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STATE OF THE ART

D-dimer diagnostics: can I use any D-dimer assay? Bridging the knowledge-to-action gap

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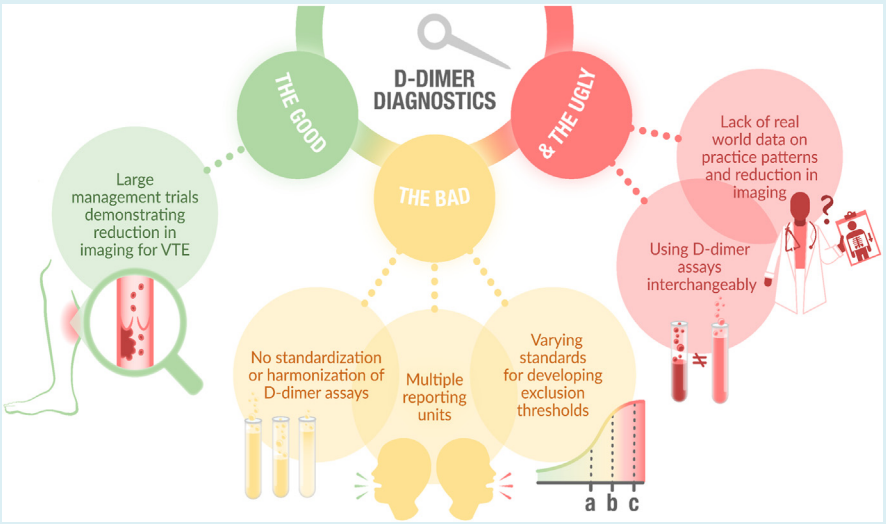
Abstract

A State of the Art lecture titled "D-dimer Diagnostics: Can I use any D-dimer assay? Bridging the Knowledge-to-Action gap" was presented at the International Society on Thrombosis and Haemostasis Congress in 2023, included in the session on the clinical impact of variability in commonly used coagulation assays. Here, we review the role of D-dimer, primarily in the outpatient diagnosis of patients with venous thromboembolism (VTE) when combined with clinical decision rules. We focus on the recent large management trials that have studied adjustments of VTE exclusion thresholds for D-dimer based on either prior clinical probability of VTE or patient age, and the resultant benefit of reduced imaging for VTE and improved diagnostic efficiency. In this context, we report on the significant variability between D-dimer results and the multiple D-dimer assays in use worldwide using data from international external quality assurance programs. This variability is particularly high at typical VTE exclusion thresholds. We discuss the potential clinical impact of D-dimer assay substitution on accuracy of diagnosis and risk stratification of patients with VTE. Finally, we summarize relevant new data on this topic presented during the 2023 International Society on Thrombosis and Haemostasis Congress and outline future priorities urgently needed to harmonize D-dimer results and reporting that will require international collaboration among multiple stakeholders with an overall goal to close this knowledge-to-action gap.



KEYWORDS
D-dimer, diagnosis, external proficiency, quality assurance, venous thromboembolism

Essentials

- Venous thromboembolism (VTE) diagnostic algorithms using D-dimer (DD) can safely reduce imaging.
- DD assays used in VTE algorithms are heterogeneous and should not be used interchangeably.
- We need urgent collaborative efforts to harmonize DD assay results and standardize reporting.
- The goal is to improve VTE diagnostic algorithm adherence and demonstrate real-world benefit.

1 | INTRODUCTION

D-dimer is a terminal soluble breakdown product of fibrinolysis generated by the action of plasmin on cross-linked fibrin [1]. D-dimer is a very sensitive biomarker of thrombosis but lacks specificity in that it can be elevated in many other health states, both physiological and pathological. D-dimer increases in pregnancy, with increasing age, as an acute phase reactant in inflammatory states, after surgery and trauma, and with malignancies [1,2].

D-dimer has been used in the diagnosis of venous thromboembolism (VTE) for at least 2 decades now, in combination with validated clinical decision rules (CDRs) [3]. Other clinical indications for D-dimer include the prediction of recurrent VTE and the diagnosis of disseminated intravascular coagulation [4,5]. Recently, D-dimer has been used to risk-stratify illness severity in COVID-19 and in diagnostic algorithms for vaccine-induced thrombotic thrombocytopenia [6,7].

Based on current laboratory proficiency data from international external quality assessment programs, there are around 30 different D-dimer assays in use worldwide, predominantly automated quantitative methods that report D-dimer results as a numerical value. A minority of laboratories still use qualitative or semiquantitative methods that are not recommended for use in VTE diagnosis.

