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Evaluating the analytical performance of four new coagulation assays for the measurement of fibrinogen, D-dimer and thrombin time

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Abstract

Introduction: New laboratory methods to measure haemostatic function require careful assessment before routine use. We evaluated the analytical performance of four new coagulation assays for the measurement of fibrinogen by Clauss assay, prothrombin time-derived fibrinogen, thrombin time and D-dimer levels.

Methods: The four assays were evaluated on the **cobas t** 711 and **cobas t** 511 analysers at four centres in Europe. Analytical performance and method comparisons with other commercially available assays were performed according to Clinical and Laboratory Standards Institute guidelines (EP09-A3, EP05-A3) using residual anonymized human sodium citrate (3.2% [0.109M]) plasma samples. Lot-to-lot variability and the equivalency of each assay on the **cobas t** 711 and **cobas t** 511 analysers were also assessed.

Results: Overall, coefficients of variance were ≤4.1% and ≤8.6% for within-run precision and total reproducibility, respectively. Method comparison experiments showed good or acceptable agreement for each assay compared with their respective comparator method, and equivalency was demonstrated for the two **cobas t** platforms (Pearson's correlation coefficient ≥0.991). A high level of consistency was observed between lots for all four assays (Pearson's correlation coefficient ≥0.994).

Conclusion: This multicentre study demonstrates excellent analytical performance for four new coagulation assays on the **cobas t** 711 and **cobas t** 511 analysers.

KEYWORDS

cobas t 511, **cobas t** 711, D-dimer, fibrinogen, thrombin time

1 | INTRODUCTION

Coagulation tests are widely used in healthcare for the screening, diagnosis, and assessment of coagulopathies, the monitoring of anticoagulant therapy, and as a component of preoperative screening.[1-3] Fibrinogen levels, thrombin time and D-dimer levels are frequently measured in clinical practice; it is important that tests for these analytes are accurate and reliable, and that results are available in a timely manner. Fibrinogen levels are measured to determine haemorrhagic or thrombotic status. Elevated

levels of fibrinogen are a risk factor for thrombotic disease and have been observed during acute-phase reactions, pregnancy, oral contraception use, menopause, malignancies, chronic inflammatory diseases and in people who smoke.[1,4-9] Low fibrinogen levels can occur during acute or chronic liver disease, disseminated intravascular coagulation (DIC), thrombolytic therapy, haemodilution and consumption coagulopathy.[9-11] Thrombin time tests can be used to investigate possible bleeding disorders or the occurrence of thrombotic episodes. Thrombin time is prolonged by: decreased fibrinogen levels; abnormal function of fibrinogen; the presence of direct thrombin inhibitors, such as dabigatran, bivalirudin or argatroban; the presence of unfractionated heparin; the presence of aprotinin; and the presence of fibrinogen/fibrin degradation products and/or increased fibrinolysis (for example, due to thrombolytic therapy).[12-17] D-dimer is a very sensitive marker for the activation of coagulation.[18-24] In DIC, fibrin degradation products, such as D-dimer, can be used to confirm or refute a tentative diagnosis, estimate the potential risk for patients with existing DIC, and monitor an initiated therapy.[25-27] D-dimer levels are particularly useful to exclude deep vein thrombosis (DVT) and pulmonary embolism (PE), and may be elevated in the presence of other causes of fibrin formation such as trauma, pregnancy complications, malignant disease or vascular abnormalities.[25-30]

High-throughput technologies designed for use in core laboratories and developed to measure fibrinogen, prothrombin time (PT)-derived fibrinogen, thrombin time and D-dimer may offer significant benefits, such as reduced error rates and increased efficiency. This multicentre study aimed to evaluate the performance of four new coagulation assays on the **cobas t** 711 and **cobas t** 511 analysers, which have been developed to measure fibrinogen, among others, PT-derived fibrinogen, thrombin time and D-dimer levels. For each assay, the analytical performance was evaluated and method comparisons with existing commercially available assays/platforms were performed.

