D-dimer testing: A narrative review

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Abstract

D-dimer containing species are soluble fibrin degradation products derived from plasmin-mediated degradation of cross-linked fibrin, i.e., 'D-dimer'. D-dimer can hence be considered a biomarker of in vivo activation of both coagulation and fibrinolysis, the leading clinical application in daily practice of which is ruling out venous thromboembolism (VTE). D-dimer has been further evaluated for assessing the risk of VTE recurrence and helping define optimal duration of anticoagulation treatment in VTE, for diagnosing disseminated intravascular coagulation (DIC), and for screening those at enhanced risk of VTE. D-dimer assays should however be performed as intended by regulatory agencies, as their use outside these indications might make them a laboratory-developed test (LDT).

This narrative review is aimed at: (1) reviewing the definition of D-dimer, (2) discussing preanalytical variables affecting D-dimer measurement, (3) reviewing and comparing the assays performance and some postanalytical variables (e.g., different units and age-adjusted cutoffs), and (4) discussing the interest of D-dimer measurement across different clinical settings, including pregnancy, cancer, and coronavirus disease 2019 (COVID-19).

1. D-dimer: a multifaceted laboratory parameter

The term 'D-dimer' is widely used to refer to a mixture of fibrin degradation products (herein abbreviated as 'FnDP') formed from digestion

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of cross-linked fibrin by plasmin. D-dimer plasma levels thus indicate in vivo activation of coagulation and fibrinolysis, but importantly not necessarily within the vasculature. They all contain the D-dimer motif [1–4]. The generation of D-dimer FnDP results from the sequential action of three enzymes: thrombin; activated factor XIII (factor XIIIa); and plasmin (Fig. 1). Prothrombin fragments 1 + 2 are cleaved from the amino terminal end of prothrombin in the process of activation by factor Xa to yield thrombin [5]. In fibrinogen, the central E-domain is connected to two outer D-domains and consists in three pairs of polypeptide chains (Aα-, Bβ- and γ-) [6,7]. By releasing fibrinopeptides (A followed with B),

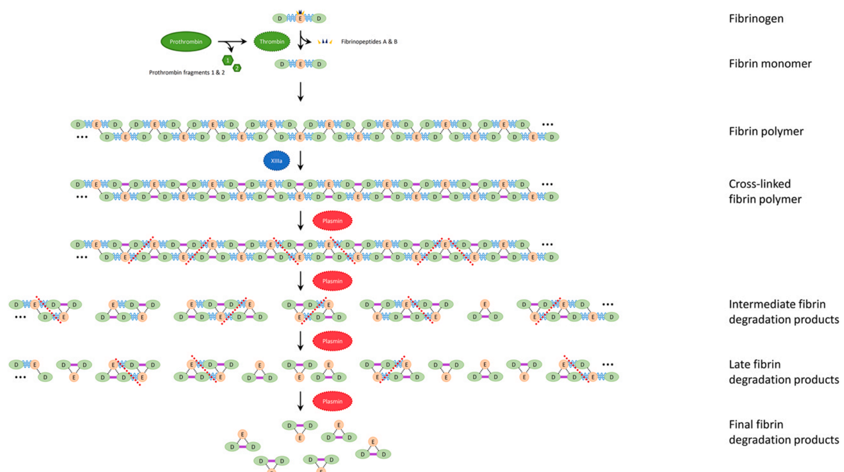


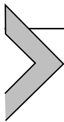
Fig. 1 Mechanism of D-dimer production [1,3,4,190]. Fibrinogen molecules are composed of two 'D' domains linked to a central 'E' domain by coiled-coils. By the action of thrombin, fibrinopeptides A (and B) are cleaved from fibrinogen molecules; exposed A-knobs in the E-domain are capable of interacting with the a-hole in the D domain of an adjacent fibrin molecule (or fibrinogen, leading the so-called 'soluble complexes' containing at least one fibrin monomer - see text). The fibrin monomers assemble to form polymers. Fibrin polymers are then stabilized by the action of activated factor XIIIa, which covalently links two adjacent D domains of two different fibrin monomers through their gamma chains and also establishes multiple covalent bonds between alpha chains extensions (not shown for sake of clarity). Once plasminogen is activated to plasmin, the latter first cleaves cross-linked alpha chains (not shown), and then the coiled-coils; it is however not able to cleave the covalent bond formed by the action of factor XIIIa between the gamma chains of two adjacent D domains. The final product of fibrin degradation is the DD/E species, which comprises two covalently linked D domains associated with an E nodule through the A-knob/a-hole interaction. DD/E: fragment D-dimer/fragment E complex; XIII = factor XIII.

thrombin generates fibrin monomers and unravels two cryptic polymerization sites located on the E domain. The highly self-assembling fibrin monomers will form a soluble network of multiple units, which becomes insoluble after reaching a critical size [1]. Fibrin monomers may also connect to fibrinogen molecules and remain in small soluble complexes (ie, soluble fibrin monomer complexes), which can be measured specifically [8]. Thrombin proteolytically activates FXIII to FXIIIa in a reaction that is enhanced by fibrin [9] and FXIIIa in turn promotes the covalent linkage between lysyl and glutamyl residues, leading to the formation of stable fibrin clots, the lysis of which is slowed down [1,4]. The generation of plasmin from plasminogen by the action of tissue plasminogen activator (t-PA) and urokinase-type plasminogen activator (u-PA) leads to degradation of fibrin by cleavages at several specific sites [4]. Fibrinolysis generates products with a wide range of molecular masses, i.e., FnDP. The final hence smallest digestion products of fibrin clots is the D-dimer/fragment E complex (DD/E), which presents two adjacent covalently bound D-domains from two fibrin monomers cross-linked by factor XIIIa [4]. The mixture of complexes formed by cross-linked fibrin digestion thus include moieties with one or several D-dimer motifs, the molecular masses of which range from 228 kDa (DD/E) to several thousand kDa (X-oligomers) [10,11]. Multiple enzymatic modulators, such as thrombin-activatable fibrinolysis inhibitor, α-2-antiplasmin and α-2-macroglobulin, exist to limit fibrinolysis, for instance in case of injury.

Initially, the term "D-dimer fragment" referred only to the DD/E complex [1,12]. Nonetheless, the range of species recognized by antibodies in D-dimer assays is much wider, including species with masses ranging from approximately 200 to >10,000 kDa [1,11]. In the circulation, the D-dimer half-life is approximately 6–8 h, which is substantially longer than other biomarkers including prothrombin fragments 1 + 2 (90–120 min), thrombin-antithrombin complexes (10–45 min), or fibrinopeptides A and B (3–5 min). Half-lives of the different species of FnDP are likely heterogeneous. Elimination occurs by renal excretion and phagocytic mononuclear cells that further catabolism [13–20]. In healthy subjects, D-dimer is low because of a physiological conversion of fibrinogen to fibrin [4,21]. Otherwise, the amount of D-dimer produced will depend on the total mass of deposited fibrin, the fibrin surface area available for plasmin action, extent of plasmin formation, timing of measurement, and initiation of anticoagulant therapy [22,23].

Importantly, fibrinogenolysis (ie, plasmin action on fibrinogen, which is not physiologic) leads to generation of fibrinogen degradation products,

referred to as fragments X, D, Y, and E [1,4]. The abbreviation 'FDP' often refers to both fibrin and fibrinogen degradation products, as early immunoassays were unable to differentiate them. To avoid confusion, the abbreviation FnDP will be used in the manuscript to refer specifically refers to fibrin degradation products [12]. Of note, the so-called fibrin-related markers (FRM) include FnDP, D-dimer and soluble fibrin. D-dimer immunoassays are designed to detect a specific epitope on degradation products of factor XIIIa-cross-linked fibrin and should therefore not recognize X, Y, D, or E fragments but only the D-dimer motif in the smallest DD-E fragment, and in larger FnDP [3]. Each monoclonal antibody has its own specificity toward FnDP [24]. In all the D-dimer assays, antigenic determinants in the D-domain need to undergo factor XIIIa and plasmin degradation to become conformationally reactive [12].



2. Preanalytical considerations

2.1 Preanalytical phase in laboratory hemostasis

The preanalytical phase is a major determinant of the quality of hemostasis testing; most errors in- and outside the hemostasis laboratory are related to this phase [25–30], which is defined by the International Organization for Standardization (ISO) 15189:2012 standard for laboratory accreditation as "processes that start, in chronological order, from the clinician's request and include the examination request, preparation and identification of the patient, collection of the primary sample(s), the transport to and within the laboratory, and end when the analytical examination begins" [31]. Contrarily to observations made years ago and due to technological progress, the analytical and postanalytical phases represent today 10–15% and 15–20% of all laboratory errors, respectively, while 60–70% occur during the preanalytical phase [30]. The existence of numerous manually intensive activities is believed responsible for the preanalytical phase vulnerability [30,32].

Preanalytical errors exist in up to 5.5% of all coagulation samples due to samples not received (49.3%), hemolysis (19.5%), clotting (14.2%) and inadequate sample volume (13.7%) [33]. Clotted samples were the major source of preanalytical errors in hematology (35–43%) and followed by inadequate volume (up to 13%) [34,35]. Sample rejection rate was higher for hemostasis tests (13.3%) than other analyses (3.2% for biochemistry tests, 9.8% for blood gases analysis, and 9.8% for urinalysis) [35].

Three main categories of variables impairing sample quality are:

(i) sample collection (needle size, collection tubes);
(ii) sample delivery to the laboratory (pneumatic tube system (PTS), temperature);
(iii) sample processing (centrifugation, hemolyzed samples).

Variables related to storage and stability of samples, including the impact of freeze-thaw cycles, are also considered as parts of the preanalytical process [36].

Importantly, each preanalytical step is vulnerable. To ensure sample integrity, strict adherence to protocol is recommended [36] (Table 1).

Although preanalytical variables may impact D-dimer assays differently than common hemostasis parameters, preanalytical requirements for D-dimer analysis are generally confused with those for other coagulation tests [37,38] (Table 2). This misperception may come from the fact that D-dimer and other hemostasis tests are generally performed from the same tube. Artifactual D-dimer production is very unlikely in citrate due to lack of plasmin activation. The impact of preanalytical variables on D-dimer measurement will be extensively discussed.

In most studies, the impact of a defined variable was assessed through determination of the bias between two conditions. The absence of statistically significant difference is often considered as a robust indicator of lack of importance. Conversely, the statistical significance of the differences in results of two groups of blood samples that were treated using different preanalytical conditions does not imply that this difference will be clinically significant [39]. To assess clinical significance, a clinical criterion should be carefully selected, i.e., total allowable error (TEa), based on relevant studies. To date, literature on D-dimer generally assumes a cutoff of around 10% to assess clinical significance of bias (mainly in interference and stability studies). However, the origins of this cutoff appear arbitrary as they were not derived from biological variation studies, i.e., reference change value (RCV) [40]. Further validation of this empirical 10% cutoff by performing biological variation studies is needed [41]. Recently, studies were performed in order to define biological variation of D-dimer and establish relevant data such as a RCV, which is calculated using the formula:

$$\mathrm{RCV} = 2^{1/2} \times Z \times (\mathrm{CV}_\mathrm{A}^2 + \mathrm{CV}_\mathrm{I}^2)^{1/2}$$

where CV_A is the analytical variation and CV_I is the within-subject biological variation [42–45].

Table 1 Stability of D-dimer.

