UCL Université catholique de Louvain

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NTHC Namur Thrombosis & Hemostasis Center

Les D-dimères en 2018: Comment? Pour qui? Pourquoi?

Prof. François Mullier

52ièmes journées de biologie praticienne

Paris, 7 décembre 2018

Summary

1. What is D-dimer
2. Preanalytical variables
3. Analytical variables
4. Postanalytical variables
5. Clinical applications

What is D-dimer

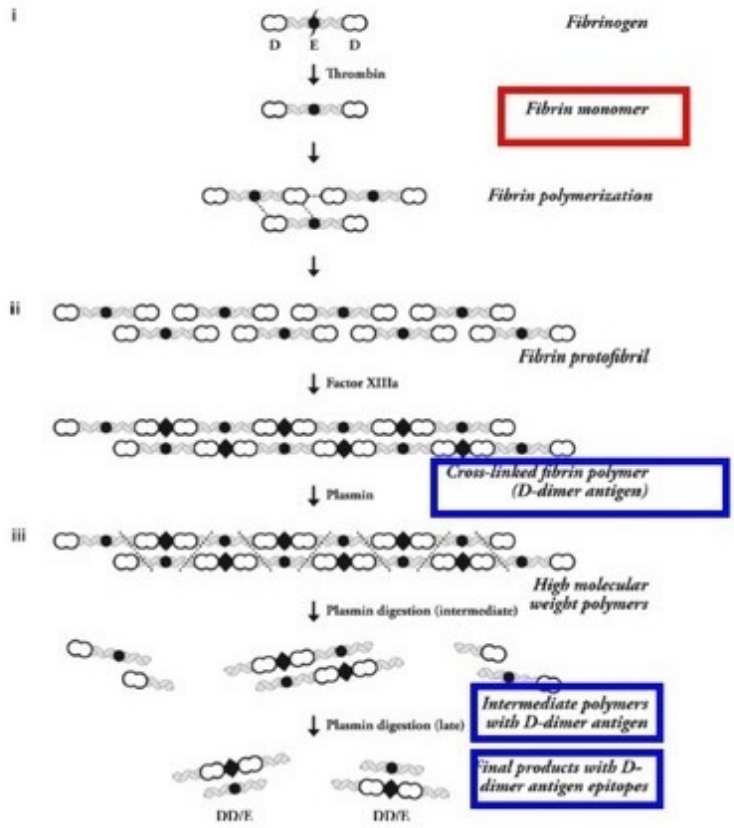


Figure 1. The stepwise process of Fibrin polymerization. The 3 major steps of D-dimer antigen formation are shown. (i) The fibrinogen molecule is cleaved by thrombin to produce fibrin monomers. These monomers associate with fibrinogen or fibrin to form protofibrils. They are held together by noncovalent forces shown as dotted lines between the intermolecular D-domain and D-E domains. (ii) Factor XIIIa formed by thrombin on fibrin polymers then covalently attaches D domains and inserts a covalent intermolecular linkage designated by the diamond-shaped figure. (iii) Plasmin must degrade fibrin at multiple sites to release fibrin degradation products, which then expose the D-dimer antigen epitope. The initial fragments are high-molecular-weight complexes followed by further degradation to produce the terminal D-dimer–E complex, which contains the dimer antigen. The 3 phases of this process are labeled on the right side of the diagram, and the different molecular forms of fibrinogen and its subsequent transformation by thrombin, factor XIIIa, and plasmin are shown on the left side of the diagram. This is a schematic representation of just one protofibril. Multiple protofibrils are aligned side by side and undergo branching to make a fibrin gel.

Adam et al. Blood 2009 Mar 26;113(13):2878-87

What is D-dimer

D-dimers not derived from fibrinogen (as opposed to PDFs)

2–3% of plasma fibrinogen converted in fibrin and then degraded → small amounts of D-dimers in the plasma of healthy subjects.