2 | MATERIALS AND METHODS

2.1 | Study design

This study was performed between June 2016 and March 2017 in core laboratories at four centres in Europe (Medical University of Vienna, Vienna, Austria; University Medical Center Freiburg, Freiburg, Germany; University of Debrecen, Debrecen, Hungary; Royal Hallamshire Hospital, Sheffield, UK). The four assays presented here (fibrinogen, PT-derived fibrinogen, thrombin time and D-dimer; Roche Diagnostics GmbH, Mannheim, Germany) were each evaluated for their analytical performance, and compared with existing methodologies/technologies in independent method comparison experiments. Lot-to-lot variability and the equivalency of each assay on two **cobas t** platforms (**cobas t** 711 and **cobas t** 511; Roche Diagnostics) were also assessed. All assays and instruments were used according to their respective manufacturers' instructions and quality control measurements were performed at least twice daily. Residual anonymized human sodium citrate (3.2% [0.109M]) plasma samples from clinics' routine were used for all experiments. Independent ethics committee approval or waiver was obtained before study initiation where required, and the study was performed according to the principles of the Declaration of Helsinki and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Good Clinical Practice guidelines.

2.2 | Experimental procedures and data analysis

Each of the four assays was independently evaluated on the **cobas t** 711 analyser (high-throughput: 390 tests/h; evaluated at all four sites) and **cobas t** 511 analyser (mid-throughput: 195 tests/h; evaluated at two sites [UK; Germany]). Within-run precision for each assay was evaluated in one run using two controls and five human plasma samples (n = 21 replicates per sample); each site performed their experiments with an individual reagent and control lot, which varied by site. Reproducibility

TABLE 1 Within-run precision and total reproducibility (across all four sites) of the four coagulation assays on the **cobas t** 711 and **cobas t** 511 analysers

Assay	Within-run precision acceptance criteria	Within-run precision, range of % CV or SD		Total reproducibility acceptance criteria (%)	Total reproducibility, range of % CV	
		cobas t 711	cobas t 511		cobas t 711	cobas t 511
Fibrinogen (mg/dL)	CV ≤ 4.0% (60-400)	0.8-2.3	0.8-1.5	CV ≤ 25.0	2.1-3.0	1.6-2.6
	CV ≤ 6.0% (400-600)	0.7-2.6	0.7-0.9	CV ≤ 25.0	3.3	2.9
	CV ≤ 10.0% (>600)	1.8-2.6	0.6-1.4	CV ≤ 25.0	4.3	4.3
PT-derived fibrinogen (mg/dL)	CV ≤ 5.0%	0.4-1.4	0.4-1.3	CV ≤ 25.0	1.4-2.2	1.1-3.1
Thrombin time (s)	CV ≤ 4.0%	0.6-2.9	0.6-4.1	CV ≤ 25.0	1.1-4.5	0.9-4.0
D-dimer (μg FEU/mL)	SD ≤ 0.02 (<0.56)	0.012-0.017	0.0096-0.016	CV ≤ 25.0	3.5-8.6	3.3-6.7
	CV ≤ 3.5% (0.56-1.7)	1.5-2.4	1.4-1.5	CV ≤ 25.0	5.4	5.5
	CV ≤ 3.0% (>1.7)	0.3-0.7	0.2-0.3	CV ≤ 25.0	1.0-1.8	0.9-2.2

CV, coefficient of variation; FEU, fibrinogen equivalent units; PT, prothrombin time; SD, standard deviation.
Ranges reported are for human plasma samples only, covering a concentration range of 70-800 mg/dL.

TABLE 2 Method comparison: **cobas t** 711 vs comparator device

Comparison	Evaluation	Acceptance criteria	Freiburg Lot 1	Sheffield Lot 2	Debrecen Lot 3
Fibrinogen vs Dade Thrombin Reagent	n		140	155	130
	Slope (Deming)	1.00 ± 0.10	0.985	0.959	0.977
	Intercept	≤25.0 mg/dL	10.506	16.489	11.605
	Pearson's *r*	≥0.900	0.996	0.991	0.990
	Relative % bias at 200 mg/dL	NA	3.78	4.10	3.48
PT-derived fibrinogen vs Fibrinogen (Clauss)	n		144	126	128
	Slope (Passing-Bablok)	1.00 ± 0.15	1.000	0.955	1.067
	Intercept	NA	14.500	16.227	−6.467
	Pearson's *r*	≥0.850	0.943	0.938	0.940
	Bias at 200 mg/dL	±20 mg/dL at 200 mg/dL	14.50	7.14	6.87
Thrombin time vs BC Thrombin Reagent	n		137	146	122
	Slope (Deming)	1.00 ± 0.35	0.670	0.868	0.960
	Intercept	NA	7.425	5.353	3.089
	Pearson's *r*	≥0.70	0.751	0.755	0.658
	Relative % bias at 17.8 s	NA	8.68	16.8	13.3
D-dimer vs Tina-quant® D-dimer	n		216	194	134
	Slope (Deming)	1.000 ± 0.100	1.006	0.995	1.033
	Intercept	≤±0.20 μg FEU/mL	0.004	−0.041	−0.012
	Pearson's *r*	≥0.950	1.000	0.999	0.999
	Relative % bias at 0.5 μg FEU/mL	NA	1.48	8.61	0.997