2 | CURRENT USE OF D-DIMER IN VTE DIAGNOSTIC ALGORITHMS

Older diagnostic management studies validated the use of CDRs and D-dimer to rule out VTE in symptomatic outpatients with a low or moderate pretest probability (PTP) of having VTE [3]. A single, binary exclusion threshold or cutoff based on the specific D-dimer assay in combination with a CDR was an effective and safe strategy, reducing the need for imaging and anticoagulation in these patients. Since 2014, large prospective diagnostic management trials have studied combining validated CDRs and adjustment of the D-dimer exclusion threshold based on increasing age or using a higher cutoff value in patients with a lower probability of having VTE [8–11]. The goal of this research was to increase the proportion of patients in which VTE can be safely ruled out, thereby avoiding the risks and costs of unnecessary imaging and anticoagulation. The results have been encouraging. Both adjusting the D-dimer exclusion threshold based on age [8] or clinical probability of VTE [9–11] in low to moderate-risk symptomatic outpatients substantially reduced the need for imaging for VTE and was safe, with a VTE incidence of <1% at 3 months follow-up without anticoagulation. These studies used up to 6 different automated high-sensitivity D-dimer assays [8–11].

3 | INTERASSAY VARIABILITY BETWEEN D-DIMER RESULTS: CAUSES AND CLINICAL IMPACT

3.1 | D-dimer assays are inherently heterogeneous

Patient plasma is a "minestrone soup" of not just D-dimer antigen but various fibrin degradation products (intermediate and high-molecular-weight fibrin polymers), which are the product of plasmin-based fibrin digestion ("fibrinolysis") [12]. Monoclonal antibodies to antigen D-dimer used in various D-dimer methods are diverse, recognize different epitopes, and have varying cross-reactivity to the D-dimer antigens present on fibrin degradation products in patient samples with elevated D-dimer [12]. In addition, D-dimer results are reported in 2 types of units (D-dimer units and fibrinogen equivalent units [FEU]) and 7 or more types of magnitude of units, with or without age adjustment, setting the stage for numerous permutations and combinations of reporting units (up to 28 possible units) [13]. Published data from external proficiency survey providers show confusion among users around the multiple reporting units and the possibility of clinical error [14,15]. This confusion extends to authors publishing in the international literature, as recently highlighted for D-dimer use in COVID-19 [16].

3.2 | D-dimer assays are not standardized or harmonized

The various D-dimer assays in clinical use worldwide are neither standardized (calibrated to a common D-dimer standard) nor harmonized (reported using a shared consensus value). There is currently no available international reference material for use as a universal D-dimer standard to calibrate D-dimer assays from various manufacturers. In 2001, Dempfle et al. [17] launched the Fibrin Assay Comparison Trial to generate basic data to develop a common D-dimer calibrator using 3 candidate reference preparations and 23 different D-dimer assays. Of the 3 reference preparations, terminal plasmin digest of a fibrin clot, pooled plasma from patients with disseminated intravascular coagulation, and a high-molecular-weight fibrin oligomer, they found that the patient plasma pool with high levels of D-dimer antigen provided the best conformity across all assay systems. In 2022, Bevan and Longstaff [18], scientists at the Biotherapeutics Division, National Institute for Biological Standards and Controls (UK), published the most recent study investigating a pool of patient plasma with high levels of D-dimer antigen as a World Health Organization international standard for D-dimer. They reported instability of the candidate standard, with a loss of reactivity of 10% to 18% per year after freeze-drying and storage at −20 °C. Efforts to develop a reference D-dimer standard are, therefore, still a work in progress. Since efforts to develop a common D-dimer calibrator reference standard have not yet been successful, efforts to harmonize D-dimer values from different assays to a common scale by applying a validated conversion factor, as recently recommended by the International Society on Thrombosis and Haemostasis (ISTH) Scientific and Standardization Committee for Fibrinolysis could be undertaken [19]. One such harmonization calculation using a method-specific conversion factor described by Meijer et al. [20] has been shown to significantly reduce interassay variability and has been externally validated in a recent study on COVID-19 [21].

