Proposal for harmonization of D-dimer assays

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Background:

Numerous, large-scale, methodologically rigorous, diagnostic management studies have validated the use of diagnostic strategies incorporating clinical decision rules and D-dimer in the outpatient diagnosis of venous thromboembolism (VTE). [1-3] Other validated indications for D-dimer include the prediction of recurrent VTE, and the diagnosis of disseminated intravascular coagulation (DIC). [4, 5] Recently D-dimer has been used as a biomarker in risk-stratifying illness severity in Coronavirus Disease 2019 (COVID-19), and in diagnostic algorithms for vaccine induced thrombotic thrombocytopenia (VITT). [6, 7]

There is significant inter-assay variability between different D-dimer assay results due to the following reasons:

(1) There are a plethora of D-dimer assays in use worldwide (over 30 unique assays) that use unique monoclonal antibodies to antigen D-dimer. These antibodies may bind different epitopes and thus have varying degrees of cross reactivity to the fibrin and fibrinogen degradation products present in patient plasma.
(2) D-dimer assays are not calibrated using a common calibrator. International efforts to produce a common reference material for calibration have been unsuccessful so far. [8] It is very likely that it may not be possible to obtain such a reference preparation in the near future.

Over a decade of data from external proficiency surveys over the last 15 years with thousands of participating laboratories worldwide, show wide inter-assay coefficients of variation of results on the same sample across the D-dimer concentration. [9-11] This inter-assay variability is especially poor at typical VTE exclusion thresholds. [9, 12] In addition, D-dimer results are reported in two types of units (D-Dimer units [DDU] and fibrinogen equivalent units [FEU]), and seven or more types of magnitude of units, setting the stage for numerous permutations and

combinations of reporting units (up to 28 possible). [13] Published data from external proficiency survey providers show confusion among users around the multiple reporting units and the possibility of clinical error. [10, 11]

The above issues have potential real-world consequences in the diagnosis of VTE which is the most common clinical indication for using D-dimer. Clinicians, unaware of this significant inter-assay variability use D-dimer assays interchangeably, generalizing efficiency and safety data from clinical management studies that have used different D-dimer assays to their clinical settings. A limited amount of published data has highlighted the significant clinical impact of misclassifying patients, and making decisions about VTE diagnosis as well as risk stratifying patients with recurrent VTE on the basis of D-dimer assay substitution. [14, 15] This issue is only just beginning to be acknowledged. In addition to using conventional D-dimer VTE exclusion thresholds, recent management trials have validated empiric adjustment of this D-dimer threshold, but again only using specific D-dimer assays, based on age or clinical probability of having VTE, thus compounding this problem. [1-3] Internationally, there have now been several publications calling for standardization and harmonization of D-dimer as well as improvements in reporting standards in the peer reviewed literature. [13, 16, 17]

Proposal:
Under the leadership of the International Society on Thrombosis and Haemostasis (ISTH) Scientific and Standardization Committee (SSC) on Predictive and Diagnostic Variables in Thrombotic Disease, we suggest publishing a guidance document in which the following actions are proposed.

(1) A call to manufacturers of the major D-dimer assays in use worldwide, to first harmonize their D-dimer reporting to one type of unit for use in VTE diagnostics. We propose the Fibrinogen Equivalent Unit or FEU rather than the D-dimer unit or DDU. Secondly, to harmonize the magnitude of this unit to 500 μg/L. We recommend these units since 500 μg/L FEU are the units that have been used in the most recent conventional and adjusted threshold studies, and are generally accepted by practicing clinicians as an exclusion threshold for VTE diagnosis. D-dimer threshold adjustment based on age or clinical probability is an empiric adjustment, and will only benefit from this step, since the D-dimer will no longer be reported in DDU.

(2) A requirement for all current and future D-dimer assay manufacturers to provide the following mandatory information about their assay on easily accessible product information monographs (1) performance characteristics – sensitivity, specificity, positive and negative predictive values for exclusion of venous thromboembolism (VTE)

(2) whether the assay is validated for exclusion of VTE or not (based on CLSI criteria), and the published and unpublished studies supporting this claim.

(3) A requirement to develop minimum reporting standards specific to D-dimer for protocols for studies using D-dimer assays and manuscripts reporting on D-dimer assays. These standards would include information on the specific D-dimer monoclonal antibody, origin of the calibrator and D-dimer reporting unit used in the assay. For clinical trials using D-dimer, a detailed description of the study population would be mandatory.

(4) To investigate and implement a sustainable harmonization procedure for D-dimer assay results on the basis of a mathematical model described by Meijer et al (2006) [18] and externally validated in one study so far [19], using common calibrant plasmas [20]. This will involve the development of a common calibrator (or set of calibrant plasmas), a procedure for harmonization, and a roadmap for implementation and sustainability of the harmonization system.

To make development and implementation of the above feasible, a close collaboration between laboratory experts, external quality assessment programs and diagnostic companies is necessary. Under the auspices of the ISTH-SSC on Predictive and Diagnostic variables, a round table meeting with relevant stakeholders will be organised during the ISTH meeting in Bangkok, Thailand in June 2024 to assess interest and develop potential next steps.

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