Stability	Conditions	Anticoagulant	Plasma/whole blood	D-dimer assay	Subjects	Stability criteria	References
24 h	RT	Heparin	Plasma	Tina-quant (Roche)	17 patients	Student t-test and regression equation	[61]
24 h	RT	Citrate	Plasma	Tina-quant (Roche)	15 patients	Student t-test and regression equation	[61]
6 h	RT	Citrate	Plasma	Innovance (Siemens)	40 patients	10% deviation from baseline, regression equation and discordance at the cutoff level of 0.5 mg/L FEU	[104]
24 h	RT	Citrate	Plasma	Innovance (Siemens)*	80 patients	10% deviation from baseline, analysis of variance, regression equation and Pearson correlation coefficient	[115]
24 h	RT	Citrate	Whole blood	Vidas (bioMérieux)	117 patients	Spearman correlation coefficient, regression equation and discordance at the cutoff level of 500 μg/L FEU	[116]

(continued)

Table 1 Stability of D-dimer. (*cont'd*)

Stability	Conditions	Anticoagulant	Plasma/whole blood	D-dimer assay	Subjects	Stability criteria	References
24 h	RT	Citrate	Whole blood	Innovance (Siemens)	44 patients	10–20% deviation from baseline, Student t-test and regression equation	[113]
24 h	RT	Citrate	Whole blood	ACL-TOP (Werfen)	26 patients	Wilcoxon's paired t-test, regression equation and bias plot	[70]
52 h	RT	Citrate	Whole blood	Asserachrom (Stago)	59 patients	Analysis of variance, 10% deviation from baseline	[111]
8 h	RT	Citrate	Whole blood	ACL-TOP (Werfen)	144 patients	Analysis of variance, Student t-test or Wilcoxon signed rank test, Bland-Altman plot and discordance at the cutoff level of 0.5 μg/L FEU	[71]

4 h	RT	Citrate	Whole Blood	Innovance (Siemens)	122 patients	Wilcoxon's matched-pairs signed rank test, 12.1% deviation from baseline, comparison to TE_a from [164]	[106]
24 h	2–8 °C	Citrate	Plasma	Innovance (Siemens)	40 patients	10% deviation from baseline, regression equation and discordance at the cutoff level of 0.5 mg/L FEU	[104]
24 h	4 °C	Citrate	Plasma	Innovance (Siemens)*	80 patients	10% deviation from baseline, analysis of variance, regression equation and Pearson correlation coefficient	[115]
24 h	4 °C	Citrate	Plasma	Vidas (bioMérieux)	20 patients	Wilcoxon's paired t-test, 10% deviation from baseline	[114]

(*continued*)

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Table 1 Stability of D-dimer. (*cont'd*)

Stability	Conditions	Anticoagulant	Plasma/whole blood	D-dimer assay	Subjects	Stability criteria	References
24 h	4 °C	Citrate	Whole blood	ACL-TOP (Werfen)	26 patients	Wilcoxon's paired t-test, regression equation and bias plot	[70]
24 months	−24 and −75 °C	Citrate	Plasma	STA-Liatest (Stago)	Plasma pool (6 patients)	Statistical change**, 5–10% deviation from baseline	[109]
2 weeks	−20 °C	Citrate	Plasma	STA-Liatest (Stago)	23 HV and 18 patients	Paired t-test, 10% deviation from baseline	[108]
36 months	−60 °C (or less)	Citrate	Plasma	Innovance (Siemens)	40 patients	10% deviation from baseline, regression equation and discordance at the cutoff level of 0.5 mg/L FEU	[104]
9 years	−80 °C	Citrate	Plasma	STA-Liatest (Stago)	60 patients	Wilcoxon's paired t-test	[107]

FEU: Fibrinogen equivalent units; HV: healthy volunteers; RT: room temperature; * : using the Sysmex CA 7000 platform; **: specific test not mentioned.

Table 2 Preanalytical considerations with D-dimer testing.

Preanalytical variables	General recommendations in hemostasis laboratories	Specific data regarding D-dimer
Sample collection		
Needle bore size	19–22 G	23–25 G also tolerated
Butterfly devices	Discouraged	Tolerated
Collection tube	Non-activating material (silicone-coated glass or polypropylene plastic)	Glass or plastic
Anticoagulant sample	Sodium citrate 3.2% (105–109 mmol/L)	Sodium citrate or heparin*
Tourniquet use	Removed as soon as the needle is in the vein (max 1–2 min)	Longer tourniquet use (i.e., 3 min) not tolerated
Sample delivery to the laboratory	At RT (15–22 °C), in vertical position, usually <1 h	PTS tolerated
Sample processing		
Centrifugation	At RT, 1500 x g for at least 15 min	Faster protocol allowed (at RT, 4500 x g for 2 min)
Interfering substances	Do not analyze samples with hemolysis	Cell-free hemoglobin i.e., <3 g/L tolerated
Stability, storage and F/T effects	At RT (15–22 °C), no more than 4 h	At least 24 h at RT or at 2–8 °C or years at −60 to −80 °C No impact of F/T procedure

F/T: Freeze/thaw; G: gauge; RT: room temperature; PTS: pneumatic tube system; * : correction factor needed (dilution).

2.2 Sample collection

2.2.1 Tourniquet use

To perform venipuncture, tourniquets are generally used by the phlebotomist to identify an accessible vein by temporarily obstructing venous blood flow. It is recommended that the tourniquet should never be so tight

to obstruct the arterial blood flow, shall not remain in place for more than 1–2 min, and should be removed as soon as the needle enters the vein or when the first tube starts to fill [32,36]. If applied longer, the obstruction of blood flow may induce hemoconcentration and thrombin generation there by interfering with accurate hemostasis testing [32,36,46]. Lippi et al. [46] studied the impact of 1 and 3 min of venous stasis and observed that D-dimer values using the Vidas DD assay (bioMérieux, France) were significantly increased 7.9% and 13.4%, respectively, vs no tourniquet use.

2.2.2 Butterfly devices, needle bore size and discard tube

Venipuncture for D-dimer determination should be as atraumatic as possible, preferably performed using ordinary straight needles with diameter between 19 and 22 gauge (G) [32]. Excessive manipulation of the vein by the needle should be avoided to limit thrombin generation [36] and potentially bias D-dimer levels [47]. The use of butterfly devices has been discouraged because the polyvinyl chloride (PVC) tubing may cause hemostasis activation and/or hemolysis [32,48,49]. However, Lippi et al. found negligible influence on D-dimer when a butterfly device (21 G, 300 mm PVC tubing) was compared to a conventional straight needle (21 G) using the Vidas DD test [50]. Negligible bias was also observed with butterfly devices of different needle bore sizes (21, 23 or 25 G) [46]. Butterfly devices, even with small size needles, might therefore constitute an appropriate alternative approach to standard straight needles, when needed [46,51]. Although specific populations might particularly benefit from butterfly use (e.g., geriatric, oncology, pediatric or emergency settings) [32,52], straight needle use is preferable to avoid detrimental impact on other parameters [52]. When using a butterfly (or IV catheters), a mandatory discard tube must be drawn prior to sample collection [53]. When performing venipuncture using a straight needle, the use of a discard tube does not induce a significant change in D-dimer and is therefore unnecessary [54], as opposed to other coagulation tests (due to the presence of tissue debris).

2.2.3 Tube composition

To prevent undesirable in vitro clot formation, collection tubes must be composed of silicone-coated glass or polypropylene plastic [36]. Different tube materials were studied to assess their effect on D-dimer assays. No significant differences in D-dimer (Asserachrom, Diagnostica Stago, France) was observed when glass or polyethylene terephthalate (PET) plastic collection

tubes (Vacutainer, Becton Dickinson (BD), USA) were used [55]. Another study found insignificant differences in D-dimer (Advanced D-dimer, Siemens Healthcare Diagnostics, Germany) when plastic (polypropylene) and glass citrated collection tubes (3.2%) (Vacutainer and Vacuette, Grenier bio-one, Germany) were used [56]. Yavas et al. [57] also found comparable results using three different plastic citrated (3.2%) tubes (Vacutainer Plus Plastic, BD, USA and Vacuette) with a standard glass tube (Vacutainer). Altogether, the choice of silicone-coated glass or polypropylene plastic tubes does not substantially impact D-dimer measurement.

2.2.4 Anticoagulants

Originally, D-dimer was measured in serum because prior removal of fibrinogen was required to mitigate cross-reactivity with polyclonal antibodies [4]. False negative results were due to FnDP entrapped in the clot [58,59].

According to the recommendations of the Clinical and Laboratory Standards Institute (CLSI) and the World Health Organization (WHO), the vast majority of hemostasis investigations today require collection in 3.2% (105–109 mmol/L) buffered sodium citrate anticoagulant [36,53]. Because sodium citrate is only available in a liquid form, it is crucial that a blood to anticoagulant ratio of 9:1 is maintained [36]. Failure to correctly fill the tube will typically prolong prothrombin time (PT), activated partial thromboplastin time (APTT) and thrombin time (TT) and may underestimate D-dimer and fibrinogen due to dilution [47]. Preanalytical quality must therefore be assured (absence of clotting, under or overfilling) [4]. Sample collection should ensure free flow and appropriate mixing (3–6 complete inversions) within 30 s [36]. Serum and heparinized/EDTA plasma samples are generally incompatible with hemostasis investigation [36,47].

A few D-dimer assays including point-of-care (POC) tests use citrated, heparinized, or EDTA plasma (Pathfast, Mitsubishi Kagaku Iatron, Japan), Tina-Quant (Roche Diagnostics, Switzerland), AQT-90 (Radiometer, Denmark), Simplify (Agen Biomedical, Australia), whereas others recommend only citrate (Vidas; STA Liatest, Diagnostica Stago, France; Immulite' Siemens Healthcare Diagnostics, Germany) [60]. Reports do not agree on heparin influence. For example, one paper observed a non-significantly increased mean D-dimer using heparin (2510 μg/L fibrinogen equivalent unit (FEU)) (Tina-Quant) vs citrate (2060 μg/L FEU) [61]. A second study only found a modest bias of D-dimer (Immulite) between lithium-heparin and sodium-citrate [62]. Slightly increased D-dimer in heparin may be attributable to dilution with liquid citrate (D-dimer Gold,

Agen Biomedical, Australia) [63]. Although a dilution factor (0.84) may be used, it would likely be confusing.

The main advantage of using heparin is that it enables the study of other analytes parameters (electrolytes, enzymes, cardiac troponins) from a single tube. Despite this, buffered sodium citrate (3.2%, 105–109 mmol/L) remains the recommended anticoagulant for coagulation studies [52]. Other matrices should be validated locally.

2.3 Specimen transport

Samples shall be delivered to the laboratory as promptly as possible (<1 h) after collection and kept at ambient temperature (15–22 °C) [53]. General recommendations state that vertical position of the tubes and airtight closure by caps must be ensured throughout transportation [32,36]. Vertical rather than horizontal transportation of the tube reduces the turbulence thus limiting microparticle generation [32]. Although proximity of collection and testing is important, most hospitals connect via PTS [32] for ease of transport and more rapid turnaround time (TAT). PTS may cause excessive acceleration/deceleration, radial gravity forces, vibration and changes in air pressure that may trigger platelet activation and hemolysis [32,64,65] that could impact D-dimer [66]. For example, Le Quellec et al. [64] reported a statistically significant impact of PTS (~2 km long) vs motor vehicle transport on D-dimer (mean difference of 7.4%) (HemosIL HS500, Werfen, USA). However, a disagreement at the 500 μg/L FEU cutoff was observed in only 1 of 39 samples (510 vs 490 μg/L FEU, PTS vs motor vehicle, respectively), though within the intra-assay imprecision.

No significant difference was observed in samples delivered by PTS (~100 m) vs hand carried (Tina-Quant) [61]. Another study found no difference in D-dimer using PTS (~500 m) vs those directly collected in the laboratory (MediRox, MediRox, Sweden) [65]. Although this suggests low impact on D-dimer, PTS should be assessed and validated locally [64,66].

2.4 Specimen processing and centrifugation

Once received, samples should be carefully examined to identify tubes eligible for rejection due to incorrect anticoagulant, under- and overfilling, presence of clots, etc [32]. Automated systems to assess serum or plasma indices are now available [67].

Plasma needs to be separated from cellular components by centrifugation (1500 g for 15 min) at ambient temperature [53], with the exception of POC assays which use whole blood. No differences in D-dimer were

reported when samples were centrifuged at high- (4500 g for 2 min) (Vidas) [68] or low-speed (3137 g for 7 min) (Innovance, Siemens Healthcare Diagnostics, Germany) [69] vs standard practice. The former enables improved TAT especially in emergency settings. Interestingly, D-dimer in citrated whole blood is stable for 8 h (room temperature) and 24 h (4 °C) [4,70,71]. Centrifugation at 4 °C did not influence D-dimer (Innovance and AxSYM, Abbott laboratories, USA) [72]. A subsequent study obtained a significant analytical difference ($p < 0.001$) in median D-dimer was reported using cold (2–4 °C) vs room temperature (25 °C) centrifugation (179.5 vs 168.7 μg/mL FEU; Dia-D-dimer, Diagon, Hungary) [73]. This bias was not, however, clinically significant.