FEU, fibrinogen equivalent units; NA, not applicable; PT, prothrombin time.

was evaluated over 5 days by measuring five aliquots of each control sample and of five human plasma samples, using the same control lots and reagent lots at all sites. Results were evaluated across the study sites.

Briefly, the fibrinogen test is a Clauss assay using lyophilized bovine thrombin at a concentration of 100 National Institutes of Health (NIH) units/mL with added stabilizers and buffers; the PT-derived fibrinogen assay is a Quick test containing recombinant thromboplastin and calcium to activate the extrinsic coagulation cascade when added to citrated human plasma; and the thrombin test is based on a lyophilized reagent containing 2000-10 000 NIH units/L of bovine thrombin per supplied vial, which was mixed with the sample in a 1:1 ratio. The D-dimer test is a particle-enhanced immunoturbidometric assay in which latex particles are coated with monoclonal antihuman D-dimer antibodies (mouse) at 0.12%. The start reagent is used together with a preservative/buffer solution at pH 8.2.

The full study methods, including evaluation of analytical performance, equivalency of the **cobas t** 711 and **cobas t** 511 analysers, lot-to-lot comparison, reference range evaluation, and data analysis have been described previously (for the evaluation of five other coagulation tests on the **cobas t** 711 and **cobas t** 511 analysers).[31]

2.3 | Method comparison

A method comparison was performed for each assay (using the **cobas t** 711 analyser) vs the following respective comparator methods, according to Clinical and Laboratory Standards Institute (CLSI) EP09-A3 guidelines:[32] fibrinogen vs Dade Thrombin Reagent on Siemens Sysmex CS-5100 or CS-2000i; PT-derived fibrinogen (lyophilized, recombinant human thromboplastin reagent containing a heparin-neutralizing substance, calcium chloride, stabilizers, and buffers; this method has been standardized against the fibrinogen method available on **cobas t** coagulation analysers and is thus traceable to the international standard WHO 09/264) vs Fibrinogen (Clauss) on **cobas t** 711; thrombin time vs BC Thrombin on Siemens BCS; D-dimer vs Tina-quant® D-Dimer Gen 2 reagent on Roche/Hitachi **cobas c** systems (**cobas c** 502, **cobas c** 701, or **cobas c** 501). Each comparison was performed at three or four sites (two reagent lots per site) using a minimum of 120 residual anonymized human plasma samples per assay (representing the appropriate measuring range of the relevant analyte).

2.4 | Reference range studies

For all assays, reference ranges were determined using anonymized residual samples (0.109M/3.2% citrate) sourced from apparently healthy adult donors at a blood bank (Freiburg, Germany). Key inclusion criteria were: 18-50 years of age, originating from Europe or the US and able to provide written informed consent; exclusion criteria were self-declared pregnancy or breast-feeding, and use of anticoagulation medication including but not limited to acetyl salicylic acid, direct oral anticoagulants, phenprocoumon, and warfarin. Samples were collected in Sarstedt

