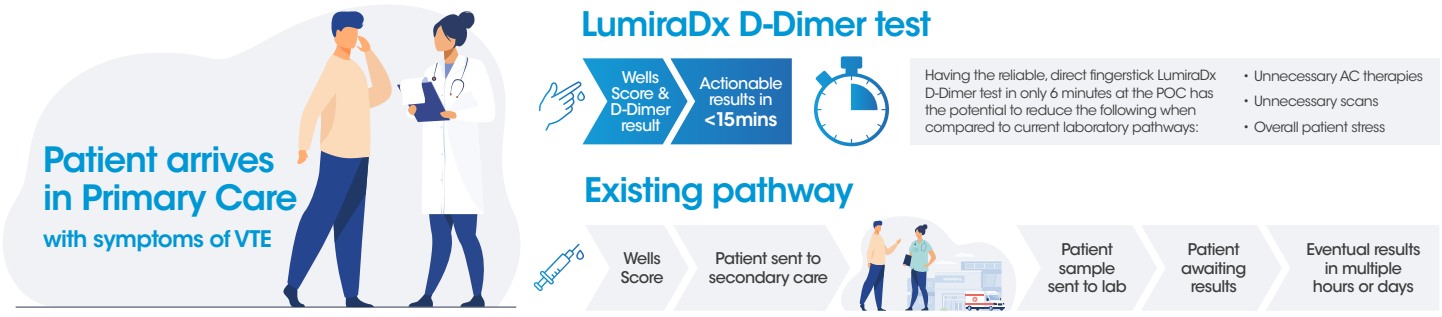
D-Dimer test
Exclude VTE with confidence in only 6 minutes*

- Clinical cut-off: 500 µg/L FEU (0.500 mg/L FEU)
- Sample size: 15 µL
- Sample types: Capillary whole blood (fingerstick), Venous (sodium citrated) or Plasma (sodium citrated)
- Time to result: 6 minutes
- Storage at room temperature

The LumiraDx point of care (POC) D-Dimer test is a fast microfluidic immunoassay designed to rapidly quantify D-Dimer levels in human capillary and venous whole blood and plasma samples (sodium citrate). It is an automated test to aid in the assessment and diagnosis of patients with suspected venous thromboembolism (VTE) such as deep vein thrombosis (DVT) and pulmonary embolism (PE) and can be used with a clinical pre-test probability assessment model to exclude DVT and PE disease.

The test result is the mean of 3 D-Dimer assays run on the unique multi-channel Test Strip. The LumiraDx D-Dimer test is the only direct fingerstick D-Dimer assay available at the point of care today**, aiding healthcare professionals to exclude deep vein thrombosis (DVT) and pulmonary embolism (PE) in symptomatic patients with confidence - all in only 6 minutes.



Exclude thrombosis (DVT) and pulmonary embolism (PE) in symptomatic patients in only 6 minutes

EMBOL-1 study

Preliminary data from the EMBOL-1 study has demonstrated that the LumiraDx D-Dimer test provides accurate results that enable its use with a low pre-test probability score (PTP) for the exclusion of VTE at the point of care when patients are presenting with symptoms of VTE. The LumiraDx D-Dimer test performance when used in combination with a low PTP assessment (Wells 'Unlikely VTE' group) for direct capillary blood, venous blood and plasma resulted in 100% sensitivity and 100% NPV for direct capillary blood, plasma and venous blood samples. The LumiraDx D-Dimer test displays agreement with analysis in the same subject cohort using the VIDAS D-Dimer Exclusion II reference method.

*In conjunction with a PTP score
**As stated at time of publication - May 2022

Clinical performance evaluation of the LumiraDx D-Dimer point of care Test for the exclusion of venous thromboembolism in symptomatic patients.