2.5 Interferences

The most frequent types of interference that preanalytically impact coagulation testing are paraproteinemia (monoclonal gammopathy) as well as hemolysis, icterus and lipemia (HIL) [30]. *In vitro* hemolysis is the most widely studied and represents one of the most frequent causes of preanalytical errors for clinical laboratories (30–70% of all rejected specimens) [33,74–77]. Hemolysis may be clinical (hemolytic anemia, metabolic disorders, infectious agents, hemoglobin-based blood substitute) or due to poor collection technique, prolonged transport and processing as well as storage [75,76]. The level of interference will also depend on the technical approach (photometric, clotting, immunometric). Immunoassay interference ranges 0.4–4.0% and may be caused by cross-reactivity, heterophilic antibodies and biotin [67]. The CLSI advises that samples with visible hemolysis should be rejected due to possible bias associated with release of pro-coagulant factors from injured cells [53].

Lippi et al. [78] studied the influence of hemolysis on D-dimer (Vidas) by performing a freeze-thaw cycle (−70 °C) and showed a significant increase in samples with a final blood lysate of at least 2.7%. However, clinically significant variation (10% cutoff) was only observed when cell-free hemoglobin >13.6 g/L (final lysate concentration of ~6.4%) [76,78]. The same authors evaluated the impact of increasing concentrations of cell-free hemoglobin obtained by mechanical hemolysis (ie, produced using a syringe equipped with a fine needle (30 G, 0.3 x 8 mm)) and observed a (non-clinically) significant decrease in D-dimer in samples from 5.5 to 7.0 g/L cell-free hemoglobin on AcuStar (Werfen, USA) (−5%) and from 11.5 to 15.0 g/L cell-free hemoglobin on HemosIL HS (Werfen, USA) (−7%) [74]. D'Angelo et al. [79] reported a significant increase in D-dimer

with mild hemolysis (cell-free hemoglobin of 0.5 g/L) (Innovance). Hedeland et al. [80] observed a clinically significant bias (≥10%) at 6 g/L hemoglobin on a STA R Max 2 instrument (Stago). Using the HIL check on a Cobas t511 (Roche Diagnostics, Switzerland), Montaruli et al. [81] reported that hemolyzed samples (1.5 g/L cell-free hemoglobin) had clinically significant decreased D-dimer (up to −25.2 μg/L FEU).

Although widely reported, it is challenging to draw conclusions on the influence of hemolysis on D-dimer due to:

(i) the existence of a variety of D-dimer assays which are commercially available and have intrinsic differences;
(ii) the fact that hemolysis may not be comparable. Techniques most generally involve freeze-thaw of whole anticoagulated blood or mechanical lysis using a fine needle and syringe or rotating blade homogenizer. Spiking with hemolysates or pure hemoglobin is generally discouraged as it does not account for potential leukocyte and platelet lysis. Fine needle aspiration is believed closest to actual hemolysis observed in a traumatic blood collection, whereas freeze-thaw lacks standardization [76,78,79];
(iii) inequity in biological variation cutoffs to assess clinical significance; analytical bias is often used instead [76];
(iv) difficulty to estimate the influence of blood origin, as differences exist between healthy patients, ICU patients or patients taking multiple drugs namely antiplatelet or anticoagulant drugs [76].

Although rejection of all hemolyzed samples is recommended by the CLSI, the majority (±95%) are only mildly hemolyzed (hemoglobin 0.3–0.6 g/L) [74,75,82]. Thus, whenever cell-free hemoglobin remains within a non-interference limit (<3 g/L), D-dimer will be reliable and safely reported [74]. Notably, avoiding rejection of all hemolyzed specimens will reduce additional blood sampling and could shorten the clinical decision making as well as favorably impact workload, patient comfort and cost [74,76].

The effect of lipemia, icterus, proteinemia (including monoclonal gammopathy) and heterophilic antibodies has been less widely discussed [76,83,84]. In an early report, Pittet et al. [85] did not observe any impact of lipemia (triglyceride 973.5 mg/dL) and icterus (bilirubin 48.5 mg/dL) on the Vidas D-dimer assay. More recently, La'ulu et al. [86] reported similar findings using the AxSYM assay (<10% of deviation from the baseline) following the addition of bilirubin (292 mg/L) and triglyceride (41.6 g/L).

The Innovance assay on CA-7000 (Sysmex, Japan) was unaffected by bilirubin (free and conjugated bilirubin up to 100 mg/dL) [87]. According to Chen et al. [88], D-dimer measured with the CS-5100 analyzer (Sysmex, Japan) was also free from triglyceride and total bilirubin interference. Recently, hemolysis, icterus, human anti-mouse antibodies and rheumatoid factor did not significantly affect the Yumizen G DDi 2 assay on the Yumizen G800 coagulation analyzer (Horiba Medical, France) whereas lipemia >5 g/L decreased D-dimer in samples with 500 μg/L FEU [89]. Icterus (up to 30 mg/dL bilirubin) did not affect the STA compact analyzer (Diagnostica Stago, France) [90].

Spurious D-dimer results were only observed with the STA reagents when free bilirubin was 80 mg/dL and above [87]. Moreover, the HIL check detected lipemia (triglyceride > 400 mg/dL) on the CS-5100 D-dimer assay in 3 of 4 samples [91].

Montaruli et al. [81] showed that D-dimer testing was not clinically affected by lipemia (triglyceride 893 mg/dL) or icterus (bilirubin 1500 mg/dL) on the Cobas t511. Negrini et al. [92] confirmed the negligible impact of lipemia on D-dimer and found that a double high-speed centrifugation was unnecessary for lipemic samples. Recently, Jensen et al.[93] identified that patients pools with low D-dimer (<750 μg/L FEU) were the most affected by lipemia (HemosIL HS500). Excessive lipemia might be decreased using high speed centrifugation (10,000 g) [94].

Multiple case-studies reported the interference of monoclonal gammopathy in D-dimer assays. One report implicated Castleman disease-associated monoclonal gammopathy in falsely increasing D-dimer [84] whereas other questioned this finding [95–97].

Few reports have examined heterophilic antibody interference with D-dimer assays [83,98–101]. Recently, such cases were also reported in coronavirus disease 2019 (COVID-19) patients [102]. Such interferences may be detected and prevented using commercially available heterophilic blocking agents [83,84] or by comparison with a second method [84,103]. The use of heterophilic blocking agents may hence be part of an algorithm to investigate potential immunoassay interference [67].

2.6 Stability, storage and freeze/thaw

The CLSI recommendations for quantitative D-dimer for the exclusion of venous thromboembolism (VTE) states that quantitation may be fulfilled up to 24 h when kept at ambient temperature. Detailed information on D-dimer stability is shown in Table 1.

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Citrated specimens were mainly used to assess stability, except for Schutgens et al. [61] who used heparinized plasma. D-dimer was stable for at least 24 h at room temperature or at 2–8 °C with many immunoassays. Although Böhm-Weigert et al. [104] and Toulon et al. [71] reported 6 and 8 h room temperature stability, longer storage was not examined. Linskens et al. [105] observed that D-dimer was stable up to 48 h, but this study focused on healthy volunteers with low D-dimer. Denessen et al. [106] observed clinically significant bias (>TEa), in baseline vs 6–12 h samples and concluded that D-dimer was stable for only 4 h. Of note, the TEa value selected to assess bias was extracted from the canonical Ricos database which was based on a single publication and is now considered outdated. The stability of D-dimer enables frozen samples to be kept for extended periods (months or years) [104,107–109]. Schutgens, Zürcher and Gosselin also studied freeze-thaw on three D-dimer assays and failed to show significant differences [61,110,111]. Four freeze-thaw cycles (−60 °C or less) did not produce clinically significant changes (<10%) [104].

The stability of measurands can be assessed using various decision criteria, i.e., RCV, total change limit (TCL), analytical coefficient of variation (CV), arbitrary 10% CV, the choice of which may strongly impact results [112]. Therefore, the use of multiple criteria is encouraged. All studies were conducted accordingly, except for Betsou et al. [107]. A statistical analysis is most frequently performed and the absence of significant bias between time points is assumed to reflect stability. The observation of a statistically significant difference in the measurand is insufficient as it does not inherently translates into clinical significance [39]. Although a 10% cutoff is most common [104,108,109,111,113–115], it should be further validated. Another reasonable approach is the analysis of disagreement based on the cutoff used to rule out deep vein thrombosis (DVT) and/or pulmonary embolism (PE) [71,104,116].

Although stability data show that D-dimer assays may be used in settings where delayed analysis occurs, most often these are performed in acute care in which a short TAT is required [52]. Specific preanalytical data regarding D-dimer testing is summarized (Table 2).

3. Analytical considerations

3.1 D-dimer assays: the origin

Due to cross-reactivity with fibrinogen, first-generation D-dimer assays were only performed in serum. Polyclonal antibodies were used and detected

fibrinogen and fibrin and FnDP [2] using various types of analyses including latex fixation and agglutination, hemagglutinin inhibition, staphylococcal clumping, immunoelectrophoresis and immunodiffusion [3]. These initial assays were plagued by false-positivity (anticoagulant treatment) and false-negativity (clot formation or when degradation products would adsorb to the clot) [58,59].

Increased assay performance was reached a decade later when monoclonal antibodies that specifically targeted D-dimer epitopes were developed [1–4,117] thus making plasma testing feasible. The first monoclonal antibody was developed by Rylat et al. in 1983 (3B6) with more than 20 monoclonal antibodies since then [11,117].

Although microtiter plate-based enzyme-linked immunosorbent assay (ELISA) was long considered the reference method, these were initially developed for research purposes [1]. Briefly, immobilized capture antibody binds the D-dimer antigen and is colorimetrically detected via a secondary enzyme linked antibody [1,2]. Despite high sensitivity, ELISA was generally labor intensive and time-consuming contributing to low reproducibility [2,118].

3.2 Current D-dimer assays

Next methods were based on qualitative agglutination using antibody-coated latex microparticles and visual inspection [1,3,4,119]. Automated second-generation latex agglutination immunoassays (or latex-enhanced immunoturbidimetric assays) enabled quantitation. Today, the sensitivity of latex-enhanced immunoturbidimetric assays is comparable to ELISA and benefits from shorter TAT [3].

Automated enzyme-linked immunofluorescence assays (ELFA) have also been developed and demonstrate analytical performance similar to microplate ELISA [3,85]. The Vidas ELFA method remains one of the most clinically validated D-dimer methods [60,72,120–123] and is considered the reference method by some [122,124,125].

Chemiluminescent enzyme immunometric assays (CLIA) are comparable to ELISA, latex-enhanced immunoturbidimetric and ELFA [3,62,124]. Briefly, magnetic particles coated with monoclonal antibodies specific to D-dimer are used. Incubation of anti-D-dimer antibodies conjugated with isoluminol generates a chemiluminescent reaction directly proportional to D-dimer concentration [3].

The main characteristics of D-dimer assays are summarized in Table 3.

Table 3 Characteristics of D-dimer assays [2,3,62,124,129,184,194].

	ELISA	ELFA	Unenhanced Latex agglutination assay	CLIA	Latex-enhanced immunoturbidimetric assay	POC assay
Type	Quantitative	Quantitative	Qualitative/semi-quantitative	Quantitative	Quantitative	Qualitative/quantitative
TAT	2–4 h	35–40 min	Rapid	25–40 min	15 min	2–20 min
Pros	Considered as the gold standard, sensitivity, observed independent	Considered as reference method, most validated method, sensitivity, automation, wide linear range (0–1000 μg/mL), automated, observed independent	Rapid, inexpensive	Sensitivity, rapid, automated, observed independent	Sensitivity, automated, rapid, observed independent	Readily available, fast, higher specificity, whole blood

Cons	Highly manual, technical skills, time-consuming, not optimal linear range, moderate specificity	Moderate specificity	Moderate sensitivity, manual, observer dependent	Lack clinical validation, moderate specificity	Moderate specificity	Sensitivity, not all FDA cleared, observer dependent, manual

CLIA: Chemiluminescent enzyme immunometric assay; ELFA: Enzyme-linked immunofluorescence assay; ELISA: Enzyme-linked immunosorbent assay; POC: Point-of-care.