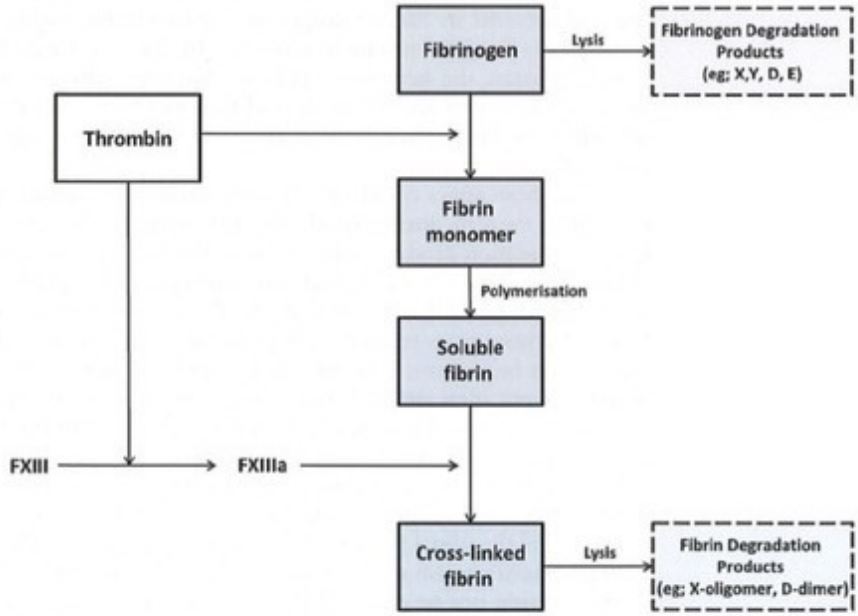
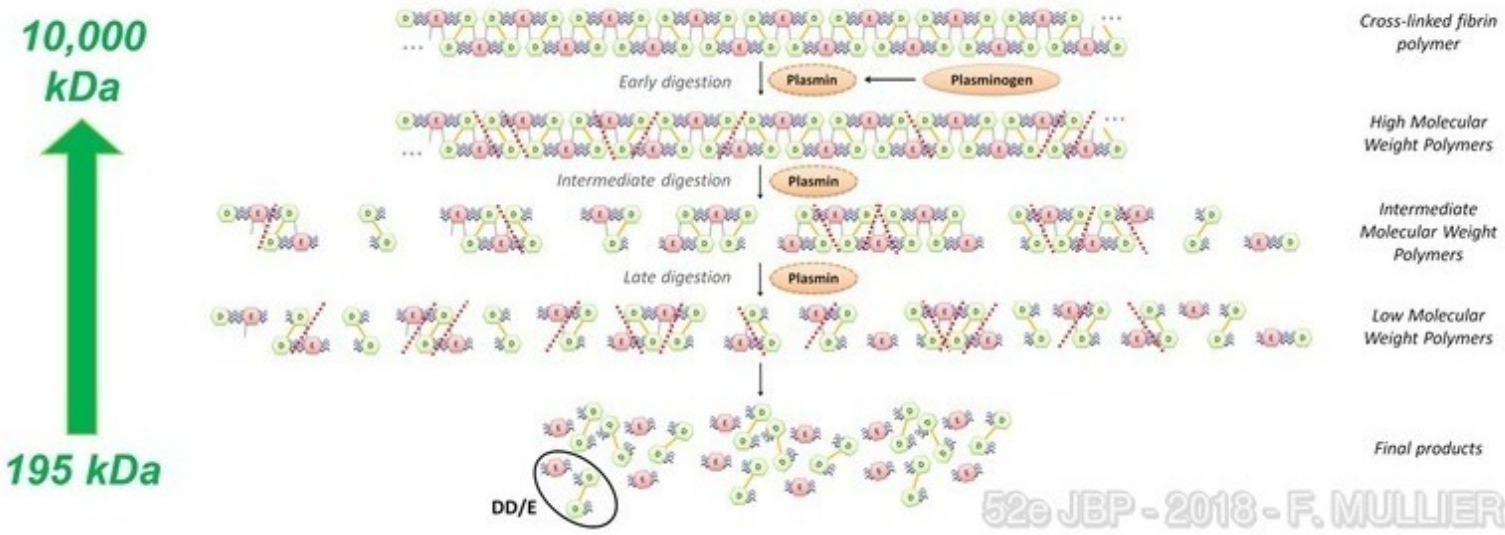


Fig. 2 Fibrinogen to fibrin conversion by thrombin. Once fibrinopeptides are removed, the resulting fibrin monomers are acted upon by activated coagulation factor XIII to form a stable cross-linked fibrin