Abstract

The EMBOL-1 Study (NCT04737954) is a prospective multicentre observational clinical study evaluating the use of the LumiraDx D-Dimer point of care test alongside a pre-test probability (PTP) assessment model (Wells Score) in patients presenting into emergency care centres with signs and symptoms of venous thromboembolism (VTE, comprising Pulmonary Embolism (PE) or Deep Vein Thrombosis (DVT)). This study was an interim data analysis. Data from capillary blood, venous blood and plasma samples were included in the evaluation. In 585 included subjects, 408 had a low PTP assessment (Wells 'Unlikely VTE' group). The LumiraDx D-Dimer test performance when used in combination with a low PTP assessment (Wells 'Unlikely VTE' group) for direct capillary blood (95% CI 72.2%-100.0%), venous blood (95% CI 74.1%-100%) and plasma (95% CI 74.1%-100%) resulted in 100% sensitivity and 100% NPV for direct capillary blood, plasma (95% CI 98.1%-100%) and venous blood samples (95% CI 98.3% - 100%). This was in agreement with analysis in the same subject cohort using the plasma sample on the laboratory reference test method (VIDAS Exclusion II D-dimer, sensitivity 100% (95% CI 74.1%-100%) and 100% NPV (95% CI 98.3% - 100%)).

Key summary points

A quantitative, point of care (POC) D-Dimer test could improve the effectiveness of the established diagnosis pathway of venous thromboembolism (VTE), thereby reducing the current rate of unnecessary referrals to secondary care along with associated cost and improve patient experience.

The primary aim of this study was to assess the performance of the new quantitative point of care LumiraDx D-Dimer test in the exclusion of VTE in a group of patients presenting with signs and symptoms VTE into emergency care. Fingerstick capillary blood, venous blood and plasma (citrate) were evaluated and compared to the laboratory reference test, VIDAS Exclusion II D-Dimer.

The quantitative LumiraDx D-Dimer test had excellent sensitivity (100%) in the assessment of VTE when used at 500 µg/L FEU cut-off and a low pre-test probability (PTP) score (Wells 'Unlikely'). The NPV was 100% also across all matrices tested. Results were equivalent to those from plasma testing on the laboratory analyser.

The LumiraDx D-Dimer test when used with a low (Wells 'Unlikely') PTP can be used at the point of care for the assessment of exclusion of VTE in symptomatic patients.

Introduction

D-Dimer testing is important when used with pre-test probability models to aid in the exclusion of venous thromboembolic events (VTEs), including deep venous thrombosis and pulmonary embolism[1,2]. D-Dimer is produced upon activation of the coagulation system and is a plasmin-derived soluble degradation product of cross-linked fibrin[3,12].

With approximately 10 million cases reported globally every year, VTE is the third leading vascular disease[4].

Across six European countries, just under half a million DVTs and 300,000 PEs occur every year. Venous thromboembolism is associated with substantial morbidity and mortality. Although the 30 day mortality rate after pulmonary embolism is decreasing, about 20% of patients with pulmonary embolism still die before diagnosis or shortly thereafter[4]. Early diagnosis of VTE is important to decrease its associated morbidity and mortality rates, as there are effective therapies available, such as anticoagulant and mechanical treatments, to stop the progression