3.3 | Not all D-dimer assays are validated for exclusion of VTE

When D-dimer is used for the purpose of excluding deep vein thrombosis (DVT) or pulmonary embolism (PE), a critical issue is developing a cutoff below which DVT or PE can be confidently excluded, known as the exclusion threshold of the assay. When the US Food and Drug Administration (FDA) clears a D-dimer assay for use, the labeling for the assay indication includes 2 levels of clearance. Assays may be used for "Exclusion of DVT or PE" or as an "Aid in the Diagnosis of DVT or PE" [22]. The level of supporting evidence and study designs that are required to obtain each of these indications are fundamentally different. Manufacturers seeking an "exclusion of DVT or PE" indication are required to perform a management study at a minimum of 3 sites and enroll consecutive ambulatory outpatients presenting to an emergency room or outpatient clinic with a suspicion of DVT or PE who are evaluated with a validated clinical PTP score plus the D-dimer assay under study [22]. D-dimer results are compared to the presence of DVT or PE by acceptable imaging techniques and, if negative, a 3-month patient follow-up to confirm the negative imaging result. The study must have sufficient power to define a required sensitivity of ≥95% (lower CI of ≥90%) and a negative predictive value (NPV) of ≥97 % (lower CI of ≥95%) for the D-dimer assay. The VTE prevalence is required to be >10%. In comparison, for manufacturers seeking clearance as an "aid in the diagnosis of DVT or PE" indication for their assay, there is no requirement to conduct a management study. The FDA requires an outcome study at a minimum of 3 sites, with a collection of a statistically significant number of outpatient samples from patients with known VTE (prevalence > 10%), comparing the D-dimer results from their assay to a predicate D-dimer device. For this indication, there is no requirement that D-dimer should be used in the context of a validated clinical score, but simply that D-dimer results should be interpreted in the clinical context. The predicate D-dimer assay must be one that is cleared by the appropriate regulatory agency for a DVT or PE exclusionary claim, and the proposed D-dimer assay should not be part of the clinical assessment used to diagnose the patient. Although the NPV is defined for these studies (≥97% with a lower CI of ≥95%), the sensitivity is not defined. Unlike the FDA, the European Union (EU) on *In Vitro* Diagnostic Medical Devices Regulation does not specify study criteria for D-dimer assays to meet an exclusionary claim. Most manufacturers that market their assays in North America and the EU will comply with FDA regulations in order to meet criteria for North America and will submit the same data to obtain CE marking

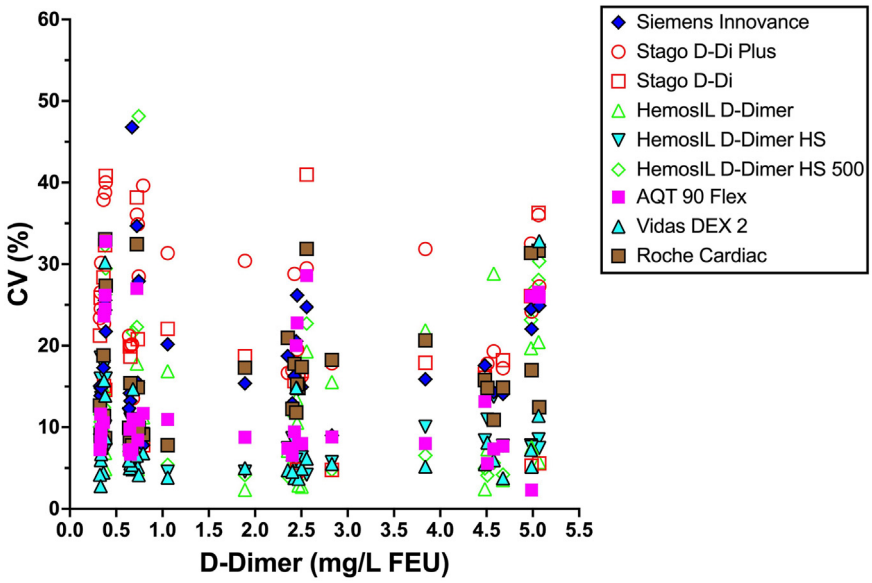


FIGURE 1 D-dimer assay variation in the Royal College of Pathologists of Australasia Quality Assurance Program. Data are shown as the coefficient of variation (CV) of participant-reported D-dimer values, expressed as a percentage and plotted against the averaged D-dimer value for each sample assessed in this program for the years 2018 to 2022 (adjusted to mg/L FEU). Data are shown separately for individual assays.

in the EU. However, assays marketed in the EU alone are not required to meet specific study criteria.

3.4 | What do real-world laboratory proficiency data tell us about D-dimer performance?

Laboratories participate in external proficiency testing programs as a component of their quality assurance programs. International providers of external quality assurance (EQA) programs send out the same homogeneous sample to multiple participating laboratories and are expected to test it the way they would a patient sample. The submitted results are analyzed by the EQA provider, giving us unique insights into interassay variability on the same sample between real-world laboratories using different assays. A review of D-dimer EQA survey results over the last 5 years by 2 large, international EQA providers, the Royal College of Pathologists of Australasia Quality Assurance Programs and the External Quality Control for Assays and Tests (ECAT) Foundation, are summarized in Figures 1 and 2, respectively. Figure 1 shows the data from 500 to 600 instruments (depending on the year of testing) from over 400 laboratories and the 9 most common D-dimer assays used between 2018 and 2022. The interassay performance between these methods on the same D-dimer sample shows significant variability with coefficients of variation ranging from less than 5% to greater than 40% across a D-dimer concentration range of <0.5 mg/L FEU to 5 mg/L FEU. Figure 2 shows the D-dimer survey data from 2017 to 2022 from the ECAT Foundation, with approximately 730 participating laboratories with 950-1000 instruments and 12 of the most common D-dimer assays in use. We see the same significant interassay variability in D-dimer results across the concentration, which is greatest at the VTE exclusion threshold of 0.5 mg/L FEU (or 500 μg/L FEU), where management decisions about VTE exclusion are generally made. The potential clinical impact of this is demonstrated in Figure 3. We used the method-specific coefficients of variation in the lower D-dimer concentration range of the ECAT data presented in Figure 2 and calculated the CI per method group for a hypothetical D-dimer value of 0.55 mg/L FEU (just above the typical VTE exclusion threshold of 0.50 mg/L for assays reporting in FEU) (Figure 3). Using the BioMerieux VIDAS assay will result in a value below 0.50 mg/L FEU for 7% of the participants, while using either of the Roche Tina-quant second-generation assays will result in a value below 0.50 mg/L FEU for 34% of the participants (Figure 3). Clinically, this means that assays that have a higher variability at the exclusion threshold have a greater chance of a false negative D-dimer result and the potential for missed VTE. It is reasonable to conclude from these laboratory performance data that D-dimer assay results are not interchangeable, and the findings of a management trial using a given D-dimer assay are not generalizable to another D-dimer assay. In addition, Figure 3 also demonstrates that some methods appear to have significantly more intra-assay variability than other methods, particularly at VTE exclusion thresholds. This may also have clinical consequences in that some D-dimer assays will have better intra-assay agreement on classifying VTE than others.