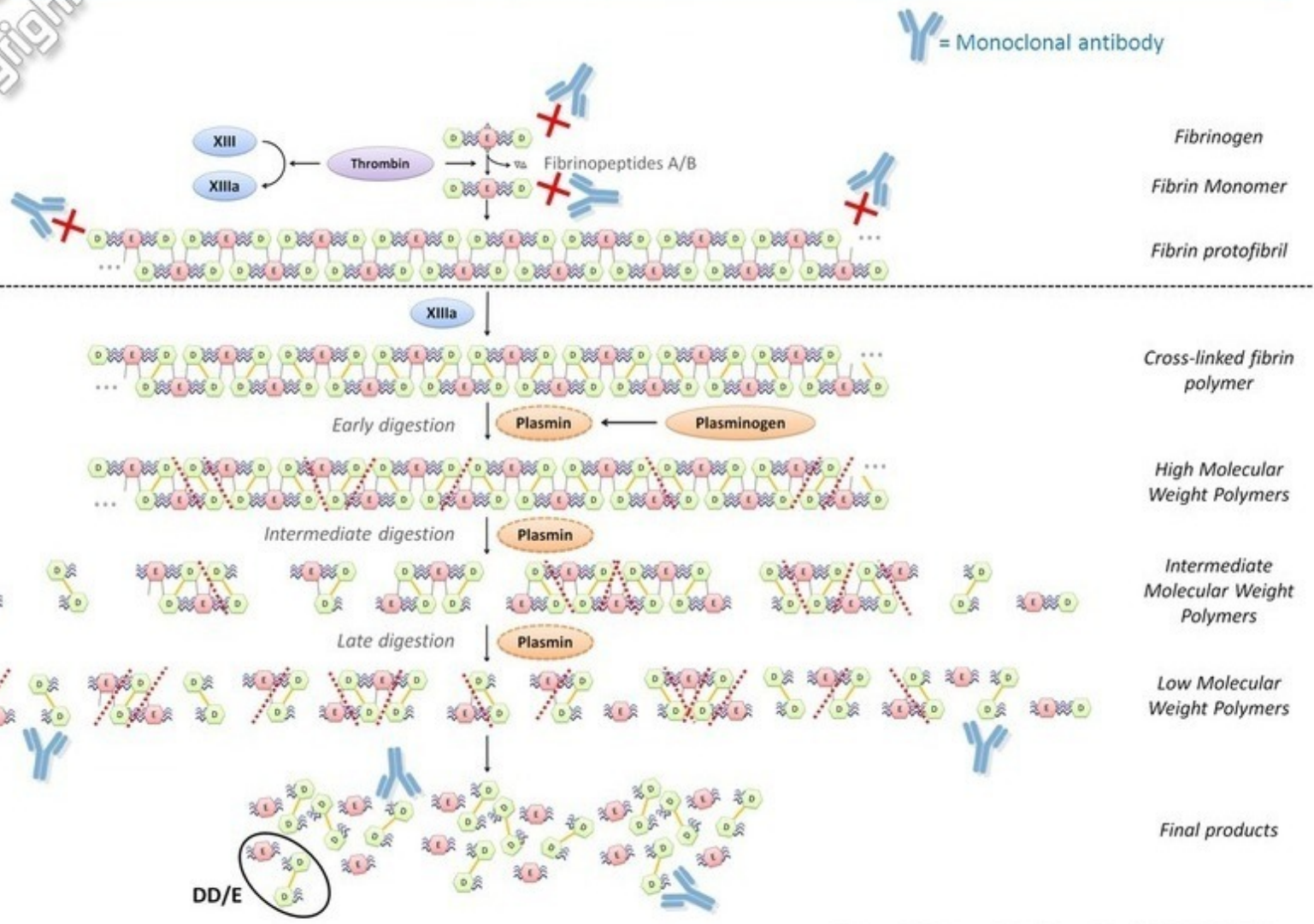
Thachil J, Lippi G, Favaloro EJ. Methods Mol Biol 2017; 1646:91-104

What is D-dimer

- "Fragment D-dimer" initially used to describe the **final plasmin digestion products** (resistant to further plasmin breakdown) of factor XIIIa–cross-linked fibrin clot (fragment D-dimer/fragment E complex)
- However, the actual D-dimer **antigen** (which can be detected by current immunoassays) is not necessarily the DD/E complex. In fact, the term D-dimer comprises a **broad mixture of degradation products of cross-linked fibrin→ difficult standardization**