of VTE[5]. Imaging methods, such as ultrasound for DVT and computerised tomography (CT and CTPA) scans for PE, are widely accepted tools for diagnosing VTE[6,7]. However, referrals to secondary care are required for these tools which are costly and time consuming and this slows down diagnosis and treatment[2]. Signs and symptoms alone have poor sensitivity and specificity for diagnosis[4]. In those with suspected VTE, prevalence of the disease is only about 20%[4], so imaging/ultrasound is needed to avoid performing expensive radiological tests. In the outpatient setting, clinical pre-test probability (PTP) using validated scoring systems such as Wells or Geneva are used[3] to guide further testing. For those with 'low/ intermediate' or 'Unlikely VTE', a D-Dimer test is the next step where a negative result (usually 500 µg/L FEU) enables rule out of VTE[1,3]. Patients with high PTP scores (Likely VTE) are subsequently referred to secondary care for further analysis; using PTP scores in combination with D-Dimer testing has been reported to lead to more specific rule out of VTE. Indeed, it was reported that with additional D-Dimer testing VTE could be ruled out in another 20-40% of patients that were initially identified to be at risk of developing VTE using Wells score alone[6,8,9]. As a consequence, several guidelines have recommended the use of Wells score in combination with quantitative D-Dimer testing to aid the diagnosis of VTE[5,7,10,11]. As well as using a general cut-off, age adjusted D-Dimer levels are recommended in some guidelines[10,11,13]. For the exclusion of pulmonary embolism/ deep vein thrombosis, D-Dimer assays need to be clinically validated and cut-off levels verified in clinical studies to avoid inappropriate use of this biomarker in routine care[12].

Point of care quantitative D-Dimer tests offer the ability to rapidly assess patients with symptoms in acute care and primary care settings. Quantitative D-Dimer point of care tests are recommended that meet the CLSI requirements of ≥98% NPV and sensitivity of ≥97% [7,14].

This study (EMBOL-1) evaluates the clinical sensitivity and specificity of the point of care (POC) quantitative LumiraDx D-Dimer test in combination with Wells scoring to rule out VTE using fingerstick blood, compared to venous and plasma on the same instrument. The results were compared to those obtained with plasma in the laboratory using the VIDAS D-Dimer Exclusion II reference method. The data represents an interim analysis of the EMBOL study with prospectively, consecutively recruited subjects between March 2021 and June 2022 in 10 clinical sites.

Methods

Study design

The EMBOL 1 study (NCT04737954) is a prospective observational study to evaluate the clinical performance of the LumiraDx D-Dimer test. The study was conducted at multiple sites in the UK and Germany between March 2021 and June 2022. The study sites were in the Emergency Departments of the following hospitals: Manchester Royal Infirmary, Manchester; Edinburgh Royal Infirmary, Edinburgh; St George's Hospital, London; University College London Hospital, London; Royal London/ St Barts, London; Homerton Hospital, London; Addenbrookes Hospital, Cambridge; South Warwickshire Hospital, Warwick; St John's Hospital, Edinburgh; University Medical Centre-Hamburg Eppendorf, Germany.

Participants were of any sex and ≥18 years old, presenting with the symptoms of a thromboembolic event. Exclusion criteria included suspected sinus or cerebral venous thromboembolism; end-stage renal failure on haemodialysis; current anticoagulant therapy with dalteparin (Fragmin) or low-molecular-weight heparin (LMWH); previous participation in this study; documented life expectancy of <30 days; haemodynamic instability; anticoagulant therapy with direct-acting anticoagulants (DOACs), warfarin or heparin within the last 30 days; patient being deemed medically unfit to participate.

From each patient a Wells Score assessment was completed (Likely or Unlikely PTP categorisation)[7]. Following this, using a finger-stick method, two 20 µL capillary blood samples were obtained for direct testing on the LumiraDx D-Dimer test. Two additional 20 µL capillary blood samples were obtained for immediate testing on the LumiraDx D-Dimer test using a transfer tube application method.

A venous blood sample, <20 mL, was also drawn from each patient into tubes containing an anticoagulant (citrate). Two 20 µL samples from the drawn blood were immediately tested on the LumiraDx D-Dimer test. The remaining venous blood samples were processed immediately (within 1 hour) to plasma using centrifugation, frozen at -80 °C and transported to the LumiraDx laboratory (Stirling, UK). At the laboratory site, plasma samples were thawed and tested in duplicate within 1 hour of thawing, on the reference test VIDAS D-Dimer Exclusion II and on the LumiraDx D-Dimer test.