3.5 | What is the potential clinical impact of using D-dimer assays interchangeably?

There is a paucity of research assessing the clinical impact of D-dimer assay substitution in clinical studies and in the real world, perhaps because it is largely (but incorrectly) assumed that all high-sensitivity D-dimer assays with VTE diagnosis claims are interchangeable. This premise was recently examined in the setting of risk stratification using D-dimer after a first episode of unprovoked VTE. The "HERDOO2 rule" is a clinically validated decision-making tool designed to identify low-risk women eligible for the discontinuation of

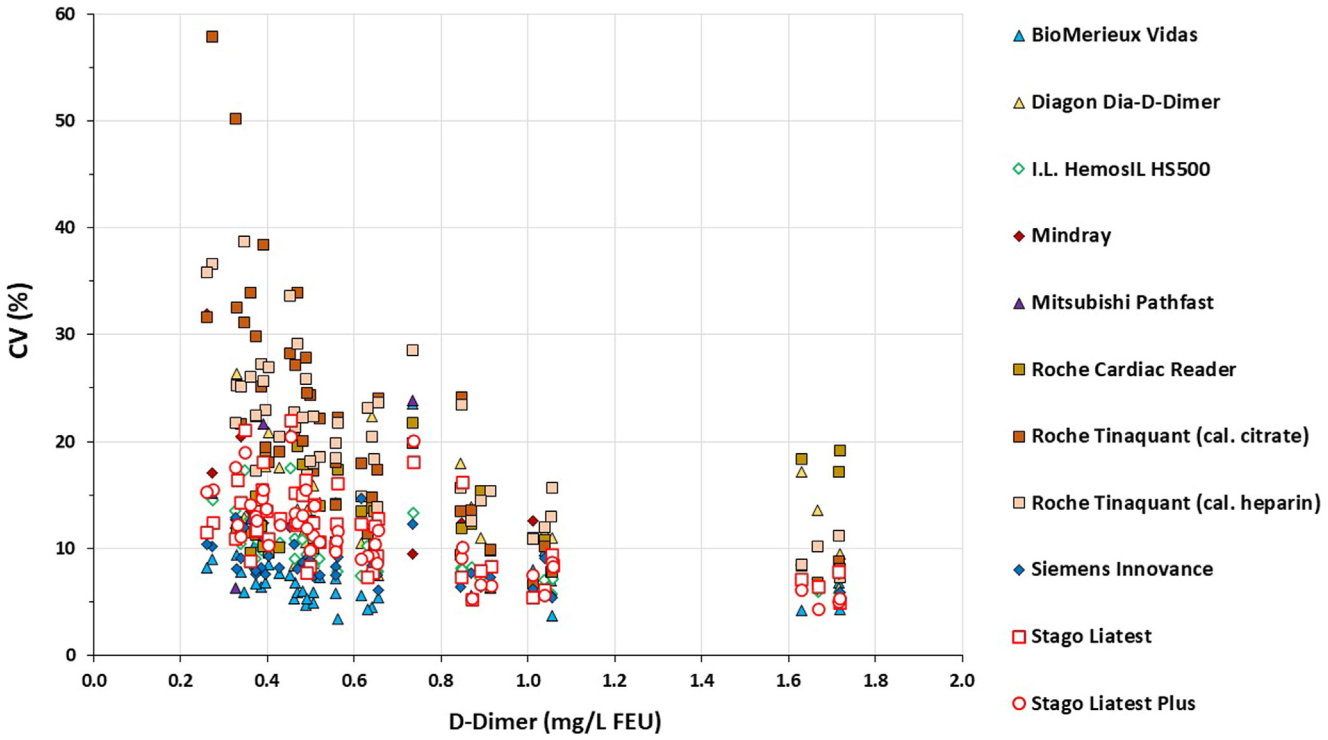


FIGURE 2 D-dimer assay variation in the External Quality Control for Assays and Tests Foundation Quality Assurance Program. Data are shown as the coefficient of variation (CV) of participant-reported D-dimer values, expressed as a percentage and plotted against the averaged D-dimer value for each sample assessed in this program for the years 2017 to 2022. Only assays reporting results in mg/L FEU are shown. Data are shown separately for individual assays.