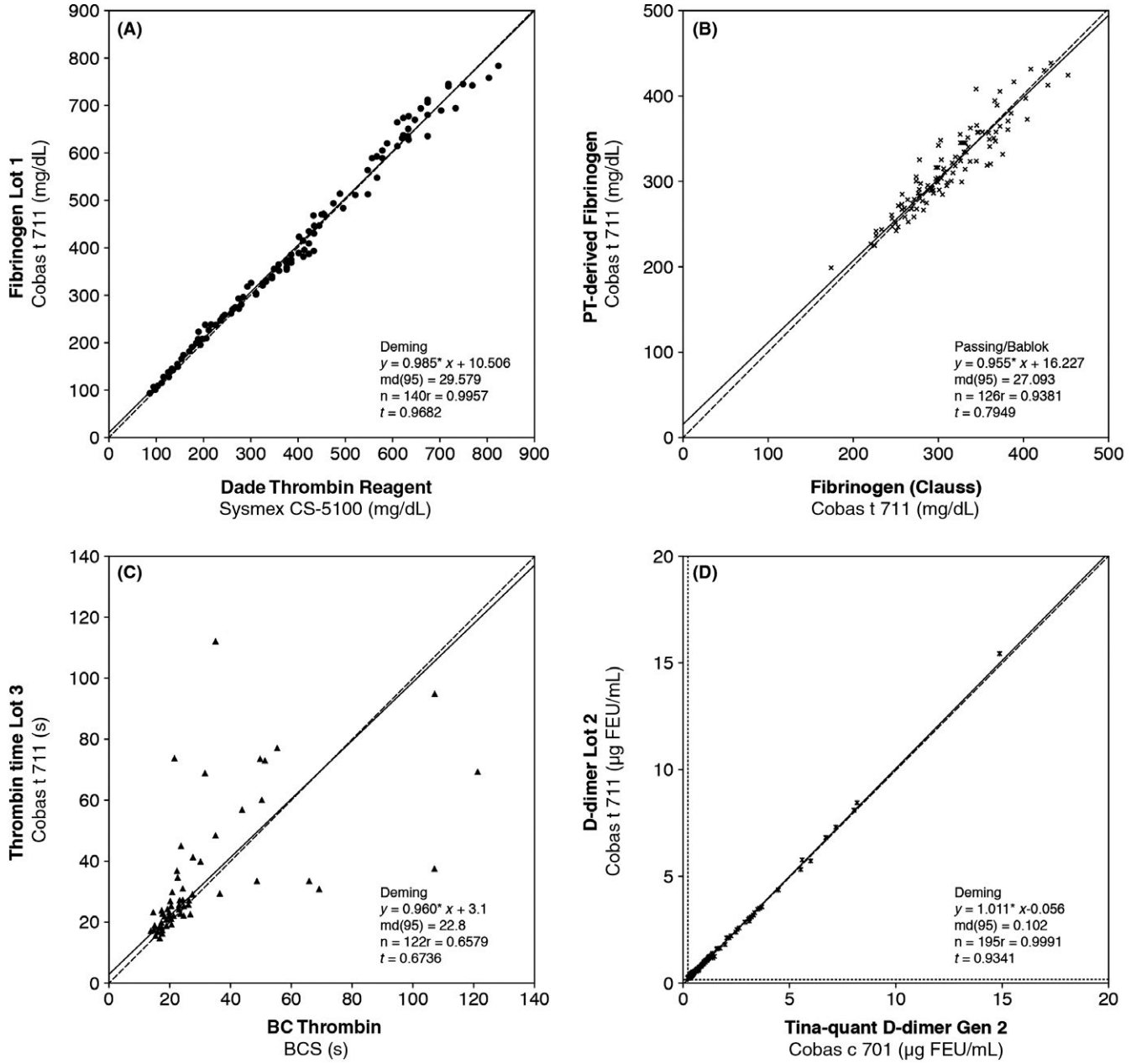

FIGURE 1 Method Comparison Between (A) Fibrinogen on **cobas t** 711 vs Dade Thrombin Reagent on Siemens Sysmex CS-5100 (Freiburg), (B) PT-Derived Fibrinogen on **cobas t** 711 vs Fibrinogen (Clauss) on **cobas t** 711 (Sheffield), (C) Thrombin time on **cobas t** 711 vs BC Thrombin on Siemens BCS (Debrecen), and (D) D-dimer on **cobas t** 711 vs Tina-Quant® D-dimer Gen 2 Reagent on Roche/Hitachi **cobas c** 701 (Sheffield). Representative examples from each site shown

tubes, and as reported previously, samples were measured fresh at the sampling site in Freiburg. All experiments were performed using three reagent lots (N = 200; n = 66 or 67 samples per lot). Reference ranges for each assay were also derived from frozen 0.109M/3.2% citrated samples (BIOMEX GmbH, Heidelberg, Germany) purchased in Becton Dickinson tubes (San Jose, CA, USA), and in frozen aliquots of the anonymized residual samples from apparently healthy adult donors, collected in Sarstedt tubes. Both types of frozen samples were measured at three different sites after thawing (one reagent lot per site). Ranges were quoted as 2.5th-97.5th percentiles with 90% confidence intervals (CI) and were accompanied by median values.