Test details

The LumiraDx Platform test comprises the Instrument and LumiraDx D-Dimer Test Strips which can be used with capillary blood (direct blood drop or transfer tube application) venous blood (citrate tube), or plasma samples (citrate)[15]. D-Dimer molecules in the sample form sandwich complexes with the fluorescent latex particles and magnetic beads on the test strip; a magnetic field is applied to retain such complexes while an air wash removes any residual sample and unbound latex particles. The fluorescence emitted by the latex particles that are bound in the complexes is detected and quantified by the spectrometer in the LumiraDx Instrument. The test provides a quantitative result in 6 minutes.

The testing device also has built-in quality control features, which include haematocrit analysis to check sample is within 25-55%, correction to Fibrinogen Equivalent Units (FEU) regardless of the sample type (capillary/venous blood or plasma), a sample volume check, automated test strip positioning and test strip expiration checks.

Statistical analysis

The performance of the LumiraDx D-Dimer test in excluding the presence of a VTE in symptomatic patients was assessed in the following analyses:

a) LumiraDx D-Dimer cut-offs of 500 µg/L FEU and 533 µg/L FEU in combination with Wells Score (PTP) – applied to all sample matrices.

b) PTP (Unlikely) subset + LumiraDx D-Dimer cut-off of 500 µg/L FEU – applied to all sample matrices.

c) PTP (Unlikely) subset + VIDAS Exclusion II D-Dimer cut-off of 500 µg/L FEU – plasma only.

The sensitivity, specificity, and negative and positive predictive values, with their 95% Wilson Score confidence intervals were calculated for each sample type and application method for ruling out VTE. Software used for the analysis was Microsoft® Excel® for Microsoft 365 MSO (16.0.14326.20900) 64-bit and Analyse-it for Microsoft Excel 5.40.2 build 7187.28957. Concurrent validation of the analysis was performed by a 2nd operator in Python 3.9.7 on JupyterLab 3.2.6.

Ethical approval

Ethics approval was granted by North West - Greater Manchester South Research Ethics Committee (UK) under REC reference 19/NW/0070. Approval in Germany was obtained from the Ethics Committee of the Ärztekammer (Ref Number: 00013476).

Results

Study participants

684 participants were prospectively consented onto the EMBOL-1 trial. Between March 2021 and June 2022. Ninety-nine subjects were excluded. Figure 1 presents the Inclusion Decision Flow Chart and reasons for exclusion. In the final included dataset, 585 subjects had a valid PTP assessment score and 54 VTE events were confirmed (all PTP Group). The mean age of participants was 51 years (range 18–97), and 59% were female. Participants were presenting in hospital with suspected VTE. Samples were collected between March 2021 and June 2022.

Of these subjects, 408 were classified as 'VTE Unlikely' by the Wells PTP score. Some subjects did not have a full set of sample matrices collected (e.g., fingerstick test failure, but venous tube / plasma collected and tested). Therefore, included subjects per matrix varies as valid data was included where available (Figure 1).

Assay validation

Analysis of sensitivity, specificity, positive and negative predictive values (PPV, NPV) were calculated and are summarised for all subjects with PTP assessments using either 500 µg/L or 533 µg/L FEU LumiraDx D-Dimer result as cut-off for positive and negative results. All results and 95% CI are presented in Table 1. Two cut-off values were analysed, as 533 µg/L is the 90th centile previously published for the LumiraDx D-Dimer test[15]. In clinical use of D-Dimer, 500µg/L is commonly used[1], therefore the study evaluated differences between using these two cut-offs. Sensitivity for all matrices using the cut-off values plus Wells PTP Score was 100% (95% CI 91.9 %-100%) and NPV was 100% (95% CI 98.1%-100%) at 500 µg/L and at 533µg/L sensitivity was 100% (95% CI 91.9 %-100%) and NPV was 100% (95% CI 98.1%-100%). There was no significant difference detectable if 500 µg/L or 533 µg/L were used as cut-off with PTP assessment.