anticoagulants after completing 5 to 12 months of treatment for unprovoked VTE [23,24]. A critical component of this rule is the VIDAS D-Dimer assay, employed at half the usual diagnostic cut-point (250 μg/L FEU) for excluding VTE during the rule's derivation and validation. In a subsequent publication, the authors aimed to assess whether other contemporary, automated, quantitative D-dimer assays

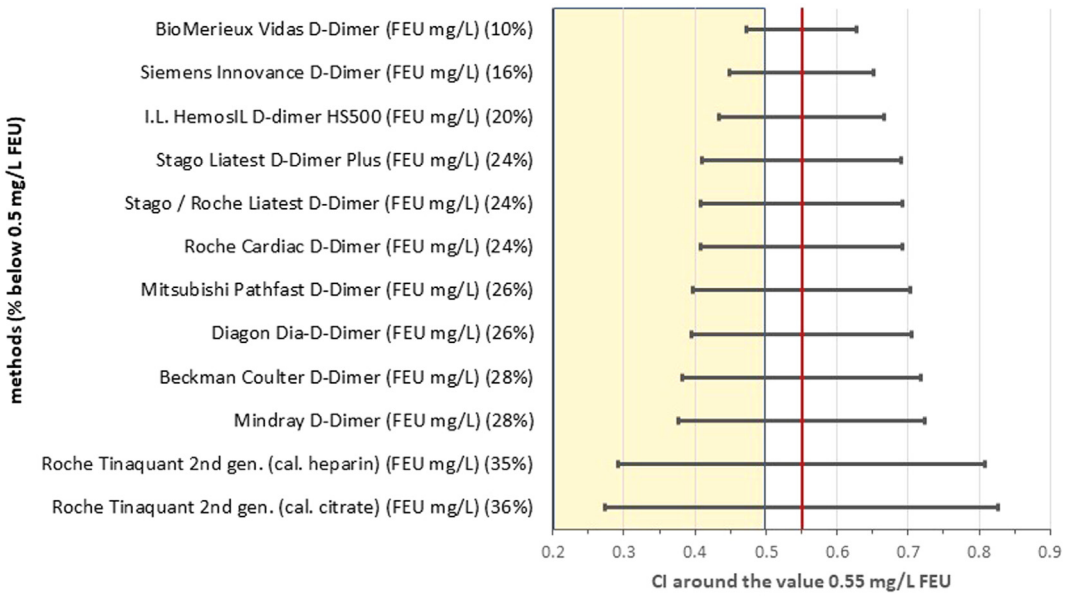


FIGURE 3 CI around a hypothetical true D-dimer value of 0.55 mg/L fibrinogen equivalent units (FEU) by the method. CI is calculated using method-specific coefficients of variation for a D-dimer value of approximately 0.55 mg/L FEU for assays shown in Figure 2. The proportion of values below 0.50 mg/L FEU is represented by the percentage between brackets.

could be substituted for the VIDAS D-Dimer Exclusion II assay (BioMerieux) [25]. The analysis involved frozen plasma samples from a subset of female participants (n = 248) in the "HERDOO2" validation study, using 5 D-dimer assays: VIDAS D-Dimer Exclusion II, INNOVANCE D-Dimer (Siemens Healthineers), HemosIL D-Dimer HS (Instrumentation Laboratory), Tina-quant D-Dimer Gen.2, and STA-Liatest D-Di (Stago). Regression analysis identified optimal cut-point values for each D-dimer assay, corresponding to a VIDAS D-Dimer cut-point of 250 μg/L FEU. There was poor concordance found between VIDAS D-Dimer results and each of the other D-dimer assays at the optimal diagnostic cut-points of each tested assay: INNOVANCE (kappa, 0.38), Liatest (kappa, 0.38), HemosIL (kappa, 0.36), and Tina-quant (kappa, 0.30). Similar poor concordance was observed when using half of the diagnostic D-dimer cut-point for each assay. The authors concluded that automated, high-sensitivity assays other than VIDAS should not be incorporated into the "HERDOO2" rule due to the poor concordance with the VIDAS D-Dimer assay, leading to unacceptable misclassification of women at high and low risk of recurrent VTE. However, the VIDAS assay, being an enzyme-linked immunosorbent assay, has been replaced in most laboratories by automated, high-sensitivity D-dimer assays that have faster turnaround times and are compatible with major coagulation analyzers in use worldwide. Less than 5% of laboratories used the VIDAS assay in the most recent ECAT and Royal College of Pathologists of Australasia Quality Assurance Programs surveys of 2022. Consequently, lack of access to the VIDAS assay will not allow most clinicians to employ the HERDOO2 rule, or they will continue to use it with other D-dimer assays, thereby risking misclassification errors.