3 | RESULTS

3.1 | Analytical performance

For each assay, the coefficients of variation (CVs) for within-run precision and total reproducibility are presented in Table 1; all values were within the prespecified acceptance criteria. Across all four sites and all four assays, CVs for within-run precision in human plasma samples ranged from 0.3% to 2.9% on the **cobas t** 711 analyser and from 0.2% to 4.1% on the **cobas t** 511 analyser. CVs for total reproducibility across all four sites and all four assays ranged from 1.0% to 8.6% on

the **cobas t** 711 analyser and from 0.9% to 6.7% on the **cobas t** 511 analyser.

3.2 | Method comparison

The fibrinogen, PT-derived fibrinogen, and D-dimer assays showed good agreement vs their respective comparator methods according to prespecified criteria (specified in Product Specifications Document) based on Deming or Passing–Bablok regression analyses (Table 2; Figure 1). Pearson's correlation coefficients (presented as a range across three sites) were as follows: fibrinogen (**cobas t** 711) vs Dade Thrombin Reagent on Siemens Sysmex CS-5100/CS-2000i, r = 0.990-0.996; PT-derived fibrinogen (**cobas t** 711) vs Fibrinogen (Clauss) on **cobas t** 711, r = 0.938-0.943; thrombin time (**cobas t** 711) vs Siemens BC Thrombin on Siemens BCS, r = 0.658-0.755; D-dimer (**cobas t** 711) vs Tina-quant® D-Dimer Gen 2 reagent on Roche/Hitachi **cobas c** systems, r = 0.999-1.000. Relative bias within the data for each assay shows some variation between sites (Figures S1-S4).

3.3 | Equivalency of cobas t 711 and cobas t 511 analysers

For each of the four assays evaluated, the **cobas t** 711 and **cobas t** 511 platforms demonstrated equivalence, according to prespecified acceptance criteria based on Passing–Bablok regression analyses (Table 3). Across all four assays and sites (two sites per assay), Pearson's correlation coefficient exceeded acceptance criteria. Bland-Altman plots (Figures S5-S8) demonstrate constant bias for the four assays and consistency in results for each site.

3.4 | Lot-to-lot comparison

A high level of consistency between lots was observed for all four assays on the **cobas t** 711 analyser (Table 4); the prespecified equivalence criteria based on Passing–Bablok analyses were met. For all four assays and comparisons (Lot 2 vs 1, Lot 3 vs 2, and Lot 1 vs 3), Pearson's correlation coefficient was ≥0.994. Bland-Altman plots demonstrate constant bias for the four assays and consistency in results for each site (Figures S9-S12).

3.5 | Reference range studies

Based on fresh samples in Sarstedt tubes, reference ranges (2.5th to 97.5th percentiles [90% CI]; 200 fresh samples per assay) were: fibrinogen = 193 (167-202) to 412 (368-432) mg/dL (Clauss assay), median = 275 mg/dL; PT-derived fibrinogen = 204 (193-212) to 412 (360-466) mg/dL, median = 267 mg/dL; thrombin time = 16.1 (15.9-16.4) to 19.7 (19.5-21.5) seconds, median = 17.8 seconds. In