3.3 D-dimer point-of-care assays

Point-of-care (POC) D-dimer assays have also been developed for ensuring rapid and accessible triage of patients suspected of thromboembolic disease [3,126–128]. The performance of tests enables shorter TAT [126,129,130]. These homogenous monoclonal antibody-based assays use whole blood [3,126]. Detection may be qualitative or semi- quantitative and include hemagglutination (SimpliRED), immunochromatography (Clearview Simplify, Agen Biomedical, Autralia), fluorescence (Vidas mini analyzer; Triage, Biosite Diagnostics, USA; Stratus CS, Siemens Healthcare Diagnostics, Germany) chemiluminescence (Pathfast) and plasma agglutination (Dimertest, Siemens Healthcare Diagnostics, Germany) [3,131]. However, not all POC D-dimer assays are appropriate for excluding VTE. Only POC-based assays validated in clinical trials and cleared by the FDA, the European Community or other similar agencies should be used. Current summaries of POC devices and tests are available [3,132].

3.4 Inter-laboratory variation

The 2001 fibrin assay comparison trial (FACT) study evaluated 23 quantitative D-dimer assays (15 latex-enhanced immunoassays, six ELISAs and two membrane-based immunoassays) [133]. The authors found that the mean values obtained in 39 samples varied from 630 μg/L to 13,350 μg/L FEU (~21-fold), with two displaying significant cross-reactivity to fibrinogen degradation products. It was also found that ELISAs and latex-enhanced immunoassays were more reactive to low-molecular weight cross-linked fibrin and high molecular weight fibrin, respectively [133]. Accordingly, the study of Meijer et al. [134], based on 353 laboratories using the seven most frequently used D-dimer immunoassays, found that some assays gave 20 times higher D-dimer concentrations compared to others. Another study comparing D-dimer values from 423 laboratories also showed high variability near the cutoff used for VTE exclusion [135]. In 2014, the Coagulation Resource Committee of the College of American Pathologists (CAP) found that the inter-method CV was as high as 42% in a survey of 3800 laboratories [136]. Recent data based on an external quality control program in the Netherlands investigated the impact of the recent COVID-19 pandemic on quality in hemostasis laboratories and reported a mean interlaboratory CV around 10% pre-pandemic, which remained stable during the pandemic (9.4% March and 10.4% December 2020) for D-dimer assays [137].

3.5 Calibrators and internal controls

The calibration phase is an important source of analytical variability. As stated above, D-dimer units vary according to the type of calibration material used [11,133,138]. Current reporting of D-dimer by clinical laboratories use FEU or D-dimer units (DDU). In the first case, calibrator are composed of plasmin degraded purified fibrinogen clotted by factor XIII, while in the second, they are composed of purified D-dimer [4]. There is a ~2:1 ratio between the molecular mass of FEU (340 kD) and DDU (195 kD) and these may therefore be used interchangeably after correction [2–4,11,52].

Calibrators are prepared through controlled lysis of fibrin are based on the quantity of purified fibrin fragment D-dimer equivalents or the amount of fibrinogen [11]. Given the heterogeneity of molecules obtained, lysis of fibrin must be controlled to ensure reproducibility regarding the size of degradation products ranging from 190 kDa to up to >10,000 kDa, i.e., low molecular weight FnDP (LMWF) vs high molecular weight FnDP (HMWF) [11,133].

Internal quality control (IQC) may also be affected thus impacting analysis. For example, De Nitto et al. [139] showed significant bias in various hemostasis parameters including D-dimer when cold (3–5 °C) vs ambient (22–24 °C) water was used to reconstitute lyophilized IQC. This bias was clinically significant when compared to a TEa criterium based on biological variation. The authors therefore suggest that water temperature is standardized to that used in IQC procedures.

3.6 Standardization and harmonization

Multiple sources of heterogeneity in D-dimer assays exist. These differences include proprietary monoclonal antibody specificity, fragment variation following digestion of cross-linked fibrin (LM vs HMWF) [11], lack of certified IQC or calibrators [140], differences in reporting units and clinical cutoffs, as well as the lack of an international reference for calibration and standardization [11,24,136,141–148]. Because of these issues, mathematical models and conversion factors have been proposed to harmonize testing [133,134,138,144,149]. In 2007, Jennings et al. [138] exploited the UKNEQAS external quality survey to improve inter-laboratory variability for laboratories reporting FEU and DDU.

Harmonization may therefore consequently benefit establishing the diagnosis of DIC and its subsequent monitoring [11,150]. To this date, and

according to harmonization efforts, it remains challenging to use a single diagnostic cutoff due to the impact of false-negativity [11].

Harmonization is achievable and should be more actively pursued [140]. Existing models should be validated to ensure comparability [11,134,138].

Recently, the Fibrinolysis and DIC Scientific Standardization Subcommittees of the International Society on Hemostasis and Thrombosis (ISTH) called again for harmonization of D-dimer assays [140]. They suggested that a stable freeze-dried reference material containing high concentration of D-dimer (LM and HMWF) may be produced from a broad scope of patients. A consensus reference line for D-dimer immunoassays might be thus obtained. Unfortunately, a recent attempt found increased instability due to structural rearrangements and amyloid formation of FnDP [151]. Another option might selectively target low and middle MW FnDP species and higher MW forms using monoclonal antibodies [143].

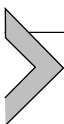
Continuous discussion among manufacturers, scientists and clinicians is essential for achieving better harmonization.

3.7 Analytical performance

Prospective studies were performed to validate cutoffs with some reagents (Vidas, AxSYM, STA Liatest) [1,4,72,120–122,146,152]. If such studies are not available, comparison with validated assays shall be performed. This will be required under the new In Vitro Diagnostic Regulation (IVDR) [153]. It is the role of manufacturers to keep up-to-date with the most recent literature and revise cutoffs as needed [154].

In CAP surveys performed from 2004 to 2011, 33% of US laboratories reported cutoff values set higher than literature recommendations or proposed by the manufacturer [136]. In a 2005 European survey, 55% of laboratories used higher cutoffs while 24% used lower cutoffs than those recommended [135]. Italian recommendations on D-dimer in the emergency department suggested the use of certified quantitative D-dimer assays [52]. Recommendations stated that a CV $<$ 10% should be observed at the diagnostic decision cutoff and linearity should extend from 50 to 5000 μg/L FEU [140]. CLSI has proposed a precision target of ≤7.5% at the threshold [155]. Importantly, there should be no cross-reaction with fibrinogen or fibrinogen degradation products and preferably not with fibrin and fibrinogen fragments released via proteolysis by enzymes other than plasmin [140].

Given these considerations, clinicians should be informed about the performance characteristics of the D-dimer assay used locally [1,11,142].



4. Postanalytical considerations

According to ISO 15189:2012, the postanalytical phase is defined as "processes following the examination including systematic review, formatting and interpretation, authorization for release, reporting and transmission of the results, and storage of samples of the examinations" [31]. Although most issues in hemostasis testing occur preanalytically (60–70%) [30], the postanalytical phase remains significant (15–20%) [142]. Recently, the SARS-CoV-2 pandemic and associated thrombotic events have significantly increased D-dimer testing and complications associated with interpretation thereof [156]. Below we discuss these postanalytical issues.

4.1 Reporting D-dimer

D-dimer is reported in FEU or DDU. In addition, the existence of various mass units (ng/mL, μg/L, mg/L, g/L, μg/mL, mg/mL and g/dL) further confuses reporting and comparison of results [2–4,142,157,158].

For example, about 60% of laboratories use FEU for D-dimer measurement with mg/L as most common followed by ng/mL [136,142]. Interestingly, a small percentage (8%) report without a unit of measure [11,136,159].

The unit of measure that best approximates the International System (IS) is μg/L (or ng/mL), which is also recommended by the Italian Consensus document [52,142].

About 33% of 1500 US laboratories use D-dimer units of measure different from those recommended by the manufacturer [136]. Standardization is key to reducing this variability to improve consistency in interpretation of test results [136,140].

The use of age-adjusted or clinical probability-adjusted cutoffs is another source of complexity for reporting D-dimer and should be standardized worldwide [142,145].

4.2 Turnaround time (TAT)

To ensure clinical usefulness in urgent situations, D-dimer TAT should be as short as feasible. An overall TAT < 1 h has been proposed by the Italian consensus document and is suitable for managing most requests [52].

Several strategies may be adopted. The use of D-dimer assays with a wide linear range (up to 5000 μg/L FEU) avoids the need for manual dilution. Others include faster transport via PTS, high speed centrifugation and the use of POC analyzers.

[3,52,61,64,65,68,130,146]. Most D-dimer assays are automated and provide rapid analysis (15–40 min) (Table 3). In a European study, 81% of participant laboratories declared offered D-dimer 24 h a day [135].

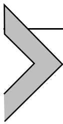
4.3 Analytical performance specifications

The current landscape of D-dimer measurement lacks official recommendations on evidence-based clinical specifications and a 10% variation threshold is widely accepted [160]. The latest consensus paper on analytical performance specifications was issued following the 2014 Milan conference and proposed a three-model hierarchy: 1st Clinical outcome (based on studies investigating the direct impact of performance of laboratory measurements on clinical outcome); 2nd Biological variation; and 3rd State-of-the-art (highest quality of analytical performance technically achievable) [161].

Literature for model 1 is lacking for most analytes, including D-dimer, and few analytes benefit from clinical outcome-based specifications (e.g., hemoglobin A1c). While the conference stated that some parameters may be considered using different models independent of the hierarchy, model 1 remains preferred to 2, whereas model 2 is preferred to 3 [161,162]. Analytical performance specifications based on meta-analysis of standardized and carefully evaluated biological variation studies are available in the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) Database for Biological variation [163]. Unfortunately, D-dimer assays do not appear here. The canonical Ricos database, which was previously the reference for biological variation, proposed a TEa of 28% for D-dimer, but was based on a single study [164]. Recently, Aarsand et al. [44] published a study of biological variation of coagulation markers based on the European Biological Variation Study population. Faced with a high distribution heterogeneity, they concluded that extracting a mean intra-individual variability estimate for D-dimer was not appropriate to calculate RCV or establish analytical performance specifications. Ercan et al. [43] also recently published a limited biological variation study (23 Turkish patients, predominantly women) which reported values of 10.6%, 9.4% and 26.8% for desirable imprecision, bias and total error, respectively (Tina-Quant). The TEa was close to that reported by BV data from Ricos, desirable bias was close to the conventionally used 10% cutoff and intra-assay imprecision was also close to

10% at the cutoff proposed by some authors [52]. The calculated index of individuality suggested that RCV (60.4%.) might be preferred to estimate D-dimer evolution in patients. In another study, Novelli et al. [165] calculated a RCV of 65% based on internal-control results for analytical variation and previously published data for within-subject biological variation (HemosIL HS).

Unfortunately, biological variation data on D-dimer remains scarce and not yet sufficient to define an appropriate threshold of clinical relevancy. Nonetheless, recently published studies suggested that this threshold might be above 10%. In the absence of sufficient data related to either of the first two models, the third model should be used, if available [44,166].



5. Clinical applications

D-dimer is a reliable marker of fibrin deposition. Plasma D-dimer concentration depends on the total mass of fibrin deposits, both intra and extravascular, surface area available for plasmin action and the magnitude of fibrinolysis [167,168]. Importantly, D-dimer is widely used as the gold-standard for ruling out VTE in patients with low-intermediate pretest probability in conjunction with a clinical decision rule [1,4,52,135,169]. In addition to almost all cases of VTE, levels of D-dimer above a certain value may also be observed in any condition where there may be tissue injury, such as infection, pregnancy, cancer, and aging, as well as in hematomas or interstitial hemorrhages [2]. The formation of clots is not limited to blood vessels and breakdown thereof leads to production of extravascular D-dimer [168,170]. In a study on causes of D-dimer increase (> 243 μg/L DDU (HemosIL HS)), infection predominated, followed by VTE, syncope, heart failure, trauma and cancer [169]. Elevated D-dimer levels may be found in 78% of hospitalized patients [171].