Investigators led by the primary author (R.S.) conducted a study evaluating the impact of introducing a standardized VTE diagnostic algorithm, including a mandatory PTP assessment and D-dimer, on radiologic test utilization for VTE in our emergency department (ED) at a tertiary academic hospital in Toronto, Canada [26]. Mandatory algorithms for the investigation of patients with suspected DVT and PE were developed, including a formal PTP assessment based on the Wells score combined with a high-sensitivity quantitative D-dimer (HemosIL D-Dimer HS) and VTE exclusion threshold of 230 ng/mL D-dimer units. D-dimer was only run if the D-dimer sample was accompanied by the PTP scoring sheet, which had been duly completed by the ordering clinician. This "force function" ensured that compliance with the algorithm was high (more than 90% of patients). Moderate to high probability patients would proceed with the appropriate imaging—either duplex ultrasound (DUS) or a computed tomography pulmonary angiogram (CTPA). A retrospective review of 1785 visits for suspected DVT and PE in the year prior and the year after the introduction of the mandatory algorithm showed that more patients were investigated for VTE after the algorithm was mandated (2.4% vs 1.9%; $P < .001$), there was no reduction in the proportion of imaging tests ordered (2% vs 1.9%; $P = .53$), and a lower proportion of patients had confirmed PE on imaging (3.8% vs 6.8%). Clearly, real-life implementation had failed to demonstrate either a substantial reduction in imaging for VTE or a yield in confirmed VTE diagnoses despite the mandatory use of a validated clinical PTP score with high compliance and a high-sensitivity D-dimer assay marketed for exclusion of VTE. This lack of generalizability of prior management studies to our real-world setting may be related to differences in patient populations, but differences in the performance between various high-sensitivity D-dimer assays, all marketed as suitable for VTE exclusion, is also a distinct possibility. A concurrent review of external proficiency data from laboratories participating in the local, provincial EQA program revealed that the D-dimer assay used in this study had a higher false positive rate in a normal population than other assay peer groups, which supported the latter possibility. A subsequent study was conducted in the same Canadian ED in patients with suspected PE to assess the impact of implementing the YEARS criteria combined with the INNOVANCE D-Dimer assay [27] using clinical probability-adjusted D-dimer thresholds as described in the original management study [9]. In patients without YEARS items and D-dimer less than 1000 ng/mL FEU or in patients with 1 or more YEARS items and D-dimer less than 500 ng/mL FEU, PE was considered excluded [27]. All other patients had CTPA. Over the 12-month period, 2695 patients were investigated for PE, with 942 undergoing CTPA. Compared to the baseline, the diagnostic yield of CTPA increased by 2.9% (from 12.6% to 15.5%), and the proportion of patients undergoing CTPA decreased by 11.4% (from 46.4% to 35%). The percentage of CTPAs ordered with a D-dimer increased by 26.3%, and only 2 missed PEs were identified within 30 days of the index visit. We showed that implementing the YEARS criteria and an adjusted D-dimer threshold using the INNOVANCE D-Dimer assay could improve the diagnostic yield of CTPAs and reduce their unnecessary use without an increase in missed clinically significant PE. Again, there could be several reasons for this reduction in imaging for PE and increased diagnostic yield in the more recent study, including the fact that this study used an adjusted D-dimer threshold, which by design increases the proportion of patients in whom PE can be ruled out. However, it is important to note that the D-dimer assay used (also a high-sensitivity automated assay validated for VTE exclusion) was well represented in the original management study being used in 1100 (32%) of the study's patients, making that study directly generalizable to this setting.

4 | CHALLENGES WITH REAL-WORLD D-DIMER USE

Although publications examining D-dimer use in VTE diagnostics abound, there is a relative paucity of data assessing the real-world impact of using conventional or adjusted D-dimer cutoffs for VTE diagnosis and on clinical outcomes like reduction in imaging, health care costs, and efficiency (eg, reduction in ED wait times). A few recent studies provide some insights into the current state of use of VTE diagnostic guidelines, including the use of CDRs and D-dimer. Kristoffersen et al. [28] aimed to investigate the diagnostic practices of physicians in EDs when evaluating patients suspected of having VTE. A questionnaire with 2 case histories (PE: case A and DVT: case B) was distributed to 487 physicians in 6 European countries. The

results showed that 60% of physicians considered the PTP of PE to be high in case A, but 7% would request only a D-dimer test, and 11% would exclude PE if the D-dimer was negative. This is hazardous since D-dimer evaluation is not indicated at all in patients who are determined to be high risk for PE, and a negative D-dimer does not rule out PE in high-risk patients. In fact, all diagnostic algorithms suggest proceeding to imaging directly without a D-dimer when a validated CDR suggests that the PTP of either DVT or PE is high. Additionally, 41% requested a D-dimer test and imaging, leading to what the study termed a "waste of resources."

