D-dimer; understanding pitfalls in comparing POCT and laboratory methods

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Background

Quantitative measurement of D-dimer, a small protein fragment released in clot degradation, is **recommended by NICE[1] as a non-invasive tool in the assessment of venous thromboembolism** (VTE; deep vein thrombosis (DVT) and pulmonary embolism (PE)). When interpreted against age-adjusted cut-offs, in combination with the clinical Wells Score, in low-risk patients a **negative D-dimer result may prevent unnecessary radiological investigation or prescribing of interim anticoagulation**.

Point of care testing (POCT) for D-dimer is recommended where lab services cannot offer a turn-around time of <4h[1]. In some settings there may be both laboratory and POCT services offered in parallel. As there is **no standardisation of D-dimer assays**, methods from different manufacturers / platforms are not expected to compare analytically, due to the lack of international standard calibration and different sources of antibody used in immunoassays. **Sample type may also differ** between POCT and lab.

Understanding the performance of different assays is important to clinical interpretation and developing appropriate testing strategies.

Aims

To understand the relative analytical and clinical performance of D-dimer POCT and lab assays in use within our network by:

a) **method comparison of paired patient samples**

b) **assessment of clinical performance by consideration of presentation, clinical findings and radiological results**

Materials and methods

Comparison of paired clinical samples from patients presenting to the Frimley Park Hospital Ambulatory Emergency Care Unit (AECU) with symptoms of VTE (unilateral leg pain and/or swelling, chest pain, breathlessness) in whom a D-dimer test was clinically required.

Where patients had received both tests taken on concurrent samples (phlebotomy episodes within 2h of each other), the results were retrieved from the LIMS (Clinisys Winpath Enterprise) and compared via linear regression in MS Excel spreadsheets.

POCT D-dimer Method:

Radiometer AQT90 Flex (AQT90): lithium heparin venous whole blood sample: 2-step biotin-streptavidin sandwich immunoassay with time-resolved fluorescence detection of europium-labelled tracer antibodies.
Analytical range 80 – 100 000 ng/mL
Analytical time ~20 minutes

Laboratory D-dimer Methods:

HemosIL D-dimer HS 500 on Werfen ACL Top 50 series analyser (HemosIL): citrated venous plasma samples: turbidimetric latex agglution immunoassay
Analytical range 215 – 7650 ng/mL, extended range up to 128 000 ng/mL (with dilution)

STA-Liatest D-di on STAGO Star platform (STAGO): citrated venous plasma sample: Latex microparticle agglutination immunoassay with photometric detection.
Analytical range 270 – 4000 ng/mL, extended range up to 20 000 ng/mL (with dilution)

Target lab turnaround time from sample receipt: 4h

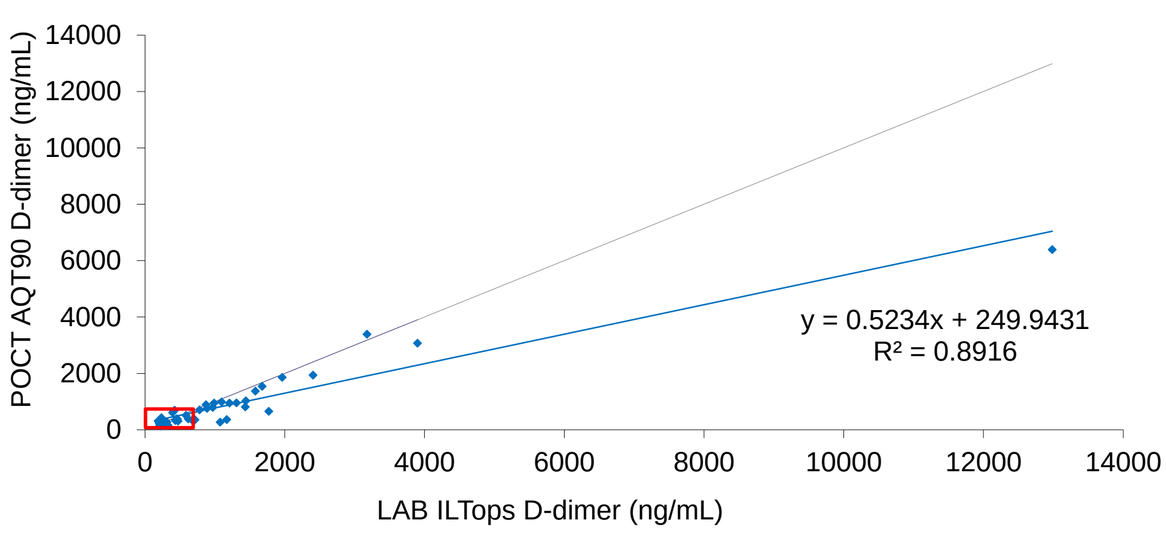
All results are interpreted against the age-related cut-off for patients over 50y (age x 10ng/mL), or 500ng/mL for patients of 50y or less[1].