TABLE 3 Method comparison between **cobas t** 711 and **cobas t** 511 analysers

			Freiburg	Sheffield	Sheffield
Assay	Evaluation	Acceptance criteria	Lot 1	Lot 2	Lot 3
Fibrinogen (mg/dL)	n		140	153	
	Slope (Passing–Bablok)	1.00 ± 0.10	1.000	0.985	
	Intercept	≤25.0 mg/dL	4.000	2.524	
	Pearson's r	≥0.900	0.999	0.998	
	Relative % bias at 200 mg/dL	NA	2.00	−0.282	
PT-derived fibrinogen (mg/dL)	n		141		131
	Slope (Passing–Bablok)	1.00 ± 0.10	1.004		1.000
	Intercept	NA	0.823		−2.00
	Pearson's r	≥0.900	0.999		0.951
	Bias at 200 mg/dL	±20 mg/dL at 200 mg/dL	1.685		−2.00
Thrombin time (s)	n		141	126	
	Slope (Passing–Bablok)	1.00 ± 0.10	0.919	0.941	
	Intercept	NA	1.424	0.976	
	Pearson's r	≥0.900	0.994	0.991	
	Relative % bias at 17.8 s	NA	−0.106	−0.397	
D-dimer (μg FEU/mL)	n		233		192
	Slope (Passing–Bablok)	1.000 ± 0.075	1.000		1.004
	Intercept	≤±0.10 μg FEU/mL	−0.009		0.007
	Pearson's r	≥0.975	1.000		1.000
	Relative % bias at 0.5 μg FEU/mL	NA	−1.8		1.84

FEU, fibrinogen equivalent units; NA, not applicable; PT, prothrombin.

TABLE 4 Lot-to-lot comparison on the **cobas t** 711 analyser

Assay	Evaluation	Acceptance criteria	Freiburg Lot 2 vs 1	Sheffield Lot 3 vs 2	Debrecen Lot 1 vs 3
Fibrinogen (mg/dL)	n		140	155	130
	Slope (Passing–Bablok)	1.00 ± 0.10	0.993	1.000	0.973
	Intercept	≤±20.0 mg/dL	1.651	1.000	3.627
	Pearson's *r*	≥0.975	0.999	0.999	0.998
	Relative % bias at 200 mg/dL	NA	0.106	0.500	−0.914
PT-derived fibrinogen (mg/dL)	n		144	132	124
	Slope (Passing–Bablok)	1.00 ± 0.10	0.962	1.01	1.025
	Intercept	NA	9.20	−2.79	−4.51
	Pearson's *r*	≥0.900	0.999	0.998	0.999
	Bias at 200 mg/dL	±20 mg/dL at 200 mg/dL	1.55	−0.789	0.529
Thrombin time (s)	n		141	126	122
	Slope (Passing–Bablok)	1.00 ± 0.10	1.055	0.970	0.991
	Intercept	NA	−1.023	0.386	0.264
	Pearson's *r*	NA	0.997	0.994	0.995
	Relative % bias at 17.8 s	NA	−0.277	−0.860	0.559
D-dimer (μg FEU/mL)	n		235	191	133
	Slope (Passing–Bablok)	1.000 ± 0.100	0.978	1.029	0.983
	Intercept	≤0.1 μg FEU/mL	0.012	−0.022	0.001
	Pearson's *r*	≥0.975	1.000	1.000	0.999
	Relative % bias at 0.5 μg FEU/mL	NA	0.246	−1.61	−1.59

FEU, fibrinogen equivalent units; NA, not applicable; PT, prothrombin time.

the D-dimer assay reference range test, 70 of 200 samples were measurable on the **cobas t** 711 instrument; the rest fell below the limit of quantification (LOQ) and were reported as <0.200 μg FEU/mL; the reference range (90% CI) was <0.200 (0.200-1.22) to 0.58 (0.200-1.22) μg FEU/mL.

Comparable reference ranges (2.5th to 97.5th percentiles [90% CI]) were obtained using frozen samples prepared from Sarstedt tubes: fibrinogen (191 samples) = 188 (176-203) to 397 (371-423) mg/dL, median = 261 mg/dL; PT-derived fibrinogen (200 samples) = 201 (188-208) to 408 (358-463) mg/dL, median = 266 mg/dL; thrombin time (199 samples) = 15.9 (15.5-16.0) to 19.3 (19.0-19.6) seconds, median = 17.4 seconds. During evaluation of the D-dimer assay, 75 of 200 samples were evaluable on **cobas t** 711, while the rest fell below the LOQ; the reference range (90% CI) was <0.200 (0.200-1.21) to 0.57 (0.200-1.21) μg FEU/mL.