Please note, the clinical applications discussed below were redacted based on literature review and do not reflect the official "intended use" by the manufacturer or as stated by US authorities. Characteristics of relevant assays that appear in the present chapter, including the method type, and "intended use" approved based on a 510(k) premarket notification by the FDA are shown in Table 4 [173]. The regulation of the use of quantitative D-dimer assays for VTE exclusion by the FDA is based on guidelines produced by the CLSI (H59 document) [155]. Where applicable, the "intended use" is the only criteria that dictates if clinical use of a D-dimer

Table 4 Characteristics of central laboratory and point-of-care D-dimer assays.

Type of assay	Assay name	Manufacturer	Methodology	Unit type	Manufacturer's cutoff	FDA intended use (VTE)
Central laboratory	Advance D-Dimer	Siemens Healthcare Diagnostics (previously Dade Berhing)	Quantitative, latex enhanced turbidimetric immunoassay	FEU	BCS System: 1.6 mg/L Sysmex CA-1500: 1.0 mg/L	Aid in diagnosis
Central laboratory	AxSYM D-dimer	Abbott laboratories	Quantitative, enzyme-linked fluorescent assay	FEU	500 μg/L	NA
Central laboratory	Diazyme D-Dimer	Diazyme Laboratories	Quantitative, latex enhanced turbidimetric immunoassay	FEU	0.5 μg/mL	Aid in diagnosis
Central laboratory	HemosIL AcuStar D-Dimer	Werfen (previously Instrumentation Laboratory)	Quantitative, chemiluminescent immunoassay	FEU	500 μg/L	Aid in diagnosis
Central laboratory	HemosIL D-Dimer (± HS)	Werfen (previously Instrumentation Laboratory)	Quantitative, latex enhanced turbidimetric immunoassay	DDU	230 μg/L	Exclusion

Central laboratory	HemosIL D-Dimer HS 500	Werfen (previously Instrumentation Laboratory)	Quantitative, latex enhanced turbidimetric immunoassay	FEU	500 μg/L	Exclusion
Central laboratory	Innovance D-Dimer	Siemens Healthcare Diagnostics	Quantitative, latex enhanced turbidimetric immunoassay	FEU	0.5 mg/L	Exclusion
Central laboratory	STA Liatest D-Di	Diagnostica Stago	Quantitative, latex enhanced turbidimetric immunoassay	FEU	0.5 μg/mL	Exclusion
Central laboratory	Tina-Quant D-Dimer	Roche Diagnostics	Quantitative, latex enhanced turbidimetric immunoassay	FEU	0.5 μg/mL	Exclusion
Central laboratory (or POCT)	VIDAS D-Dimer	bioMérieux	Quantitative, enzyme-linked fluorescent assay	FEU	500 μg/L	Exclusion
POCT	AQT90 FLEX D-dimer	Radiometer Medical ApS	Quantitative, time-resolved fluorometry	NA	500 μg/L	NA
POCT	Clearview Simplify	Agen Biomedical	Qualitative, solid-phase immunochromatography	Neg/ pos	80 μg/L	NA

(*continued*)

Table 4 Characteristics of central laboratory and point-of-care D-dimer assays. (*cont'd*)

Type of assay	Assay name	Manufacturer	Methodology	Unit type	Manufacturer's cutoff	FDA intended use (VTE)
POCT	Pathfast D-Dimer	Mitsubishi Kagaku Iatron	Quantitative, chemiluminescent immunoassay	FEU	0.686 μg/mL	NA
POCT	Roche Cardiac D-dimer	Roche Diagnostics	Qualitative, solid-phase immunochromatography	FEU	0.5 μg/mL	NA
POCT	Stratus CS Acute Care D-dimer	Siemens Healthcare Diagnostics	Quantitative, fluorescent immunoassay	FEU	450 μg/L	Exclusion: PE; aid in diagnosis: DVT
POCT	Triage D-dimer	Biosite Diagnostics	Quantitative, fluorescent immunoassay	DDU	350 μg/L	Aid in diagnosis

assay may serve as an aid in diagnosis or to exclude VTE and/or PE and DVT with non-high pretest probability. The following data should therefore be considered concomitantly with local regulations that may apply to VTE exclusion, as some uses of the tests cited may fall outside the requirements of the intended use approved by the regional regulatory agency [155,173,174].

Other indications for D-dimer testing include assessing the risk of recurrent thrombosis and guiding anticoagulant therapy, diagnosing and monitoring DIC, excluding acute aortic dissection (AAD), and predicting and managing thrombotic complications in patients with severe infections – sepsis [1,4,175]. Other clinical applications of D-dimer have been proposed, but still require clinical validation, such as prognosis of peripheral artery disease, identification of vaso-occlusive crisis in sickle cell disease, screening of intracardiac thrombus and prediction of VTE in sleep apnea or cancer [4,176,177]. It is important to note that all these latter applications might constitute a laboratory developed test (LDT).

Here, we aim at discussing the use of D-dimer testing for VTE exclusion, prediction of VTE recurrence, prediction of thrombosis in medical hospitalized patients, along with diagnosis and monitoring of DIC and COVID-19. We will also briefly present some indications addressed in the literature, namely cerebral venous thrombosis (CVT), AAD, and acute mesenteric ischemia.

5.1 Exclusion of venous thromboembolism

5.1.1 Epidemiology

The term VTE includes both DVT and PE. VTE has an incidence of 104–183 per 100,000 person-years in Europe [178]. Worldwide, the estimated incidence of VTE is 3.0–3.3 cases per 100 hospitalizations per year, with a rate of hospital readmission 5–14% [178–181]. Prevalence was estimated at 422 cases per 100,000 individuals for isolated DVT (69.9%), PE (23.7%) or both (6.4%) [182]. It also appears that female gender is associated with a higher number of cases in the USA [182]. Aging also markedly increases the incidence of VTE [21,178,183,184]. The risk of VTE is increased due to major surgery, acute care hospitalization (heart failure, diabetes or pneumonia), trauma/fracture, thrombophilia, obesity, active cancer, pregnancy or postpartum, extended periods of immobility, and oral contraceptives [178,183,185,186]. This condition has substantial healthcare costs [160].

During the last decades, it has been hypothesized that the increased use of thromboprophylaxis in hospitalized patients may lead to a significant decrease in VTE [187]. However, while the incidence of DVT has decreased, the number of patients with isolated PE increased proportionately, which may result from increased CT-scanning in suspected PE and higher spatial resolution leading to diagnosis of smaller clots.

Short-term outcomes after PE have improved significantly [188]. Age-standardized annual risk of PE-related mortality decreased from 12.9 to 6.5 deaths per 100,000 subjects in Europe (2000–2015). Long-term sequelae of PE and DVT include chronic thromboembolic pulmonary hypertension and post-thrombotic syndrome, respectively.

A recent meta-analysis from Patel et al. [189] reported recurrent VTE in 1.38% and major bleeding in 0.90% of patients with a first PE event. A meta-analysis of patients with lower extremity DVT reported that 0.85% and 0% developed recurrent DVT and PE, respectively, at 3 months [190]. Patients with upper extremity DVT, 0.49% and 1.98% developed recurrent DVT and PE, respectively.

5.1.2 D-dimer diagnostic performance

D-dimer assays may usually be classified as high sensitivity (>95%) and low specificity (<40%) or moderate sensitivity (80–94%) and high specificity (up to 70%) [191]. General recommendations from the US Food and Drug Administration (FDA) are ≥95% (lower limit of CI ≥90%) sensitivity and ≥97% (lower limit of CI ≥95%) negative predictive value (NPV) [192], while the CLSI suggests ≥97% (lower limit of CI ≥90%) sensitivity and ≥98% (lower limit of CI ≥95%) NPV to rule out VTE. As the NPV is dependent on prevalence, the ISTH Subcommittee on Predictive and Diagnostic Variables in Thrombotic Disease recommends stricter limits of the rate of false negative tests (lower limit of NPV CI ≥98%) [193].

Quantitative assays generally have a higher NPV than qualitative or semi-quantitative assays [3]. The following assay methods, ELFAs (Vidas; Stratus DS, Siemens Healthcare Diagnostics, Germany; AxSYM), microplate ELISAs (Asserachrom; Enzygnost, Siemens Healthcare Diagnostics, Germany) and latex quantitative immunoassays (second generation of latex-based assays [2]) (Tina-Quant, STA Liatest) have high sensitivity (median, ≥95%) but low specificity (median, ±50%) [172,194]. Enzyme-linked fluorescence immunoassays had the highest and whole blood agglutination the lowest exclusion values [195].

Accurate estimation of performance of D-dimer immunoassays is pivotal and required by the IVDR [153]. Because NPV is directly related to prevalence [60], the negative likelihood criterion and the number needed to test (NNT) index were suggested as the most appropriate indicators to assess performance [184,196–199]. The negative likelihood ratio translates the change in the pretest odds or probability of the disease after considering test result, while the NNT represents the number of patients that should undergo D-dimer testing to rule out one case of VTE without imaging [184,196–199].

Regarding the performance of POC assays, whole blood D-dimer assays display slightly higher specificity (71% vs 69%) and lower sensitivity (83% vs 87%) for DVT and PE, than laboratory assays, respectively [129,194]. It should be noted that all POC tests are not suitable for VTE exclusion and have not been cleared by FDA for this use, so that they cannot be used solely for ruling out VTE [146]. Their use in combination with clinical pretest probability scores should be further investigated. Few POC assays meet CLSI specifications for ruling out VTE [131,146]. Among them, quantitative POC assays should be preferred to qualitative, especially when pretest probability for VTE is moderate vs low, as the higher the pretest probability, the higher the required exclusion performance [129,146,200].

5.1.3 Clinical prediction rules (CPR)

Although current guidelines do not endorse D-dimer as a standalone test to rule out VTE without imaging, the recently introduced YEARS algorithm excludes PE in those with a D-dimer <500 μg/L FEU regardless of pretest probability [1,2,4,52,60,175,191,201–204]. This approach reduces the risk of underdiagnosing VTE, a potentially fatal condition [202,205]. Today, guidelines recommend the use of CPR combined with D-dimer to identify patients with suspected VTE in whom imaging can be withheld [2,4,52,183,201,206]. This lowers the risk of withholding imaging in patients with a false-negative D-dimer in case of hypofibrinolytic state, small thrombi, anticoagulant therapy, or inappropriate timing for D-dimer after the thrombotic event (too early or too late) [1,2,4,52,72]. Notably, the traditional approach of not using D-dimer as a standalone was questioned with the YEARS algorithm that, in essence, excluded PE in all patients with a high-sensitive D-dimer <500 μg/L FEU, while a CPR is still used in those with a D-dimer >500 μg/L FEU. However, in this management study, among 331 patients with at least one item of the YEARS rule and D-dimer <500 μg/L FEU, computed tomography pulmonary

angiography (CTPA) was performed in 24 patients (protocol violation) of which 3 had PE (12.5%) (Vidas, Tina-Quant, STA Liatest, Innovance D-dimer) [204]. The recent PEGeD study, which also uses a D-dimer threshold dependent on pretest probability, maintained the use of CPR and D-dimer in all patients with suspected PE [207].

Although the use of CPR assigns a score to an individual based on signs, symptoms and risk factors to classify patients into categories for VTE risk (low, intermediate or high), two-level scores are preferred [183,201]. The Wells PE and revised Geneva scores for suspected PE are widely used and have comparable diagnostic performance [1,204,208–211]. In suspected DVT, the Wells DVT score is generally used [184,185,200,212].

To ensure accurate diagnosis, a CPR should comprise objective variables, display high accuracy, reproducibility, memorability, and offer a standardized approach, as opposed to clinical assessment alone [1,185]. Pretest probability may, however, still involve subjective assessment [213,214]. Currently, the use of different algorithms involving both CPR and D-dimer testing are endorsed by international guidelines [52,185,191,215]. The D-dimer assay is performed in patients with "low" or "unlikely" probability and VTE is consequently ruled out if the result is below the method-specific threshold therefore avoiding time-consuming, costly and potentially harmful investigations [2]. Combined CPR and D-dimer is considered safe if thromboembolic events are below 1–2% after 3 months in patients in whom VTE was considered excluded without imaging [193,202]. This threshold is, however, dependent on PE prevalence [193].

D-dimer measurement is unnecessary in "high or likely" or "moderate/high" classified patients for whom imaging is recommended [2,202,205].