For case B, 92% of physicians assessed the PTP of DVT to be low. While 66% correctly requested only a D-dimer test, 26% requested imaging, either alone or in addition to D-dimer, representing another "waste of resources." The study concluded that these findings highlight the need for better dissemination and knowledge of current recommendations for the diagnosis of VTE by scientific societies. Mousa et al. [29] conducted a retrospective review of the use of DUS for DVT diagnosis in patients presenting with leg swelling at 2 high-volume tertiary care US centers. Analyzing data from 1909 patients, the study found that combining D-dimer with a Wells clinical probability score had 100% NPV and sensitivity in ruling out VTE. However, despite this, 762 patients with a low Wells clinical probability score and negative D-dimer underwent unnecessary immediate DUS, suggesting potential overutilization. Similarly, a prospective observational study in 17 US EDs, also published in 2018, examined the application of the YEARS criteria in assessing consecutive patients for PE [30]. The study aimed to determine if adjusting the D-dimer threshold based on the clinical probability determined by the YEARS criteria would reduce the need for imaging while maintaining diagnostic accuracy. Of the 1789 patients evaluated using the standard D-dimer threshold, 53% would not have needed imaging, with 0.2% missed PE. Adjusting the D-dimer threshold based on YEARS criteria or considering “alternative diagnoses less likely than PE” resulted in 67% and 69% of patients not requiring imaging, respectively, with 0.5% missed PE for both adjusted thresholds. This study validated, in a North American context, that D-dimer adjustment based on clinical probability determination could decrease the need for imaging to evaluate PE with a minimal increase in missed cases and no decrease in NPV. Riporto et al. [31] conducted a retrospective review of all patients assessed for suspected DVT at 2 EDs in France over a 2-month period in 2019 to assess adherence to the European Society of Cardiology guidelines for diagnosing DVT. The study included 107 patients with suspected DVT. Only 24% of patients received diagnostic management according to the guidelines, with 67% lacking a clinical probability score assessment. Only 35 patients had a clinical probability score calculation, of which 5 patients had an unnecessary D-dimer, and 2 patients had unjustified imaging. Adherence to guidelines resulted in a median ED time of 185 minutes compared with 250 minutes without adherence, with increased overall costs. In a unique qualitative research study designed to evaluate barriers to the use of diagnostic guidelines in investigating PE, Zarabi et al. [32] conducted interviews with 63 Canadian emergency physicians, which revealed significant insights into the implementation challenges for a CDR plus D-dimer strategy. Physicians expressed anxiety about missing PE, and several barriers to using evidence-based guidelines were identified, such as lack of knowledge about VTE diagnostic algorithms, time pressure in the ED, and patient expectations of getting an imaging test. They identified difficulties with applying the Wells score in the ED and a clear preference for gestalt estimation over evidence-based testing, which frequently led to an overestimation of PE and obtaining a CTPA. These real-world implementation studies collectively underscore the benefits of, but also challenges associated with, adhering to validated CDRs combined with D-dimer and the potential impact of this lack of adherence on diagnostic risks, patient outcomes, and health care costs. To this clinical milieu, we now add the confusion created by multiple D-dimer assays, reported in several different magnitudes and types of units, with significant interassay variability and incorrect assumptions on the part of clinicians, that assays can be used interchangeably [14,15]. The advent of threshold adjustment based on the age of the patient or clinical probability of VTE, generalizing from management studies that may not have used the particular D-dimer assay in the study, has further complicated this landscape since the assays are not only being used interchangeably but at thresholds that have not been locally verified by the laboratory. Such local laboratory revalidation of adjusted D-dimer thresholds is not feasible for any clinical service laboratory. It essentially requires conducting a local management study in outpatients with suspected VTE, managed on the basis of the published CDR plus D-dimer strategy, and followed for 90 days to determine the safety of withholding anticoagulation based on that strategy. At a minimum therefore, clinicians and laboratories must at least ensure that the D-dimer assay they are using has been adequately represented in the management study that the VTE diagnostic strategy is being imported.

Finally, there is a dire need to improve basic D-dimer reporting in the peer-reviewed literature where often, even names of the D-dimer assay used and reporting units are not available. 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 [13,19,33].