PTP assessments are commonly used with D-Dimer when low/ intermediate or 'Unlikely VTE' scores are determined. A further performance analysis was completed with the LumiraDx D-Dimer test was used in combination with a low PTP assessment (Wells 'Unlikely VTE' group) at the 500 µg/L cut-off. This was completed for direct capillary blood, capillary blood by transfer tube application, venous blood (citrate) and plasma (citrate) (Table 2).

The LumiraDx D-Dimer test sensitivity at 500 µg/L when used in combination with a low PTP assessment (Wells 'Unlikely VTE' group) for direct capillary blood (95% CI 72.2%-100.0%) and , capillary blood by transfer tube application (95% CI 67.6%-100.0%) was 100.0% and NPV was 100.0% (95% CI 98.1%-100.0%). Both direct capillary application to the test strip and transfer tube methods gave equivalent results (Table 2).

The LumiraDx D-Dimer test sensitivity at 500 µg/L when used in combination with a low PTP assessment (Wells 'Unlikely VTE' group) for venous blood (sodium citrate) was 100.0% (95% CI 74.1%-100.0%) and NPV was 100.0% (95% CI 98.3%-100.0%).

The LumiraDx D-Dimer test sensitivity at 500 µg/L when used in combination with a low PTP assessment (Wells 'Unlikely VTE' group) for plasma (sodium citrate) was 100.0% (95% CI 74.1%-100.0%) and NPV was 100.0% (95% CI 98.1%-100.0%).

Analysis of 500 µg/L and 533 µg/L as cut-off with and without PTP assessment (all subjects Wells score) indicated no significant difference. This together, with the independent analysis of the Unlikely PTP + D-Dimer, supports use of 500 µg/L as the cut-off with the Unlikely PTP assessment.

The results from the cut-off assessment (EMBOL-1 study interim analysis 2) are aligned with the CLSI recommendation for a D-Dimer test with PTP assessment model (low/ intermediate) of NPV ≥98% and sensitivity ≥97%[14].

The same analysis was completed using the low PTP assessment (Wells 'Unlikely VTE' group) and VIDAS Exclusion II D-Dimer test with citrated plasma at the 500 µg/L cut-off. Results in agreement were found with the LumiraDx point of care test (Table 3).

Discussion

The LumiraDx D-Dimer point of care test is a quantitative test that has been previously shown to have accurate results compared to the laboratory reference test and also demonstrated to be easy to use by users in POC settings[15]. The study results show that this novel quantitative POC test provides accurate results that enable its use with a low pre-test probability score (PTP) for the exclusion of VTE at the point of care when patients are presenting with symptoms of VTE, and a quantitative D-Dimer test result is quickly needed. When utilized in line with the diagnostic guidance, this could facilitate more accurate referrals for imaging diagnostics of VTE and has the potential to save costs due to unnecessary referrals and lab D-Dimer tests.

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Figures and tables

Table 1

Clinical Performance of LumiraDx D-Dimer cut-offs of 500 µg/L FEU and 533 µg/L FEU in combination with PTP assessment (Wells) applied to all sample matrices.