What is D-dimer

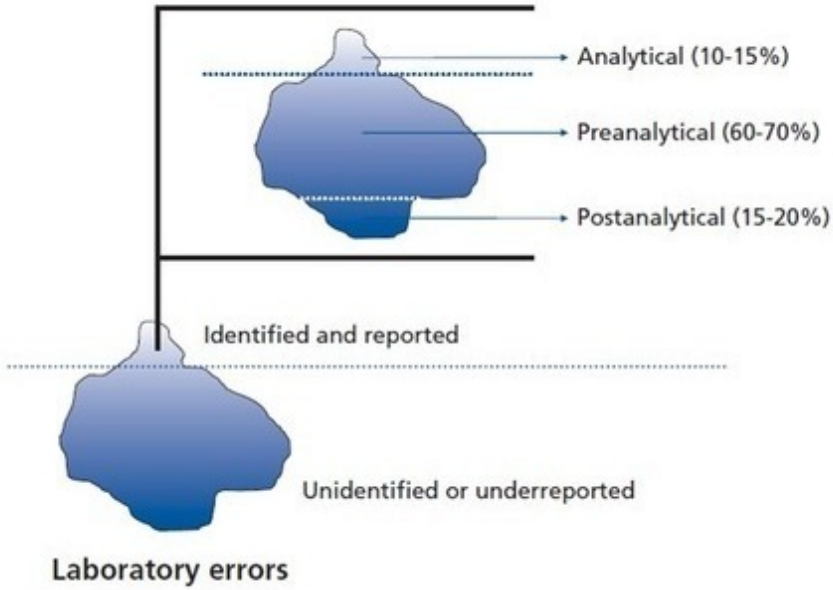


By Nicolas Bailly

2. Preanalytical variables

Preanalytical phase in medical laboratories

- Preanalytical errors have a frequency of **60-70%**, thus much higher than those occurring in the analytical phase (i.e., **10-15%**) and in the postanalytical phase (i.e., **15-20%**). Preanalytical errors are mainly related to intensive manual activities.



Lippi and Favaloro. Quality in Laboratory Hemostasis and Thrombosis. Causes of Errors in Medical Laboratories. 2013: p. 22-31
Magnette et al. Thromb J. 2016;14:49

Sample collection

1. Butterfly devices and needle bore size

Recommendations	Specific data regarding D-dimer
19 to 22 G	19 to 25 G
Butterfly deviced discouraged	Tolerated*

*A discard tube is mandatory for removing air contained within the tubing, which may be associated with collection of an inadequate volume of blood

Adcock. Quality in Laboratory Hemostasis and Thrombosis. Sample Integrity and Preanalytiocal Variables. 2013: p. 45-56
Magnette et al. Thromb J. 2016;14:49
Lippi et al. Clin Chem Lab Med 2006;44(8):1009-14
Lippi et al. J Thromb Haemost. 2005 Feb;3(2):389-91

Sample collection

2. Anticoagulant type and tube material

Recommendations	Specific data regarding D-dimer
- 105–109 mmol/L sodium citrate, buffered anticoagulant - Serum, heparinized/EDTA plasma samples cannot be accepted	- EDTA or heparinized plasma sample tolerated* - Serum discouraged**
Respect the required ratio of sodium citrate to whole blood (1:9)	Underestimation
Non-activating material (silicone-coated glass or polypropylene plastic)	Glass or plastic

* Dilution factor has to be taken into account

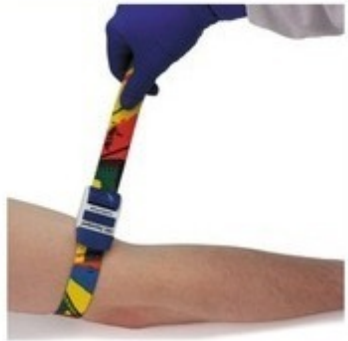
** False positive results were frequently encountered in patients under anticoagulant treatment, whilst negative values were also seen when FDP were entrapped in the clot

Clinical and Laboratory Standards Institute (CLSI). H21-A5. 2008
Magnette et al. Thromb J. 2016;14:49
Adcock. Quality in Laboratory Hemostasis and Thrombosis. Sample Integrity and Preanalytiocal Variables. 2013: p. 45-56
Leroy-Matheron et al. Trhomb Res. 1994;74:399-407
Gosselin et al. Am J Clin Pathol. 2004;122:843-8
Yavas et al. Turk J Haematol. 2012;29:367-75

Sample collection

3. Tourniquet use

Recommendations	Specific data regarding D-dimer
Never remain in place for more than 1-2 min	↗ 13.4% after 3 min venous stasis



Adcock. Quality in Laboratory Hemostasis and Thrombosis. Sample Integrity and Preanalytiocal Variables. 2013: p. 45-56
Magnette et al. Thromb J. 2016;14:49
Lippi et al. J Thromb Haemost. 2005;3:289-91

Venous blood sampling

DE GRUYTER Clin Chem Lab Med 2018; aop

EFLM Paper

Ana-Maria Simundic*, Karin Bölenius, Janne Cadamuro, Stephen Church, Michael P. Cornes, Edmée C. van Dongen-Lases, Pinar Eker, Tanja Erdeljanovic, Kjell Grankvist, Joao Tiago Guimaraes, Roger Hoke, Mercedes Ibarz, Helene Ivanov, Svetlana Kovalevskaya, Gunn B.B. Kristensen, Gabriel Lima-Oliveira, Giuseppe Lippi, Alexander von Meyer, Mads Nybo, Barbara De la Salle, Christa Seipelt, Zorica Sumarac and Pieter Vermeersch, on behalf of the Working Group for Preanalytical Phase (WG-PRE), of the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) and Latin American Working Group for Preanalytical Phase (WG-PRE-LATAM) of the Latin America Confederation of Clinical Biochemistry (COLABIOCLI)