Patients/Samples:

- 43 paired samples for POCT AQT90 vs lab HemosIL
- 73 paired samples for POCT AQT90 vs STAGO

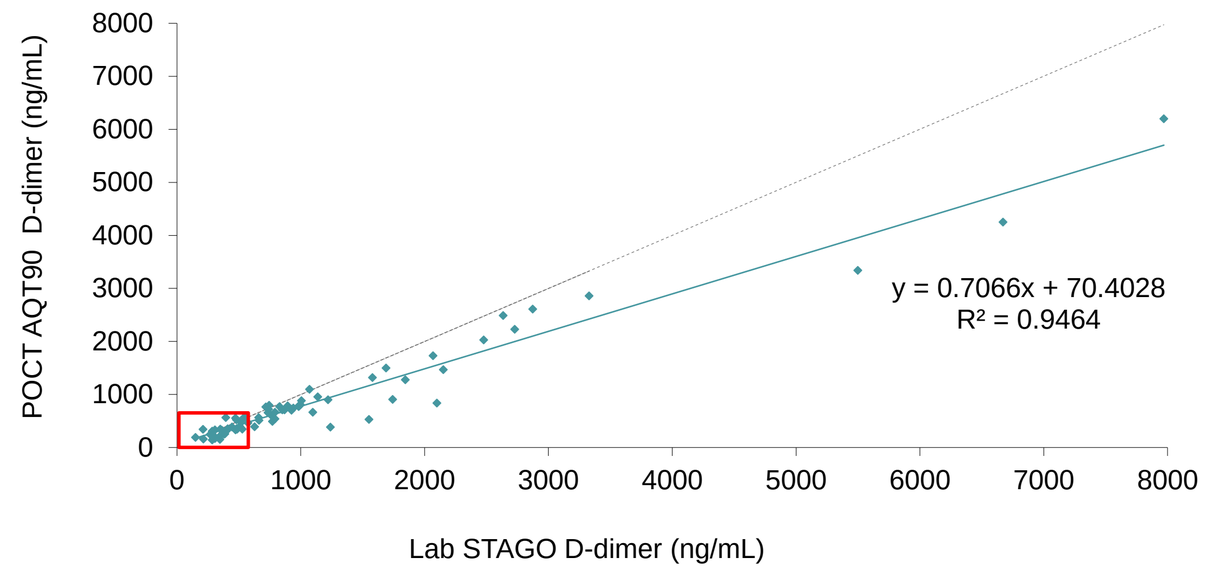
Results

POCT AQT90 vs Lab HemosIL



Linear regression
Line of equivalence (y = x)
Delineates cut-off of 500ng/mL

POCT AQT90 vs Lab STAGO



Linear regression
Line of equivalence (y = x)
Delineates cut-off of 500ng/mL

	Slope (proportional bias)	Intercept (constant bias)	R^2 (fit)
AQT90 vs HemosIL	0.5234	+249.9	0.8916
AQT90 vs STAGO	0.7066	+70.4	0.9464

Discussion

The data demonstrates the potential variability in reported D-dimer results between assays due to due to the **lack of standardised calibration and differences in antibodies and target epitopes** used.

Clinical assessment of test performance showed that **all 3 assays had 100% negative predictive value** against the age-related cut-off[1]. However, there was more variability in the **clinical specificity; POCT AQT90 66%, Lab HemosIL 51%, Lab STAGO 61%.** Poor specificity for D-dimer is well-established, and is due to non-specific elevations in conditions including (but not limited to) pregnancy, malignancy, trauma, surgery, infection, liver / renal disease and Covid-19.

Advice provided to our clinical users:

- **Avoid duplication** between POCT and lab, as different numerical results cause clinical confusion, plus sustainability concerns and financial waste.
- If a POCT result is in doubt, repeat on POCT with a fresh sample first
- The **POCT AQT90 method has fewer false positives** than the lab.
- Use **age-related cut-off for patients over 50y**, and Wells Score, as per NICE[1] to improve rule-out performance of the assay.

References

1. NICE NG158 Venous thromboembolic diseases: diagnosis, management and thrombophilia testing (2020)

Acknowledgements:

Thanks to the staff of BSPS Frimley Park Blood Sciences department for collaboration and support. To the AECU team for engagement with this work, and to the POCT team for assistance with data extraction and analysis

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