Efforts are still to be made to improve the use of CPR and D-dimer. Unfortunately, these tools are generally underused. Only 70% of clinicians used pretest probability scores and 10% excluded or confirmed DVT only based on D-dimer with clinical probability assessment. D-dimer was also used in high probability cases, increasing cost and potential harm [213,214]. Inappropriate management of PE (rule-in or rule-out) was observed in 43% of patients [216]. Unfortunately, clinical algorithms are not always followed and harmonization of their use is a major goal for VTE diagnosis and management [213,214].

5.1.4 Age-adjusted cutoff

Increased D-dimer parallels aging [1,4,52,142,182,217,218], a phenomenon that decreases specificity in diagnostic management of VTE in the elderly

(0–18%, ≥80 y vs 49–67%, <50 years). Because a larger proportion have D-dimer >500 μg/L FEU, many may be subject to unnecessary investigation [217]. Accordingly, an age-adjusted D-dimer cutoff was proposed (i.e., age times 10 μg/L in those aged 51 y or older) while the traditional threshold of 500 μg/L FEU is used in those 50 y or younger. The age-adjusted cutoffs combined with a clinical score (Wells or Revised Geneva) enabled PE rule-out without additional CTPA [206,219]. Other studies also demonstrated the clinical and cost-effectiveness of this approach in excluding VTE [184,198,202,206,219]. Validated age-adjusted cutoffs are now recommended for patients with suspected PE to enhance clinical specificity while maintaining a clinically usable NPV [52,199,208,220–222]. For example, the European Society of Cardiology endorsed the use of age-adjusted cutoffs to rule-out PE [223].

The performance of the age-adjusted threshold may not be consistent across all D-dimer assays. Although the most validated is the Vidas assay (bioMérieux) [206], the strategy has been retrospectively validated for PE and VTE using numerous D-dimer assays [60,198,206,208,220]. The NPV was >97% for nine assays (Vidas, Innovance, Pathfast, HemosIL HS500, Tina-Quant, AQT90, and STA Liatest) and >99% for five others (STA Liatest, AxSYM, Vidas, Innovance, and HemosIL HS) [60,198]. Unfortunately, inter-assay performance may not be comparable [224] and caution is advised for insufficiently validated assays [145].

According to the latest International Survey, an age-adjusted D-dimer cutoff for suspected PE has not been widely implemented (<10%) [142] despite improving quality of care and reducing cost [225]. The use of age-adjusted cutoffs may constitute an LDT.

5.1.5 Clinical probability-adjusted cutoffs

Clinical probability-adjusted D-dimer cutoffs can improve diagnostic management of VTE by identifying a larger group of patients in whom imaging can be withheld [2,226–228]. Adapting cutoffs based on clinical pretest probability might decrease ultrasonography with no impact on NPV [229].

Based on this principle, two important prospective management studies have been performed. The YEARS study validated the use of an algorithm combining a clinical decision rule (CDR) based on clinical signs of DVT, hemoptysis and PE as the most likely diagnosis combined with different D-dimer cutoffs (500 or 1000 μg/L FEU (Vidas, Tina-Quant, STA Liatest, Innovance) [204]. This study reported a low number of thromboembolic events during the follow-up, as well as a 14% decrease in CTP. In a

subsequent study, age-adjusted cutoffs showed no added value to the YEARS algorithm [230].

The adjustment of D-dimer cutoffs based on Wells' clinical probability score was studied by Kearon et al. [207]. This study demonstrated that PE can be ruled out safely in patients with a D-dimer <1000 μg/L FEU and a low clinical pretest probability or those with a D-dimer <500 μg/L FEU and a moderate clinical pretest probability (mostly using STA Liatest, HemosIL HS500, Innovance, Triage). These findings were consistent with the YEARS study. No patients with low or moderate clinical pretest probability and negative D-dimer (<1000 or <500 μg/L FEU, respectively) were diagnosed with VTE during follow-up.

Freund et al. [231] investigated the use of combined YEARS rule and the age-adjusted cutoff in emergency department patients with suspected PE who were not excluded by the PE rule-out criteria (PERC). The three-month risk of a missed thromboembolic event was 0.15% which was much lower than the conventional strategy (0.80%). Chest imaging was also lower (10%).

Roy and colleagues recently derived and retrospectively validated in three large cohorts a four-level clinical probability (CP) score (4PEPS) by combining several strategies: ruling-out PE without any testing including D-dimer when the score <0 (very low CP); ruling-out PE by D-dimer <1000 μg/L FEU when the score is 0–5 (low CP); ruling out PE by D-dimer <age-adjusted cutoff when the score is 6–12 (moderate CP); and indication to imaging testing without preceding D-dimer when 4PEPS is up to 12 (high CP). Although the 4PEPS strategy compared favorably, it should be prospectively validated [232].

Based on the current evidence, clinical probability-adjusted cutoffs and combined strategies may hence prove more efficient than the age-adjusted cutoffs for limiting imaging studies. Further prospective studies using various D-dimer immunoassays may be worthwhile.

5.1.6 VTE in specific populations

5.1.6.1 Pregnancy

D-dimer increases during pregnancy and postpartum. For example, in a cohort of 1343 pregnant women, D-dimer above the 500 μg/L FEU cutoff was 15%, 71% and 96% in the first, second and third trimester, respectively (STA Liatest) [233]. Similar results were observed with other assays (MDA, bioMérieux, France and HemosIL HS) [234,235]. D-dimer returns to normal around the 6th week postpartum.

The risk of VTE is increased four- to five-fold during pregnancy (all trimesters) and peaks postpartum [236]. Although VTE is infrequent (1–2 per 1000 pregnancies), acute PE is still one of the leading causes of maternal death in Western countries [237]. However, diagnosis of VTE and PE during pregnancy remains challenging due to normal physiologic changes that overlap symptomatically with symptoms of DVT [238]. Due to the consequences of a missed diagnosis, the threshold for testing for VTE during pregnancy is relatively low leading to low prevalence of confirmed VTE in this population.

Until very recently, the main pretest probability assessment tools used in the general population, i.e., the Wells [239] and Geneva scores [240], had not been validated. Some scores and algorithms have been developed to offset the limitations of these CPR.

In the Diagnosis of PE in Pregnancy (DiPEP) study, D-dimer did not prove relevant to rule out PE because no diagnostically useful threshold for diagnosing or ruling out VTE/PE could be identified [241,242]. However, the YEARS algorithm has recently been adapted to pregnant women and demonstrated that PE could be safely ruled out across all trimesters [204,243]. The use of CTPA could be avoided in 32–65% of patients without safety concerns, i.e., a single case of DVT was reported in a cohort of 498 (195 with negative assessment) [243]. Another study using the revised Geneva score also found that a diagnostic strategy based on assessment of clinical probability, D-dimer, compression ultrasonography (CUS), and CTPA safely ruled-out PE in pregnancy [244]. This study of 395 pregnant women (28 with confirmed PE), reported that the rate of symptomatic VTE during 3-month follow-up was 0.0% among untreated women after exclusion of PE on the basis of negative diagnostic work-up results. Application of the YEARS algorithm in this cohort resulted in safe exclusion of PE in one out of five pregnant women without the need for radiation exposure [245]. Secondary analysis of the DiPEP cohort using the adapted YEARS and Geneva strategies were inconclusive vs imaging [246]. Fortunately, the relatively low prevalence of PE would result in only few missed cases among those discharged without imaging or treatment. Furthermore, missed PE diagnoses were reported as small or segmental in the DiPEP study. Of these, many had the lowest D-dimer. These two findings indicated that the emboli and/or lung tissue volume affected was probably small and that the two scores may be effective for detecting larger PE. However, they noted that ignoring small PE was not a safe strategy as these may portend subsequent larger PE.

A recent meta-analysis included prospective and retrospective studies that used plasma D-dimer with or without pretest probability to rule out VTE in pregnant women with suspected PE and/or DVT [193]. Imaging tests (ventilation-perfusion lung scan, CTPA, pulmonary angiography, lower limb venous CUS) or clinical follow-up at 3 months were used as the reference standard. They reported that three-month thromboembolic risk in pregnant women left untreated after a negative diagnostic algorithm was 0.2%, i.e., well below the 2% threshold recommended by the ISTH for VTE [193]. Three-month thromboembolic risk in pregnant women left untreated in cases of a non-high clinical probability and negative D-dimer was 0.32%,u corresponding to a 99.5% sensitivity and 100% NPV [247]. As such, D-dimer measurement in association with a clinical score, may help to safely rule out PE in pregnant women, thus reduce exposure to ionizing radiation and intravenous contrast for mother and fetus.

5.1.6.2 Cancer

Thrombosis is a leading cause of death in cancer, i.e., nine-times higher vs age-matched controls [248,249]. The association of thrombosis with cancer was described in the 19th century by Armand Trousseau and contemporary studies report a prevalence of VTE and PE of 4–20% in cancer [250]. Diagnosis, risk assessment and prediction of VTE in cancer is important in clinical decision making.

In cancer, accurate and timely diagnosis of DVT is essential to mitigate morbidity and mortality. Unfortunately, D-dimer alone for diagnosing VTE is insufficient [146]. Due to high prevalence of VTE in cancer, the NPV is reduced [146,251]. A large meta-analysis of patients with clinically suspected DVT reported that a low Wells score and a negative D-dimer was only 9% in patients with cancer [252] and 88–94% of patients with cancer required additional testing to rule out VTE [253]. Similarly, the Wells rule with fixed D-dimer testing was 9% in patients with active cancer and suspected PE [254]. Although this approach was successful in excluding DVT in patients without cancer, this was not the case for those with cancer [255]. Reasons may include missed diagnosis as well as the development of a new VTE in patients with a strong persistent risk factor. Despite low diagnostic accuracy of the Wells rule and D-dimer [256], a very high prevalence of thrombosis was observed in cancer patients with suspected DVT (about 40%) and consequently, DVT could only be excluded in 4% of patients with cancer using a cancer-specific diagnostic prediction model. The high pretest probability in this population makes it almost impossible

to rule out DVT without imaging. Accordingly, direct referral for CUS without D-dimer appears preferable in terms of diagnostic efficiency and patient convenience for cancer patients with suspected DVT [256]. In the setting of cancer, D-dimer incorporated in a risk assessment model may be useful to identify low or high VTE risk [257,258].

D-dimer is also used in conjunction with other biomarkers and clinical characteristics as a risk assessment model for cancer-associated VTE in ambulatory patients. The Khorana score combines different biomarkers, including platelet and white blood cell count and hemoglobin with cancer type to assess VTE risk [259]. This score has been developed and validated for predicting cancer-associated VTE in ambulatory patients and in a randomized controlled trial of primary thromboprophylaxis in cancer patients undergoing systemic antic-cancer therapy in ambulatory settings [260,261]. Unfortunately, the Khorana score was unable to identify all patients who will develop VTE, even at a cutoff of two or higher [262]. Accordingly, further refinement of risk assessment and prediction of VTE in cancer is necessary. A study by Pabinger et al. [258] found that tumor-site category and D-dimer better predicted VTE risk in ambulatory patients with solid cancers. Although this model showed promising performance in a post-hoc analysis of a primary thromboprophylaxis trial in cancer patients, it needs further external validation before clinical use [263].

D-dimer might also predict VTE recurrence in cancer. A recent meta-analysis revealed that increased D-dimer was associated with onset and thrombosis recurrence in cancer (1.79 hazard ratio (HR)) [264]. A prospective study by Jara-Palomares et al. [265] also found that D-dimer might be predictive of recurrent VTE after cessation of anticoagulation therapy. However, the Recurrent VTE Biomarkers (REMARK) study did not find D-dimer predictive in patients with various active cancers and diagnosed with acute symptomatic VTE [266]. It should be noted, however, that D-dimer was measured one to two weeks post-enrollment, a questionable design since patients were treated with anticoagulants for six months. Thus, timing of D-dimer testing is of particular importance when evaluating performance. In the study of Jara-Palomares et al. [265], D-dimer evaluated 21 days after anticoagulant withdrawal was 100% and 90% sensitive for VTE recurrence at three and six months, respectively. Similar to other biomarkers such as prothrombin fragment 1 + 2, FVIII and fibrinogen that indicate hypercoagulability, D-dimer was associated with mortality risk and poorer chemotherapeutic response in advanced colorectal, lung and pancreatic cancers [267–271].