Joint EFLM-COLABIOCLI Recommendation for venous blood sampling

v 1.1, June 2018

https://doi.org/10.1515/cclm-2018-0602
Received June 9, 2018; accepted June 10, 2018

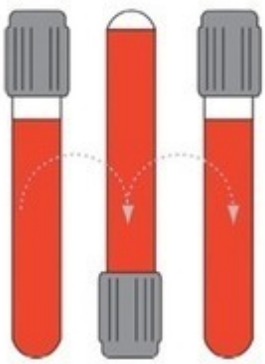


Figure 5: One mixing cycle. One inversion involves turning the tube vertically for 180° and putting it back to the starting position. Reprinted from [25] with kind permission of the Croatian Society of Medical Biochemistry and Laboratory Medicine.

Table 2: Venous blood sampling – the order of steps.

	Step	Strength of evidence
1.	Identify a patient	1C
2.	Verify patient is fasting and properly prepared	1B
3.	Obtain supplies required for blood collection	2C
4.	Label/identify tubes	1C
5.	Put on gloves	1C
6.	Apply tourniquet	1A
7.	Select venepuncture site	1B
8.	Clean sampling site	1B
9.	Puncture the vein	1A
10.	Draw first tube	1A
11.	Release the tourniquet	1A
12.	Gently invert the tube once (one full inversion)	1B
13.	Draw additional tubes following order of draw	1B
14.	Remove needle from the vein and activate safety feature	1A
15.	Dispose of the needle	1A
16.	Bandage the puncture site	1C
17.	Tell a patient to apply a gentle pressure for 5–10 min and not to bend the arm	1C
18.	Invert all tubes 4 times	1B
19.	Remove gloves	1A
20.	Advise patient to rest for 5 min and ensure bleeding has stopped before leaving the site of venous blood collection	1B

Simundic et al. Clin Chem Lab Med 2018, Epub ahead of print

Sample delivery to the laboratory

Recommendations	Specific data regarding D-dimer
At ambient temperature (15-22°C)	4°C or less possible
Vertical position	Pneumatic system tube tolerated*
Usually <1 hour, no more than 4 hours	Stable at various conditions

*It is advisable that each laboratory assesses its local PTS, since the systems are rather heterogeneous in terms of length, internal diameter, maximal acceleration force and speed

Adcock. Quality in Laboratory Hemostasis and Thrombosis. Sample Integrity and Preanalytiocal Variables. 2013: p. 45-56
Magnette et al. Thromb J. 2016;14:49
Schutgens et al. Clin Chem. 2002;48:1611-3
Wallin et al. Clin Chem Lab Med. 2008;46:1443-9
Le Quellec et al. Thromb Res. 2017;153:7-13

Sample processing

1. Centrifugation

Recommendations	Specific data regarding D-dimer
1,500 x g for at least 15 minutes at RT	- 4,500 x g for 2 minutes at RT - 4°C or 12° also possible

Clinical and Laboratory Standards Institute (CLSI). H21-A5. 2008
Bernard et al. Clin Chem Lab Med. 2002;40 (Suppl. S9):S350
Lippi et al. Clin Chem. 2006 Mar;52(3):537-8

Sample processing

2. Interfering susbtances

Recommendations	Specific data regarding D-dimer
Not analyse if visible hemolysis*,**	Cell-free hemoglobin (i.e., <3 g/L)
Icterius	Less widely discussed in the literature
Lipemia	
Paraproteinemia	

* *In vitro* hemolysis still represents one of the most frequent causes of preanalytical problems in clinical laboratories, with a prevalence ranging between 30-70% of all unsuitable specimens

** The majority of hemolyzed samples (±95%) from clinical laboratories are only mildly hemolytic (cell-free hemoglobin 0.3-0.6 g/L)

Clinical and Laboratory Standards Institute (CLSI). H21-A5. 2008
Adcock. Quality in Laboratory Hemostasis and Thrombosis. Sample Integrity and Preanalytiocal Variables. 2013: p. 45-56
Magnette et al. Thromb J. 2016;14:49

Hémolyse, ictère, lipémie

Tableau des seuils HIL			
Seuil	Hémolyse (g/L)	Ictère (mg/dL)	Lipémie (mg/dL)
1	0 ≤ H < 0.3	0 ≤ I < 1,5	0 ≤ L < 160
2	0.3 ≤ H < 0.6	1,5 ≤ I < 6	160 ≤ L < 300
3	0.6 ≤ H < 2.0	6 ≤ I < 10	300 ≤ L < 500
4	2.0 ≤ H < 5.0	10 ≤ I < 18	500 ≤ L < 700
5	5.0 ≤ H < 10.0	18 ≤ I < 30	700 ≤ L < 1000
6	10 ≤ H	30 ≤ I	1000 ≤ L