	Matrix	500µg/L D-Dimer	533µg/L D-Dimer
PPA	Venous	100% (93.24% - 100%)	100% (93.24% - 100%)
	Capillary Direct	100% (92.87% - 100%)	100% (92.87% - 100%)
	Capillary Transfer	100% (91.97% - 100%)	100% (91.97% - 100%)
	Plasma	100% (93.24% - 100%)	100% (93.24% - 100%)
NPA	Venous	44.92% (40.58% - 49.34%)	44.95% (42.58% - 51.37%)
	Capillary Direct	41.26% (36.99% - 45.66%)	42.53% (38.19% - 46.99%)
	Capillary Transfer	40.46% (36.17% - 44.90%)	42.53% (38.19% - 46.99%)
	Plasma	38.11% (34.08% - 42.32%)	40.19% (36.10% - 44.42%)
PPV	Venous	16.36% (12.73% - 20.78%)	16.88% (13.14% - 21.42%)
	Capillary Direct	14.75% (11.37% - 18.92%)	15.20% (11.72% - 19.48%)
	Capillary Transfer	13.29% (10.05% - 17.37%)	13.71% (10.37% - 17.90%)
	Plasma	13.91% (10.79% - 17.75%)	14.32% (11.12% - 18.26%)
NPV	Venous	100% (98.29% - 100%)	100% (98.36% - 100%)
	Capillary Direct	100% (98.14% - 100%)	100% (98.23% - 100%)
	Capillary Transfer	100% (98.07% - 100%)	100% (98.16% - 100%)
	Plasma	100% (98.13% - 100%)	100% (98.23% - 100%)
Prevalence	Venous	9.72%	9.72%
	Capillary Direct	9.23%	9.23%
	Capillary Transfer	8.37%	8.37%
	Plasma	9.09%	9.09%
N	Venous	545 (VTE = 53)	545 (VTE = 53)
	Capillary Direct	542 (VTE = 50)	542 (VTE = 50)
	Capillary Transfer	526 (VTE = 44)	526 (VTE = 44)
	Plasma	583 (VTE = 53)	583 (VTE = 53)

Table 2

Clinical Performance of LumiraDx D-Dimer in the Low PTP (PTP Unlikely group from Wells) at cut-off of 500 µg/L FEU applied to all sample matrices.

Estimate	Matrix	Patients with Suspected VTE
		Unlikely PTP
Sensitivity % (95% CI)	Venous	100.0% (74.1%-100.0%; n = 378)
	Capillary Direct	100.0% (72.2%-100.0%; n = 377)
	Capillary Transfer	100.0% (67.6%-100.0%; n = 374)
	Plasma	100.0% (74.1%-100.0%; n = 406)
NPV % (95% CI)	Venous	100.0% (98.3%-100.%; n = 378)
	Capillary Direct	100.0% (98.1%-100.0%; n = 377)
	Capillary Transfer	100.0% (98.1%-100.0%; n = 374)
	Plasma	100.0% (98.1%-100.0%; n = 406)
Specificity % (95% CI)	Venous	60.2% (55.1%-65.1%; n = 378)
	Capillary Direct	55.3% (50.2%-60.3%; n = 377)
	Capillary Transfer	53.3% (48.2%-58.3%; n = 374)
	Plasma	51.1% (46.2.%-56.0; n = 406)
PPV % (95% CI)	Venous	7.0% (4.0%-12.1%; n = 378)
	Capillary Direct	5.7% (3.2%-10.3%; n = 377)
	Capillary Transfer	4.5% (2.3%-8.6%; n = 374)
	Plasma	5.4% (3.0%-9.4%; n = 406)