5.1.6.3 Kidney disease

The exclusion of VTE in kidney disease remains challenging given that D-dimer fragments are mostly eliminated by renal clearance and catabolism by mononuclear cells [14]. Accordingly, Robert-Ebadi et al. [272] showed that D-dimer increased with impaired renal function and negative D-dimer results decreased from 46% to 11% in subjects with normal (≥90 mL/min) or moderate (30–59 mL/min) estimated glomerular filtration rate (eGFR), respectively. In addition, Lindner et al. [273] showed that 100% of patients with low chronic kidney disease - epidemiology collaboration (CKD-EPI) eGFR (< 30 mL/min) had positive D-dimer results. Because D-dimer specificity decreases proportionately to renal impairment, the use of renal function-adjusted cutoffs has been advocated [273,274].

A single center study performed by Schefold et al. [275] suggested that renal function-adjusted D-dimer cutoffs were reliable and safe to assess the risk of thromboembolic disease. In patients with moderate or severely reduced eGFR (< 60 mL/min), the number of false positive D-dimer results were remarkably reduced when adjusted cutoff values are used. Furthermore, eGFR-adjusted D-dimer cutoffs appear reliable in patients with acute and/or "acute on chronic" renal dysfunction. In contrast, ten Cate et al. [276] reported that age-adjusted cutoffs were superior in patients with mild to moderate renal disease, while C-reactive protein-adjusted D-dimer performs better in those with severe renal dysfunction.

5.2 Predicting VTE recurrence

Preventing recurrence is crucial in patients with previous VTE. Current guidelines advise to classify patients as high or low risk. The main question is to determine if the length of anticoagulant treatment should be definite or indefinite. In this context, the classification of VTE events involves the crucial concept of provoked (after surgery, lower limb trauma and orthopedic immobilization or hospitalization for acute medical illness) vs unprovoked events. Risk of recurrence at two years is considerably lower in provoked vs unprovoked VTE [277]. Despite wide use, the "(un)provoked" term was not used in the latest ESC guidelines because it was considered 'potentially misleading and not helpful for decision-making regarding the duration of anticoagulation' [223].

Risk of recurrence one-year after a first unprovoked VTE episode was higher in men (9.5%) than women (5.3%), and cumulative incidence increases with time (9.1% and 19.7%, for men and women after three years, respectively) [278]. Increased D-dimer was associated with increased risk of

recurrent VTE [175,279–281]. In the PROLONG study, recurrent VTE occurred in 15% of patients who stopped vitamin K antagonist therapy vs those who did not (2.9%, 4.26 HR) [282]. Furthermore, the VTE rate in anticoagulated patients with increased D-dimer was significantly higher in those taking direct oral anticoagulants (DOACs) vs those treated with warfarin. This finding indicates that additional studies should be performed to reassess the D-dimer in recurrent VTE for those treated with DOACs. After discontinuation, positive D-dimer results were also observed at day 30 [282]. Patients with unprovoked VTE and positive D-dimer one month after discontinuation of oral anticoagulants had higher incidence of recurrence vs those with negative values [283].

A post-hoc analysis of the PROLONG study determined age-specific cutoffs for several quantitative assays and identified a higher cutoff in the elderly (70 y or older) for: Vidas, 1200; Innovance, 900; STA Liatest, 1000 μg/L FEU and HemosilL HS, 450 μg/L DDU [283]. Method-specific cutoffs, adjusted for age and gender and quantitative methods are advised for more accurate prediction of VTE recurrence [283–285].

The meta-analysis of Di Minno et al. [286] showed that absolute risk of VTE recurrence was 16.1% in patients with a positive D-dimer vs 7.4% with negative values (2.1 OR), suggesting that D-dimer may help identify VTE patients at higher risk of recurrence with better discrimination for provoked events. Kearon et al. [287] also investigated D-dimer as a decision factor to stop anticoagulant therapy following first unprovoked VTE. Anticoagulant therapy was stopped in cases of negative D-dimer. Five-year follow-up found that risk of recurrence was 21.5% overall, 29.7% in men, 17.0% in non-estrogen women, and 2.3% in women on estrogen at the time of their VTE.

Overall, D-dimer above the diagnostic cutoff after three months of anticoagulant therapy in patients with a first unprovoked VTE event was associated with a 2-fold risk of recurrence vs those with low D-dimer [2,288]. Risk of VTE recurrence was similar in the young and elderly. In a study on proximal DVT, Nagler et al. [289] showed that increased D-dimer (Vidas and Innovance) significantly predicted recurrence one month after discontinuing anticoagulant therapy (HR 3.3) and was associated with male sex (HR 2.8) and use of oral contraceptives (HR 0.1). Increased factor VIII was also predictive (HR 2.2). A recent post-hoc analysis of the study by Palareti et al. [290] concluded that serial D-dimer in patients <65 y may help clinicians to evaluate risk of recurrence and decide whether to extend or discontinue anticoagulation [291].

The same authors more recently studied adults who received oral anticoagulants for at least twelve months following a first unprovoked VTE [292]. Patients with serially negative D-dimer 15, 30 and 60 d post-discontinuation were not treated, whereas patients with a positive D-dimer at any time were provided low dose apixaban (2.5 mg bid) for 18 months. A substantially higher rate of adverse outcomes (recurrent VTE, bleeding, death) was observed in the group without anticoagulation (7.3%) vs those treated (1.1%). The authors concluded that the decision to extend anticoagulation should not be solely based on D-dimer.

Prediction models to assess the risk of recurrence after a first VTE involve D-dimer combined with various risk factors such as age, male sex, obesity, proximal DVT, residual vein thrombosis, hormonal therapy [293]. The definition of provoked vs unprovoked events may vary and potentially lead to poorer prediction. The HERDOO2 rule (Hyperpigmentation, Edema, or Redness in either leg), D-dimer ≥ 250 μg/L FEU (Vidas) on anticoagulants; obesity with body mass index ≥ 30, older age, ≥ 65 y may help identify women at higher risk [294–296].

Tosetto et al. [297] found that increased D-dimer following anticoagulant therapy discontinuation (cutoff, 500 μg/L FEU with a quantitative assay or "positive" with a qualitative assay), age (< 50 y), male sex and VTE not associated with hormonal therapy best predicted VTE recurrence (area under the curve (AUC): 0.71). The D-dimer, Age, Sex, Hormonal therapy (DASH) score performed better than D-dimer alone in predicting VTE recurrence (AUC: 0.61; P < 0.001). External validation concluded that DASH performed better in younger subjects (< 65 y) [298]. Recently, a single-center study failed to find low recurrence rates in low-risk groups as defined by DASH [299]. Algorithms such as the Vienna prediction model (D-dimer (Asserachrom), sex and site of index event) [295,300] was validated in external populations, but interventional studies have not been performed [301]. Although an interventional study was performed to validate the HERDOO2 model [302], caution is advised because D-dimer assays, length of discontinuation and cutoffs are not interchangeable [295]. It is recommended that the measurement method used in the design and validation in these scores (HERDOO2 and DASH) be consistent. For example, in studies used to establish and validate the DASH score, the time interval between anticoagulant discontinuation and D-dimer measurement was variable, i.e., 20 days [298] to 3 months [303].

Weighing the risk of recurrence and bleeding is essential [223]. Recently, a systematic review by de Winter et al. [304] investigated various

models for VTE recurrence and bleeding in an initial oral anticoagulant therapy of at least three months in a VTE population. Unfortunately, none were judged low risk and had satisfactory predictive performance. They concluded that current evidence does not support the use of prediction models to continue or stop anticoagulant therapy.

Thus, current evidence on D-dimer in the long-term management of VTE is insufficient with contradictory guidelines [305]. D-dimer in combination with demographic and clinical factors (validated risk model) may better predict VTE recurrence.

5.3 Predicting VTE in hospitalized patients or with recent surgery

Baseline D-dimer in hospitalized patients was independently associated with symptomatic VTE during a period of about three months (HR 2.22) [306]. Because patients hospitalized for acute illness (ischemic stroke, heart failure, respiratory failure, rheumatic disorders, infection) have an increased risk of VTE [306–309], an assessment is needed before initiating thromboprophylaxis [306]. The International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) assessment tool to risk stratify hospitalized patients includes many clinical variables such as previous VTE, known thrombophilia, current lower-limb paralysis, current cancer, immobilization for ≥ 7 days, intensive care or coronary care units admission, and age > 60 y [306]. A D-dimer ≥ 2-times the upper reference limit (STA Liatest) was assigned two more points in the new scoring system (IMPROVEDD). The APEX study, used to validate this approach, demonstrated substantially improved risk discrimination and reclassification [310].

In patients with recent surgery, D-dimer is usually increased thus complicating diagnosis of VTE. The lack of validated CPR and subjectivity thereof complicates assessment [311]. Consequently, imaging is typically advised in cases of suspected VTE. Penaloza et al. [312] developed a score to assess high-sensitivity D-dimer (Vidas, STA Liatest and MDA). They found nine variables independently associated with risk of falsely positive D-dimer including:

sex female, + 1; age 65–84 y, + 4 or ≥ 85 y, + 8; heart rate ≥ 95/min, + 1; oxygen saturation < 95%, + 2; temperature ≥ 38.5 °C, + 3; history of VTE, + 1; surgery under general anesthesia within four weeks, + 2; active malignancy, + 3; and pregnancy or postpartum within four weeks, + 4. In patients with non-high CPR and relevance score ≤ 8, at least 10% had

D-dimer < 500 μg/L FEU, suggesting that D-dimer may still be useful in patients with recent surgery, in the absence of other risk-factors [311].

5.4 Cerebral venous thrombosis

The American Heart Association (AHA) and of the American Stroke Association guidelines state that a normal D-dimer performed with a sensitive assay may be included in the diagnosis of patients with low probability of cerebral venous thrombosis (CVT). In low class (IIb) and level of evidence (B), the use of D-dimer is considered unnecessary in cases of high clinical suspicion [313]. Although the gold standard, imaging rarely confirms CVT [314]. Validated pretest clinical probability scores to assist clinicians is also lacking [314]. Dentali et al. [314] found that D-dimer had 93.9% sensitivity and 89.7% specificity in suspected CVT. Risk of falsely negative D-dimer was associated with symptom duration, limited sinus involvement and isolated headache. Alons et al. [315] showed that D-dimer had a high NPV in low risk patients with isolated headache for excluding CVT. Low risk patients were defined by normal neurologic examination and standard head computed tomography (CT), and absence of risk factors such as puerperium and pregnancy. D-dimer demonstrated 97.8% sensitivity, 84.9% specificity, 33.1% positive predictive value and 99.8% NPV for diagnosing CVT. As such, a negative D-dimer may reduce unnecessary neuroimaging studies.

5.5 Acute aortic dissection

Currently, AAD is generally diagnosed by imaging studies (magnetic resonance imaging, echocardiography, contrast-enhanced CT) (Class I; Level of evidence B) [316,317]. Classic symptoms include back and/or abdominal pain, acute onset of tearing chest, asymmetric blood pressure and widened mediastinum on chest x-ray [316]. Presentation may also be nonspecific and a missed diagnosis may be fatal. D-dimer is increased in AAD and might potentially to rule out in patients with low clinical probability [4,316,318]. Meta-analyses by Cui et al. [316] and Watanabe et al. [319] demonstrated 94.5% and 95.2% sensitivity and 69.1% and 60.4% specificity for D-dimer, respectively, to exclude AAD in patients with low likelihood of disease. The American College of Cardiology Foundation and the AHA guideline indicate that D-dimer should not be used rule out AAD in high-risk patients and that D-dimer screening is not recommended in patients evaluated for aortic dissection (AD) [317]. The AD detection risk score (ADD-RS) is a tool allowing standardized assessment of the

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pretest probability for acute aortic syndromes [320]. The sensitivity and the failure rate of ADD-RS at 0, ≤1 and 1 (high risk of AD) were 100% and 0%, 98.7% and 0.8%, and 97.5% and 4.2%, respectively [321]. The combined ADD-RS (0 or ≤1) with negative D-dimer is superior to D-dimer alone in AAD diagnosis [321–323]. However, in patients at high risk (ADD-RS 1), D-dimer was unacceptable to rule out the diagnosis of AD because of lower accuracy (4% failure rate) [323]. Consequently, a negative D-dimer result combined with the absence of ADD risk markers argues strongly against the diagnosis of AD [321,323]. ADD-RS combined with D-dimer may potentially standardize diagnostic AD rule out [323].