Réactifs	Tests	Niveaux d'alertes		
		Hémolyse	Ictère	Lipémie
STA-PTTA 5	TCA	2*	NA	NA
STA-Liquid Anti-Xa	HNF	3	4	4
	HBPM	3	4	4
	Fondaparinux/Arixtra	3	4	3
	Rivaroxaban/Xarelto	4	5	6
	Apixaban/Eliquis	4	5	4
	Edoxaban/Lixiana	3	4	3
STA-ECA II	ECA II	4	5	4
STA-Liatest D-Di Plus	D-Di	4	5	/**
STA-Liatest FM	FM	5	5	/
STA-Stachrom ATIII 3	ATIII	5	5	5
STA-Stachrom Protein C	PC	5	5	6
STA-Liatest Free Protein S	PS	5	6	/
STA-Liatest VWF	FVW	5	4	/
STA-VWF:RCO	VWFRCO	5	5	3
STA-Strachrom Plasminogen	Plasminogène	5	6	6
STA-Stachrom Antiplasmin	Antiplasmine	5	6	5

*Pas d'interférence analytique grâce au système de détection viscosimétrique du caillot mais risque aléatoire de raccourcissement ou d'allongement du TCA, qui n'est pas proportionnel à l'intensité de la coloration. Le TCK avec CK Prest ou le TCA avec Cephascreen ne sont pas concernés.

** en l'absence d'indication particulière dans la notice, il serait préférable de mettre une alerte ≥ 2

Déterminé à partir des notices

Courtesy of Stago

Haemolysis

Original articles

A collaborative study by the Working Group on Hemostasis and Thrombosis of the Italian Society of Clinical Biochemistry and Clinical Molecular Biology (SIBioC) on the interference of haemolysis on five routine blood coagulation tests by evaluation of 269 paired haemolysed/non-haemolysed samples

Chiara Novelli*[1], Matteo Vidali[2], Bruno Brando[1], Benedetto Morelli[3], Giovanna Andreani[4], Marina Arini[5], Paola Calzoni[6], Roberta Giacomello[7], Barbara Montaruli[8], Emanuela Muccini[9], Angela Papa[10], Paola Pradella[11], Lucia Ruocco[12], Fosca Siviero[13], Filomena Gemma Viola[14], Mario Zanchetta[15], Lorena Zardo[16], Giuseppe Lippi[17]

Received: March 02, 2018 Accepted: August 20, 2018

https://doi.org/10.11613/BM.2018.030711 Biochem Med (Zagreb) 2018;28(3):**030711**

- Recruitment: 15 hospital laboratories
- 269 paired samples (109mM buffered sodium citrate): second non haemolysed plasma sample available within 4h
- 15 min 1500g room temperature
- Immediate storage at -80°C
- Analysis in one central lab: ACL TOP750-CTS (Werfen)
- D-dimer HemosIL HS-DD (Werfen)
- Haemolysis: visual assessment AND measurement by spectrophotometry

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	Apixaban/Eliquis	4	5	4
	Edoxaban/Lixiana	3	4	3
STA-ECA II	ECA II	4	5	4
STA-Liatest D-Di Plus	D-Di	4	5	/**
STA-Liatest FM	FM	5	5	/
STA-Stachrom ATIII 3	ATIII	5	5	5
STA-Stachrom Protein C	PC	5	5	6
STA-Liatest Free Protein S	PS	5	6	/
STA-Liatest VWF	FVW	5	4	/
STA-VWF:RCO	VWFRCO	5	5	3
STA-Strachrom Plasminogen	Plasminogène	5	6	6
STA-Stachrom Antiplasmin	Antiplasmine	5	6	5

*Pas d'interférence analytique grâce au système de détection viscosimétrique du caillot mais risque aléatoire de raccourcissement ou d'allongement du TCA, qui n'est pas proportionnel à l'intensité de la coloration. Le TCK avec CK Prest ou le TCA avec Cephascreen ne sont pas concernés.

