INR meters.[29] Discussions with POC instrument representatives reveal that they too lack information on patient populations that may not be good candidates for monitoring by their POC instrument.

This study showed 20% of Coagsense INRs and 60% of Coagucheck XS INRs in the APS patients did not correlate within 20% of the laboratory INR. Of the 2 patients with poor Coagsense correlations, 1 had a laboratory INR of 3.4, Coagsense INR 6.2, and Coagucheck XS 6.9, demonstrating an APS patient who should be monitored only by laboratory INR. The other APS patient with poor Coagsense correlation has previously shown a very consistent 0.7 positive bias with Coagucheck XS but a random plus or minus bias on Coagsense on subsequent visits. This also demonstrates the importance of validating each POC device in APS patients to ensure reliable INR measurements for that specific patient.

It is important to note how difficult it is to diagnose APS as testing for the presence of aPLs is not routine with initial clotting events. Our experience is many patients do not get hypercoagulation panels drawn, patients may be taking interfering medications when laboratories are drawn, or laboratories that are drawn during hospitalization but reported after hospital discharge can be lost to follow-up. Antiphospholipid antibodies are positive in approximately 13% of patients with stroke, 11% of patients with myocardial infarction, 9.5% of patients with DVT, and 6% of patients with pregnancy morbidity.[22] The unknown presence of these antibodies in other patients not tested and diagnosed with APS could lead to INR variability, suggesting that any patients experiencing unusually erratic INRs for no known reason may benefit from laboratory-to-POC comparison studies.

Other hypercoagulable disorders such as factor V Leiden, protein C deficiency, protein S deficiency, or other genetic mutations are not mentioned in the literature regarding potential INR variability. However, our past clinic comparisons showed that 88% of factor V Leiden patients and 74% of all types of hypercoagulopathy patients had high INR bias with Coagucheck XS. In this study, the Coagucheck XS had the worst performance in this group of patients, with 85% (11/13) of the patients outside the acceptable 20% bias, with 8 of those patients potentially getting an inappropriate dosage change. The Coagsense INRs were very well correlated except 1 patient who could have remained out of range without an appropriate dose increase. This group of patients is at higher risk of DVT and PE than the general public, and laboratory-to-POC INR testing appears to be warranted to rule out INR monitoring and warfarin dosing problems.

Autoimmune disorders including calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia (CREST) syndrome includes patients with lupus with no APS, rheumatoid arthritis, Raynaud syndrome, unusual connective tissue or skin conditions, and patients with esophageal dysmotility requiring endoscopic stretching of the esophagus. Although this group includes scleroderma patients, none of the patients in our study had this diagnosis. The package insert for both POC devices mentions lack of studies in scleroderma patients as a potential warning using POC INRs.[4,5] This study showed that 60% of Coagucheck XS and 20% of Coagsense patients did not correlate well within 20%. One patient who fell outside the 20% bias for Coagsense during the study visit was noted to have a strong alcohol smell but denied any recent alcohol intake. On subsequent clinic visits, this patient's Stago, Coagsense, and Coagucheck INRs all correlated well within 0.3 INR. We have since noted very elevated Coagsense INRs, sometimes "no clot detected" in several well-controlled patients who recently used fragrant or alcohol-based foam cleansers or handled adhesives, stains, or marijuana leaves despite wiping the finger well with an alcohol pad. Once these patients washed their hands with plain soap and water, the Coagsense measured a normal therapeutic INR confirmed with a Stago INR. This hand residue interaction was not observed with Coagucheck XS but is now mentioned in the Coagsense user manual stating to wash any oil, lotions, or foreign matter from the site, which can interfere with results.[30]

PVD and peripheral arterial disease (PAD): We have always performed laboratory-to-POC comparison tests in PVD because of a concern that a peripheral, capillary blood sample may not be as accurate as a venous blood sample, with 76% of our previous correlation tests with Coagucheck XS outside the 20% range. This study showed that 10% of Coagsense INRs and 60% of Coagucheck XS INRs in the PVD patients did not correlate within 20% of the laboratory INR. It appears that another process may interfere with POC INR readings in PVD patients. Interestingly, the patient who correlated poorly with Coagsense had reproducibly good correlations to Coagucheck XS numerous times in the past. Again, this patient population may warrant the need for POC-to-laboratory comparison testing on each specific POC device.

MHV: These patients have a higher INR range, typically 2.5 to 3.5. Coagucheck XS has shown a higher INR bias greater than 3.0, creating a challenge in interpreting POC INRs for this patient population.[13–17] Our previous correlation tests on patients with erratic Coagucheck XS INRs had an 82% fail rate with the Coagucheck XS in MHV patients. Antiphospholipid antibodies have been implicated in inflammatory processes leading to cardiac valve lesions,[28] so unknown antibody interactions may be present in a subset of MHV patients and POC-to-laboratory correlations may be indicated in some patients with questionable or erratic POC INR results. This study showed 50% of Coagucheck XS INRs in the MHV patients did not correlate within 20%, but all of the Coagsense INRs correlated well.

Atrial fibrillation and routine clots: These 2 patient groups were designed to be the low-risk control group. We expected these patients to correlate well with both POC instruments. Three patients in each group fell outside the 20% range for Coagucheck XS, but all patients compared well with the Coagsense meter.

This study has a few limitations. Coagsense POC meter was superior to the Coagucheck XS when compared with the reference Stago laboratory instrument and the reagents used in this study (Appendix A). Other institutions that use other laboratory instruments or different reagents may find more laboratory-to-POC INR variation. Laboratory analyzers testing platelet poor plasma have shown up to 17% variability in INR results in a survey of 115 laboratories in North America.[7] This intralaboratory variability is a result of the lack of consensus in the medical community on a standardized thromboplastin preparation and lack of large clinical trials showing the superiority of one laboratory INR method over others.[3,6,7,10] The recall of Coagucheck XS test strips in 2018 was based on Roche adopting a new World Health Organization ISI thromboplastin reference rating for test strips manufactured that year.[9] We suspect that the thromboplastin reagent sensitivity and ISI plays more of a role in INR variability than the method of clot detection of the POC instrument used.[3,6,10] Larger trials are needed to address ongoing laboratory INR variability, thromboplastin, and ISI standardization and further evaluate if certain disease states are associated with more POC INR variability.

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Appendix A. Reagents Used During Study

Instrument	Reagent Lot No.	Thromboplastin and ISI
Stago laboratory Local calibration of ISI completed week before starting the study*	Lot 252774	ISI 1.27 Recombinant neoplastin, secondary standard of rabbit brain thromboplastin
Coagsense POC	Lots 180594, 180610	ISI 0.96 (1.0 in literature) Recombinant rabbit tissue factor
Coagucheck XS POC	Lot 35350212	ISI 1.0 (Code 356 chip) Recombinant human thromboplastin Best comparison laboratory reagents: Dade Innovin reagent on a Sysmex 560 Analyzer

*Local calibration of ISI values helps each laboratory eliminate variability and guesswork between different reagent/instrument systems for ISI values when performing PT/INR assays and potentially improve the clinical accuracy of their patients' PT/INR results.[31]