Similar reference ranges (2.5th to 97.5th percentiles [90% CI]) were also obtained using frozen samples stored in Becton-Dickinson tubes: fibrinogen (198 samples) = 190 (160-198) to 407 (380-444) mg/dL, median = 276 mg/dL; PT-derived fibrinogen (198 samples) = 214 (186-226) to 427 (407-453) mg/dL, median = 285 mg/dL; thrombin time (197 samples) = 14.9 (13.5-15.5) to 19.7 (19.3-21.9) seconds, median = 17.3 seconds. During evaluation of the D-dimer assay, 71 of 200 samples were evaluable on **cobas t** 711; the rest fell below the LOQ. The reference range (90% CI) was <0.200 (0.200-2.50) to 0.67 (0.200-2.50) μg FEU/mL.

4 | DISCUSSION

Each of the four coagulation assays tested demonstrated excellent analytical performance on both the **cobas t** 711 and **cobas t** 511 analysers. Overall, the CVs for all four assays were ≤4.1% for within-run precision and ≤8.6% for total reproducibility; lot-to-lot comparisons with each assay showed a high level of consistency across all sites. The fibrinogen, PT-derived fibrinogen, and D-dimer assays performed on the **cobas t** 711 analyser showed good agreement with the commercially available assays/platforms used as comparator methods, which have previously demonstrated acceptable performance.[33,34] Each assay produced high correlation coefficients at all sites (fibrinogen, *r* = 0.990-0.996; PT-derived fibrinogen, *r* = 0.938-0.943; D-dimer, *r* = 0.999-1.000). Thrombin time showed less close agreement (*r* = 0.658-0.755), but the results were still within acceptable limits. Thrombin time is an uncalibrated test used to check for anticoagulants or clotting abnormalities. Results are reported in seconds, and reagents differ between suppliers, so as a result thrombin time tests from different manufacturers are generally less comparable than other tests. Heparin sensitivity of the thrombin time reagents also differs if heparinized samples are used.

Importantly, equivalency was demonstrated between the **cobas t** 711 and **cobas t** 511 analysers. Both analysers are built from functionally identical components and process assays using the same reagents and disposables. The main difference between the

two systems is in terms of throughput: the high-throughput **cobas t** 711 can process 390 tests/h, and the medium-throughput **cobas t** 511 can process 195 tests/h. The **cobas t** coagulation analysers offer innovative features, including high processing power and increased walkaway time for mid- to high-volume coagulation laboratories. Connectivity, automated reagent reconstitution, and optimized reagent and sample management also provide laboratories with improved workflow and operating efficiency.

These four new coagulation assays could provide core laboratories with accurate and reliable tests for the screening, diagnosis and assessment of a range of coagulopathies in routine clinical practice. The fibrinogen assay using the Clauss method is intended as an aid in the detection of hypo- and hyperfibrinogenaemia, dysfibrinogenaemia and afibrinogenaemia.[35,36] The PT-derived fibrinogen assay is an alternative method for measuring fibrinogen, but may be less reliable than the Clauss method.[36] Thrombin time provides a measure of the time taken for a clot to form in plasma to which thrombin has been added, and can be used as part of an investigation into potential bleeding disorders, and/or to detect the presence of drugs that prevent conversion of fibrinogen to fibrin.[37] While the D-dimer assay is used as an aid in the exclusion of DVT/PE, it is intended to provide a fast and cost-effective test for triaging patients that present with signs and symptoms suggestive of venous thromboembolism.[38]

This study was designed to avoid biases in the evaluation of analytical performance by obtaining samples from various sources, including different collection sites and commercial vendors, and by conducting experiments at four core laboratories in different European countries. Furthermore, method comparisons were performed with existing commercially available assays and in accordance with CLSI EP09-A3 guidelines.[32] A full range of abnormalities were included in the test samples so that the methods were evaluated at all relevant levels of analyte. This study was primarily aimed at evaluating analytical performance of the four assays and did not assess the clinical performance of the assays.

In conclusion, this multicentre study demonstrates the excellent analytical performance of four new coagulation assays on the novel **cobas t** 711 and **cobas t** 511 analysers. Each coagulation assay showed good or acceptable agreement with other commercially available assays, and the improved technologies used offer core laboratories a number of advantages over existing methods for the assessment of a range of coagulopathies in routine clinical practice.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

All authors made substantial contributions to the conception or design of the work, or the acquisition, analysis or interpretation of data for the work; drafted or revised the manuscript critically for important intellectual content; approved the version to be published; and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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