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- Haemolysis: visual assessment AND measurement by spectrophotometry

Hemolysis and D-dimer

- Median (IQR) D-dimer

Haemolysed: 392 (203-923) vs non haemolysed: 317 (173-668) $p<0.001$

- 17,1% samples exceed the critical difference for D-dimer (65%) $CD\% = 2.77\sqrt{(Cva^2 + CVi^2)}$
- Bias is not directly proportional to the degree of haemolysis → impossible to use correction formulas
- Overall agreement of the two laboratory technicians with automatic HIL assessment on ACL-TOP 750-CTS was unsatisfactory (0.62 and 0.65) →the visual assessment of plasma quality should be definitely abandoned

Novelli C. et al. Biochem Med (Zagreb) 2018;28(3):030711

Specific preanalytical data regarding D-dimer testing

Pre-analytical 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
- Tube material	Non-activating material (silicone-coated glass or polypropylene plastic)	Glass or plastic
- Anticoagulant sample	Sodium citrate 3,2% (105-109 mmol/L)	Heparin and EDTA tolerated*
- Tourniquet use	Removed as soon as the needle is in the vein (max 1-2 minutes)	Longer tourniquet use (i.e., 3 min) not tolerated
Sample delivery to the laboratory	At RT (15-22°C), in vertical position, usually <1 hours	PTS tolerated
Sample processing		
- Centrifugation	At RT, 1,500 x g for at least 15 min	Faster protocol allowed (at RT, 4,500 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 hours	At least 24h at RT or at 2-8°C or years at -60 to -80°C No impact of F/T procedure

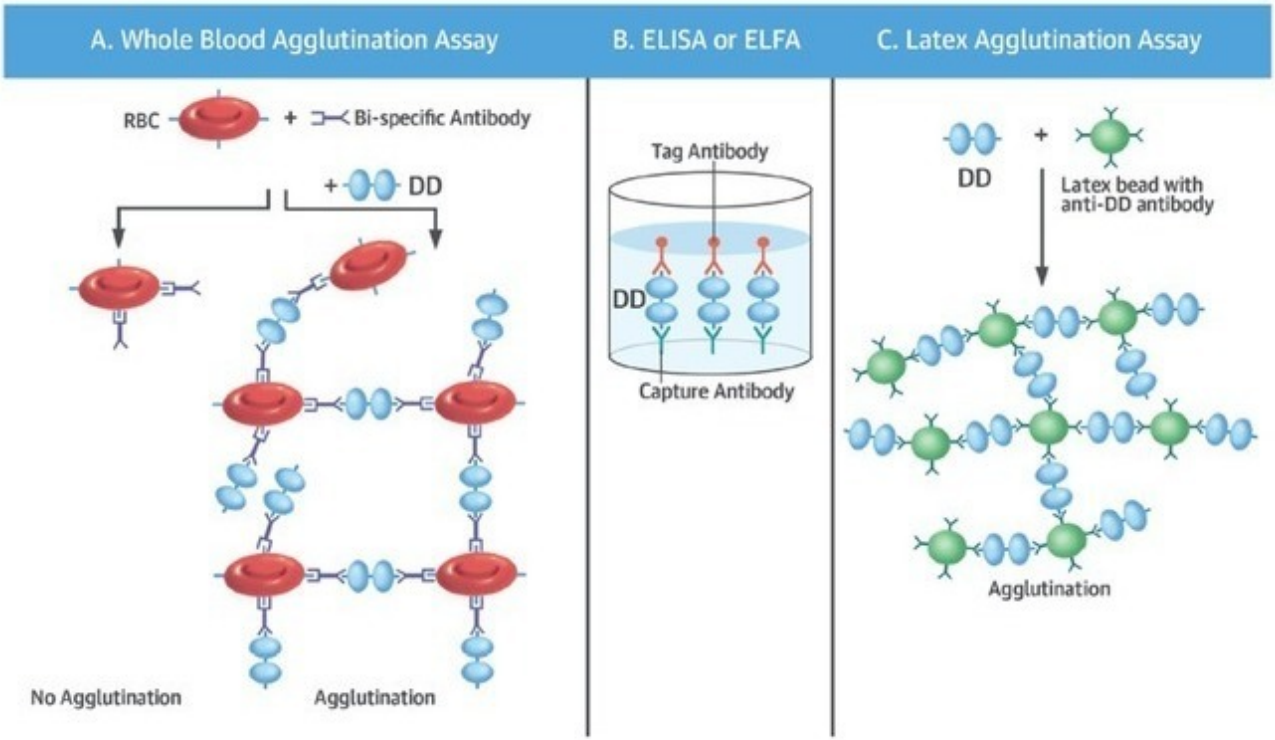
G = gauge, RT = room temperature, PTS = pneumatic tube system, F/T = freezing/thawing, * correction factor needed (dilution).

Favresse et al. Crit Rev Clin Lab Sci. 2018, accepted manuscript

3. Analytical variables

Inter-laboratory variations

- D-dimer assays



(A) Whole blood agglutination assays utilize a bi-specific antibody directed against an epitope on D-dimer (DD) and an epitope on red blood cells (RBC). In the presence of D-dimer, RBC agglutination is monitored by turbidity. **(B)** Enzyme-linked immunosorbent assays (ELISA) or enzyme-linked immunofluorescent assays (ELFA) involve capture of D-dimer with an immobilized antibody specific for D-dimer. A second antibody tagged with horseradish peroxidase or a fluorescent marker binds D-dimer and is used to generate a chromophore or fluorophore that is detected with a spectrophotometer or fluorimeter. **(C)** The latex agglutination assay uses latex beads coated with D-dimer specific antibodies. In the presence of D-dimer, latex bead agglutination is detected by turbidity.