5.6 Acute mesenteric ischemia

Acute mesenteric ischemia is associated with high mortality [324] and caused by arterial thrombosis (15–20%), venous thrombosis (5%), arterial embolism (50%) and non-occlusive mesenteric ischemia (20–30%) [324,325]. Spiral CT scan was 93.3% sensitive and 95.9% specific for detecting acute mesenteric ischemia [326]. D-dimer may also prove useful [327–330]. According to the European Society for Trauma and Emergency Surgery , D-dimer lacks discrimination [324] and was not associated with severity [328]. A meta-analysis, however, reported 94% sensitivity and 50% specificity for D-dimer in "acute intestinal ischemia" (acute strangulated intestinal obstruction, acute intestinal necrosis and two with mixed type of acute intestinal ischemia) [331]. Further validation in large multi-center clinical studies is clearly needed.

5.7 Disseminated intravascular coagulation

Disseminated intravascular coagulation (DIC) is a life-threatening condition characterized by persistent activation of hemostasis with intravascular thrombin generation, fibrin deposition, and platelet and coagulation factor consumption [3]. Patients with DIC may present with bleeding, thrombosis or both [191]. Early recognition is paramount to initiate the appropriate treatment, which entails eliminating or containing the underlying condition (sepsis, malignancy, trauma or burns, obstetrical diseases, toxins, drugs, immunological disorders and other inflammatory diseases) [1]. Various scoring systems have been proposed for diagnosis and management of DIC. These include ISTH overt-DIC [332], the Japanese Ministry of Health and Welfare DIC [333], the Japanese Society on Thrombosis and Hemostasis (JSTH)-DIC [333], the Japanese Association for Acute Medicine (JAAM)-DIC [334], and the sepsis-induced coagulopathy (SIC) [335].

Comparison with the ISTH overt-DIC diagnosis criteria yielded similar diagnostic performance for DIC [1,336]. In septic shock, the SIC score had lower performance than JAAM-DIC and ISTH overt-DIC scores and was not improved when combined with those scores [337]. As such, JAAM-DIC and ISTH overt-DIC alone are therefore appropriate to diagnose DIC in septic shock. Laboratory parameters in the scoring include platelet count, fibrinogen concentration, PT and FRM [332,333,338]. Although D-dimer is the most common FRM, some suggested that soluble fibrin complexes containing fibrin monomers may be more specific to detect intravascular thrombin generation. Using the ISTH overt-DIC score, D-dimer is considered positive at >3.0 μg/mL or >7.0 μg/mL FEU (Vidas), i.e., 2 or 3 points, respectively [150]. The DIC score is impacted by large D-dimer inter-assay variability [133,135,150]. For example, cutoffs for 2 or 3 points are: 3500 or 11,100 (STA Liatest); 4000 or 13,000 (Innovance); and 6000 or 24,000 μg/L FEU (Liasauto (Sysmex, Japan).

In VTE, a "normal" D-dimer excludes a diagnosis of DIC [175]. Although serial testing is important in monitoring DIC [333,338,339], the half-life (6–8 h) of D-dimer should be taken into account [52]. Combined D-dimer and fibrin monomer testing identified those with poorer survival in septic shock [340,341].

5.8 Severe acute respiratory syndrome coronavirus 2

The emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) resulted in a high incidence of thromboembolic events worldwide [342–344]. Increased D-dimer was one of the most commonly associated alterations in hemostatic parameters especially in the severely affected, i.e., 'COVID-19-associated coagulopathy' [345–348]. It is widely accepted that these disturbances were a consequence of the intense inflammatory response to lung damage accompanied by endothelial dysfunction and concomitant pathologic processes (neutrophil extracellular traps, lupus anticoagulant, platelet-leukocyte aggregation) [348,349].

Although some suspected that increased D-dimer reflected diffuse activation of intravascular coagulation (DIC-like pattern), most patients often had normal platelet counts and high fibrinogen [350]. D-dimer, however, could originate from the extravascular space [167,168]. In the presence of significant inflammation, plasma fluid extravasates into the pulmonary alveoli, with formation of extensive fibrin [351]. These deposits are degraded via tissue fibrinolysis with subsequent production of D-dimer which then diffuses into the bloodstream.

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Several arguments point to an extravascular origin of D-dimer [352]. Histologic studies have consistently identified extensive fibrin deposits in the alveoli and other extravascular pulmonary spaces [353]. Several studies found that D-dimer was associated with the extent of lung involvement by CT [354,355]. Finally, in the majority of patients admitted to the ICU, fibrin monomers remain low and within the normal range [356,357]. The soluble complexes, i.e., two fibrinogen molecules complexed with a fibrin monomer, have a molecular mass that prevents diffusion from the extravascular space.

Recently, Planquette et al. [358] suggested that a D-dimer < 900 μg/L FEU (Vidas, STA Liatest or Innovance) may rule-out PE in COVID-19 patients with limited lung damage.

On the other hand, D-dimer may increase abruptly in the presence of additional intravascular thrombin generation, i.e., in the presence of a VTE event or overt DIC [356]. Indeed, several reports identified an association between D-dimer increase and subsequent VTE [359,360]. However, baseline D-dimer is often increased in COVID-19 and sometimes to very high levels in the critically ill. Unfortunately, large inter-individual variability prevents the establishment of an alert threshold [361]. As such, serial D-dimer changes may, however, better predict a thrombotic event.

D-dimer has also been used as a prognostic monitor in COVID-19 patients, thus guiding management. Studies have shown that D-dimer was associated with disease severity [362–367], risk of adverse outcome (including death) [362–364,366,368] and thromboembolic risk [343,360,362]. Accordingly, it has been included in various risk classification scores. Although it may also guide thromboprophylaxis [369], its benefit has been debated [370–374].

After hospital discharge, D-dimer can be variably increased for up to six months [375,376]. Unfortunately, the significance of this finding is unclear. Some proposed using D-dimer as a criterion for maintaining post-discharge thromboprophylaxis with rivaroxaban (10 mg/day) due to reduced incidence of thrombotic events [377]. Others used D-dimer for identifying patients at risk for readmission with variable results [378,379]. Others suggested that persistently increased D-dimer (> cutoff for VTE exclusion) may reflect persistent pulmonary abnormalities [380]. Additional data are clearly needed to assess the significance of these findings.

In response to the pandemic, COVID-19 vaccines were developed and widely administered. Adverse effects include vaccine-induced immune thrombosis and thrombocytopenia (VITT). This unusual phenomenon,

Table 5 Vaccine-induced immune thrombosis and thrombocytopenia (VITT) following ChAdOx1 nCoV-19 vaccination: Summary of current guidance/guidelines.

Guideline	Definite case	Probable case	Possible case	Suspected case	Unlikely case
ISTH [385]	D0 to D+ 20 Acute thrombosis PLT $<$ 150 10^9/L Raised D-dimer Positive anti-PF4 Abs (ELISA) Positive platelet activation assay	D0 to D+ 20 Acute thrombosis PLT $<$ 150 10^9/L Raised D-Dimer Positive anti-PF4 Abs ELISA	/	D0 to D+ 20 Acute thrombosis PLT $<$ 150 10^9/L Raised D-dimer	Negative anti-PF4 Abs ELISA
UK EHP [386]	D+ 5 to D+ 30 Acute thrombosis PLT $<$ 150 10^9/L D-Dimer $>$ 4000 μg/L FEU Positive anti-PF4 Abs (ELISA)	D-dimer $>$ 4000 μg/L FEU but one criterion not fulfilled (Timing, Thrombosis, Thrombocytopenia, anti-PF4 Abs)	/	D-dimer unknown or 2000–4000 μg/L FEU with one other criterion not fulfilled, or two other criteria not fulfilled (Timing, Thrombosis, Thrombocytopenia, anti- PF4 Abs)	PLT $<$ 150 $\times$ 10^9/L without thrombosis with D-dimer $<$ 2000 μg/L FEU, Or thrombosis with PLT $>$ 150 $\times$ 10^9 /L and D dimer $<$ 2000 μg/L FEU, And/or alternative diagnosis more likely

ASH [387]	**1.** COVID vaccine 4–42 days prior to symptom onset[#] **2.** Any venous or arterial thrombosis (often cerebral or abdominal) **3.** Thrombocytopenia (PLT $< 150 \times 10^9$/L) **4.** Positive PF4 "HIT" (heparin-induced thrombocytopenia) ELISA **5.** Markedly elevated D-dimer (> 4 times the cut-off used for VTE exclusion)		/	**1.** Confirmed thrombosis *AND* at least one of the following low PLT *OR* markedly elevated D-dimer *OR* both **2.** If thrombocytopenia and very high D-Dimer in absence of known thrombosis, particularly in the presence of severe headache	If thrombocytopenia but no thrombosis and negative PF4 ELISA: likely ITP VITT is excluded if: PF4 ELISA is negative and there is no thrombocytopenia
Australia/ New Zealand [388]	VITT is confirmed by positive "VITT" ELISA, AND positive "VITT" functional testing in cases of suspected VITT	VITT is probable if there is evidence of thrombosis in suspected VITT	VITT is possible if there is no evidence of thrombosis in suspected VITT	VITT is suspected if PLT $< 150\ 10^9$/L AND either D-dimer is elevated ($5 \times$ the cut-off used for VTE exclusion) OR fibrinogen is reduced	PLT $> 150\ 10^9$/L (Less likely: elevated D-dimer or reduced fibrinogen Much less likely: D-dimers are not elevated AND fibrinogen is normal)

Abs: Antibodies; ELISA: enzyme-linked immunosorbent assay; FEU: fibrinogen equivalent unit; ITP: immune thrombocytopenic purpura; PF4: platelet factor 4; PLT: platelet count; ULN: upper limit of normal; VITT: Vaccine-induced immune thrombosis and thrombocytopenia.

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caused by platelet-activating antiplatelet factor 4 (PF4) IgG antibodies, has been linked to two adenovirus vector–based vaccines, ChAdOx1 nCoV-19 (AstraZeneca) and Ad26. COV2. S (Johnson & Johnson/Janssen) [381]. Although VITT generates an extremely serious adverse syndrome at 5–30 days post vaccination, it is rare [382].

D-dimer greater than five-times the cutoff for VTE exclusion is one of the most important predictors of VITT in vaccinated individuals [174].

A combination of thrombocytopenia, thrombosis, increased D-dimer and antiplatelet factor 4 (PF4) antibodies are used to identify VITT post vaccination (Table 5). Although the clinico-pathologic spectrum is much wider than first considered [383], increased D-dimer may be more consistent than thrombocytopenia [384]. In fact, some guidelines do not place sufficient emphasis on D-dimer at triage. For example, a patient presenting with thrombocytopenia but with normal or only mildly increased D-dimer (two-times the cutoff for VTE exclusion) is more likely to have immune thrombocytopenic purpura (ITP), than VITT. Monitoring of D-dimer with fibrinogen and platelet count may also help identify therapeutic efficacy [384].

6. Conclusions

Although D-dimer has now become one of the most requested tests in laboratory hemostasis especially in acute care settings, it remains misunderstood due to preanalytical, analytical and postanalytical variability. As a reliable biomarker of coagulation and fibrinolysis, a negative D-dimer along with low clinical probability can safely rule out VTE in suspected cases. It is currently recommended that highly sensitive D-dimer assays be used to maximize NPV. Among patients with suspected VTE, a D-dimer above a validated cutoff should trigger additional imaging testing to confirm or refute the diagnosis. Because a wide range of disease states and disorders may be associated with increased D-dimer levels, the use of age- and clinical probability-adjusted cutoffs have been proposed to increase specificity. Despite these findings, current guidelines do not necessarily reflect these recommendations and major efforts are thus needed for broader implementation. These efforts should include standardization of all testing phases and a thorough validation of analytical and clinical sensitivity and specificity.

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Conflicts of interest

None declared.

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