5 | ISTH CONGRESS REPORT

At the latest ISTH Congress held in Montreal, Canada, in July 2023, there were a few abstracts reporting on using adjusted D-dimer cut-offs in VTE diagnosis. Willan et al. [34] assessed the performance of a validated and previously published clinical probability-adjusted D-dimer threshold in the investigation of DVT in a retrospective cohort of 12,365 presentations of suspected DVT over a 10-year period for whom a complete Wells’ score and D-dimer were available. They found that the modified algorithm would have detected the majority of DVTs, with a miss rate of 0.61% (95% CI, 0.61%-0.62%), while reducing the number of ultrasounds required by 42%, missing 1 DVT diagnosis for every 171 scans saved with resultant decreases in health care system resources, travel time, and uncertainty for patients. Gaugler et al. [35] presented a secondary analysis of a previously

published multinational, prospective study in which patients with suspected PE were managed according to the age-adjusted D-dimer strategy, and followed for 3 months. They reported on the association between body mass index and PE in patients with suspected PE and found that body mass index and obesity were not predictors of confirmed PE. The age-adjusted D-dimer strategy appeared safe in ruling out PE in obese patients, demonstrating increased efficiency without compromising safety. Finally, Jaouen et al. [36] reported on a prospective study including 2530 patients admitted to the ED of a university hospital in France with suspected PE and a low PTP of PE for whom D-dimer testing was requested. When comparing the performance characteristics of D-dimer for excluding PE according to a conventional fixed, age-adjusted, or doubly-adjusted cutoff using age and fibrinogen levels, adopting an age and fibrinogen-adjusted D-dimer cutoff significantly improved specificity and NPV without compromising sensitivity, providing a more accurate tool for PE diagnosis in patients with a low PTP.

As the field of adjusting D-dimer cutoffs progresses, seeking to maintain D-dimer sensitivity in excluding VTE while enhancing specificity for VTE, and an increasing number of management trials are published, validating the safety of these diagnostic strategies, there is a growing imperative for further knowledge translation research. This research must focus on overcoming barriers to the implementation of diagnostic guidelines and ensuring positive study outcomes in the real world.

6 | FUTURE DIRECTIONS

So, what can we do to improve D-dimer diagnostics for VTE and bridge this knowledge-to-action gap? We all have a role to play. Scientific societies and manufacturers must come together to harmonize D-dimer reporting units to a single magnitude and type and begin work on developing and implementing a sustainable harmonization procedure for D-dimer assay results. Manufacturers must ensure that the mandatory information about the performance characteristics of their assay and the studies supporting the exclusion of VTE claims are readily available and accessible to laboratories using their assays. Scientific societies must develop minimum reporting standards specific to D-dimer for protocols for studies using D-dimer assays and manuscripts reporting on D-dimer assays. These reporting standards would include information on the specific D-dimer monoclonal antibody, the origin of the calibrator, and the D-dimer reporting unit used in the assay. For clinical trials using D-dimer, a detailed description of the study population and the use of D-dimer assays that only exclude VTE claims must be mandatory. Laboratory professionals must select assays validated for exclusion that have been well represented in rigorous management trials and educate users that D-dimer assay results are assay-specific and must not be used interchangeably. Increasing adherence to VTE diagnostic guidelines in real-world clinical settings needs a system-based approach, using all the tools in our knowledge translation armamentarium that can remove barriers to evidence-based use. Finally, once implemented, the local impact of the selected VTE diagnostic strategy on desired clinical outcomes like reduction in imaging, improved VTE yield, reduction in ED wait times, and cost savings should be evaluated.

7 | CONCLUSIONS

In conclusion, the evolution of VTE diagnostic algorithms, incorporating validated CDRs and adjusting D-dimer exclusion thresholds based on age or clinical probability, has shown promise in safely reducing the need for imaging without compromising patient safety. However, the landscape of D-dimer assays is complex and heterogeneous. With more than 30 different assays in use globally, together with the potential to report D-dimer assays in up to 28 different ways (considering units and potential age adjustment), the lack of standardization and harmonization poses significant challenges. The inherent heterogeneity of D-dimer assays, diverse monoclonal antibodies, reporting units, and the absence of a universal reference standard contribute to interassay variability. This variability, as evidenced by proficiency testing data and some clinical studies, emphasizes the noninterchangeability of results among different assays. These challenges extend to the regulatory framework, with differences between FDA and EU requirements for clearance of D-dimer assays, especially concerning exclusion claims for DVT or PE. Real-world implementation studies reveal low adherence to VTE diagnostic guidelines complicated by adjusting D-dimer assay thresholds and pervasive D-dimer assay substitution. To bridge this knowledge-to-action gap, a collaborative effort involving scientific societies, manufacturers, laboratories, and clinicians is needed now. We must harmonize D-dimer assay results and reporting units, improve accessibility to assay performance information, and establish minimum reporting standards for studies involving D-dimer. Additionally, knowledge translation efforts must focus on educating clinicians about the noninterchangeability of D-dimer results and adopt systems-based approaches to implementing VTE diagnostic algorithms in EDs. We must strive for a more standardized, safe, and effective use of D-dimer in VTE diagnosis.

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