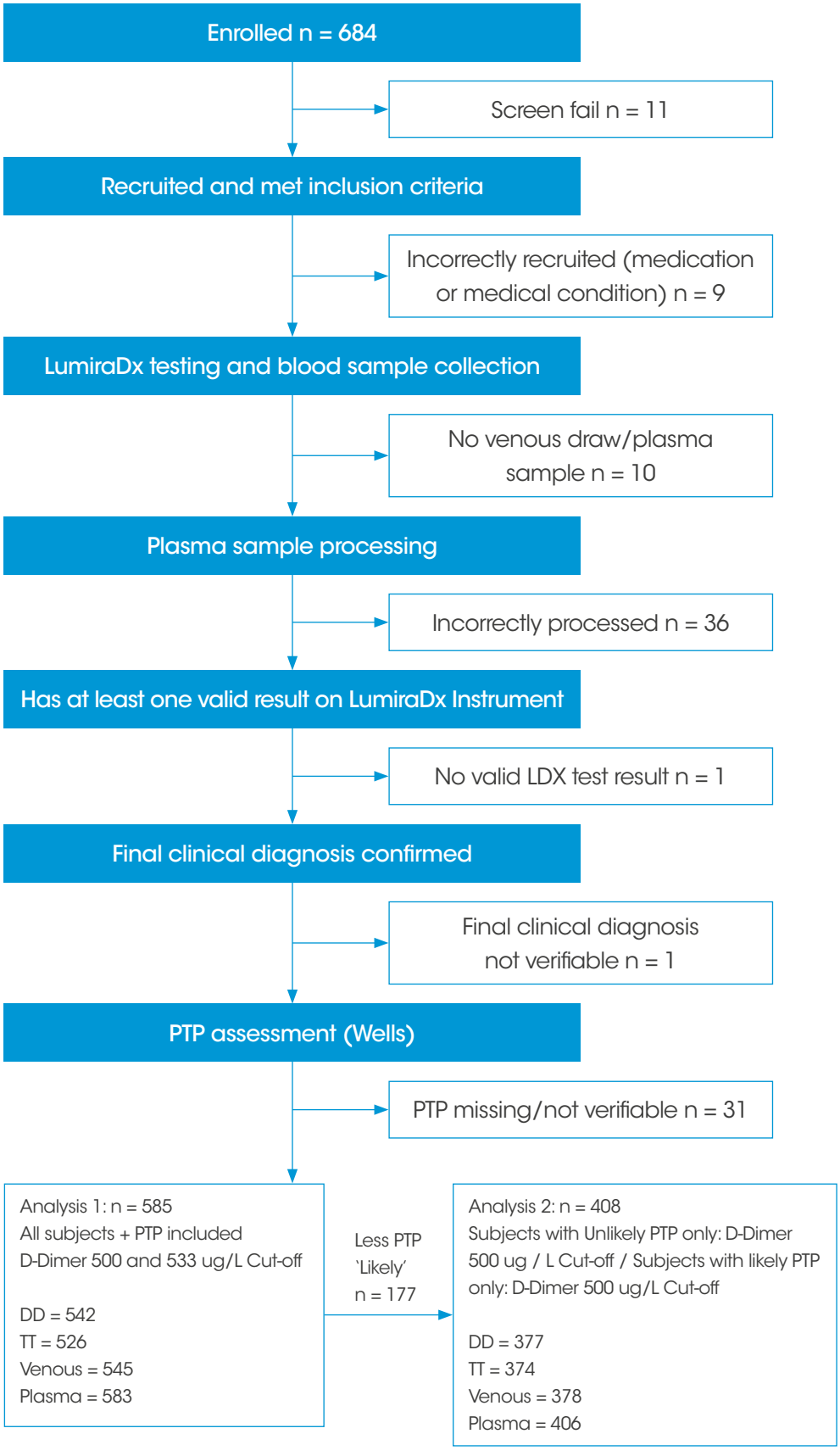
Table 3

Clinical Performance of LumiraDx D-Dimer (capillary blood direct application) and VIDAS Exclusion II D-Dimer (citrate plasma) in the Low PTP (PTP Unlikely group from Wells) at cut-off of 500 µg/L FEU applied to all sample matrices.

Estimate	LumiraDx D-Dimer (Capillary Direct)	VIDAS Exclusion II D-Dimer (Plasma)
Sensitivity (95% CI)	100% (72.2% - 100%)	100% (74.1% - 100%)
NPV (95% CI)	100% (98.1% - 100%)	100% (98.3% - 100%)
Specificity (95% CI)	55.3% (50.2% - 60.3%)	56.5% (51.5% - 61.3%)
PPV (95% CI)	5.7% (3.2% - 10.3%)	6.0% (3.4% - 10.4%)

Figure 1. Inclusion/Exclusion decision flowchart.

Sample types and subject numbers: DD – Direct capillary fingerstick blood; TT – Transfer tube fingerstick blood.



EMBOL-1 study sites and investigators

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