Weitz et al. J Am Coll Cardiol. 2017 Nov 7;70(19):2411-2420

Characteristics of D-dimer assays

	ELISA	ELFA	Unenhanced Latex agglutination assay	CLIA	Latex-enhanced immunoturbidimetric assay	POC assay
Type	Quantitative	Quantitative	Qualitative/semi-quantitative	Quantitative	Quantitative	Qualitative/quantitative
TAT	2-4h	35-40min	Rapid	25-40min	15min	2-20min
Pros	Considered as the gold standard, Sensitivity, observed independent	Considered as reference method, most validated method, sensitivity, automation, wide linear range (0-1,000 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
Example	Asserachrome® (Stago), Enzygnost® (Dade Behring)	Vidas® (bioMérieux), AxSYM® (Abbott), Stratus CS® (Dade Behring)	Dimertest latex® (IL); Fibrinosticon® (bioMérieux) ; Dade Dimertest® (Siemens)	AcuStar® (Werfen), Immulite® (Siemens)	Tina-quant® (Roche), STA-Liatest® (Stago), HemosIL HS® (Werfen) Innovance® (Dade-Behring)	SimpliRed® (Agen), Clearview Simplify® (Agen)

ELISA = Enzyme-linked immunosorbent assay, ELFA = Enzyme-linked immunofluorescence assays, CLIA = Chemiluminescent enzyme immunometric Assay, POC = Point of care.

Favresse et al. Crit Rev Clin Lab Sci. 2018, accepted manuscript

Recommendations about performances of D-dimer assays

- **Quantitative assays**
- **Precision**
  - <10% close to diagnostic cut-off
- **Linearity**
  - Between 50 and 5,000 µg/L FEU
- **Reproducibility**
  - Interassay CV ≤ 10%

- D-dimer is prevalently metabolized by kidneys and the reticuloendothelial system, with an approximate half-life of 6 – 8 h. Repeated testing of D-dimer earlier than this period is thereby unjustified.

Inter-laboratory variations

- High inter-laboratory variability

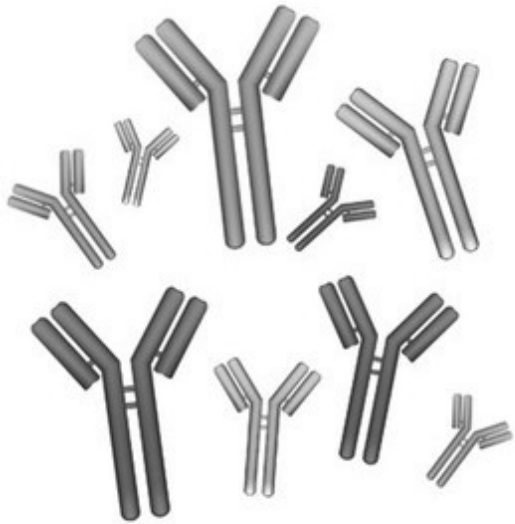
Reference	Number of assays	Differences	Number of labs
Dempfle et al. 2001	23	from 630 to 13,350 µg/L (21x)	12
Meijer et al. 2006	7	20x	357
Olson et al. 2013	13	CV high as 42%	3,800

Demfle et al. Thromb Haemost. 2001 Apr;85(4):671-8
Meijer et al. Thromb Haemost. 2006 Mar;95(3):567-72
Olson et al. Arch Pathol Lab Med. 2013 Aug;137(8):1030-8

Inter-laboratory variations

- **Leading sources of inter-laboratory variability**

1. Use of different monoclonal antibodies with different specificity towards D-dimer epitopes (>20 differents)



Inter-laboratory variations

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2. Heterogeneity of fragments derived from plasmin digestion of cross-linked fibrin (from LMWF to HMWF)

Inter-laboratory variations

Heterogeneity of D-dimer containing fragments

D-dimer-containing fragments	D-trimer-containing fragments	D-tetramer-containing fragments	Size kDa*	Generic formula
D-D or D dimer	—	—	190	D_2
DY or D-DE	—	—	430	D_4E
—	DXD or D-DED-D	—		
—	—	E ED-D-DE	435	D_3E_3
YY or ED-DE	—	—		
XD or DED-D	—	—	480	D_4E_2
—	DXY or D-DED-DE	—		
—	—	—	530	D_4E_3
XY or DED-DE	YXY or ED-DED-DE	E ED-D-D-DE		

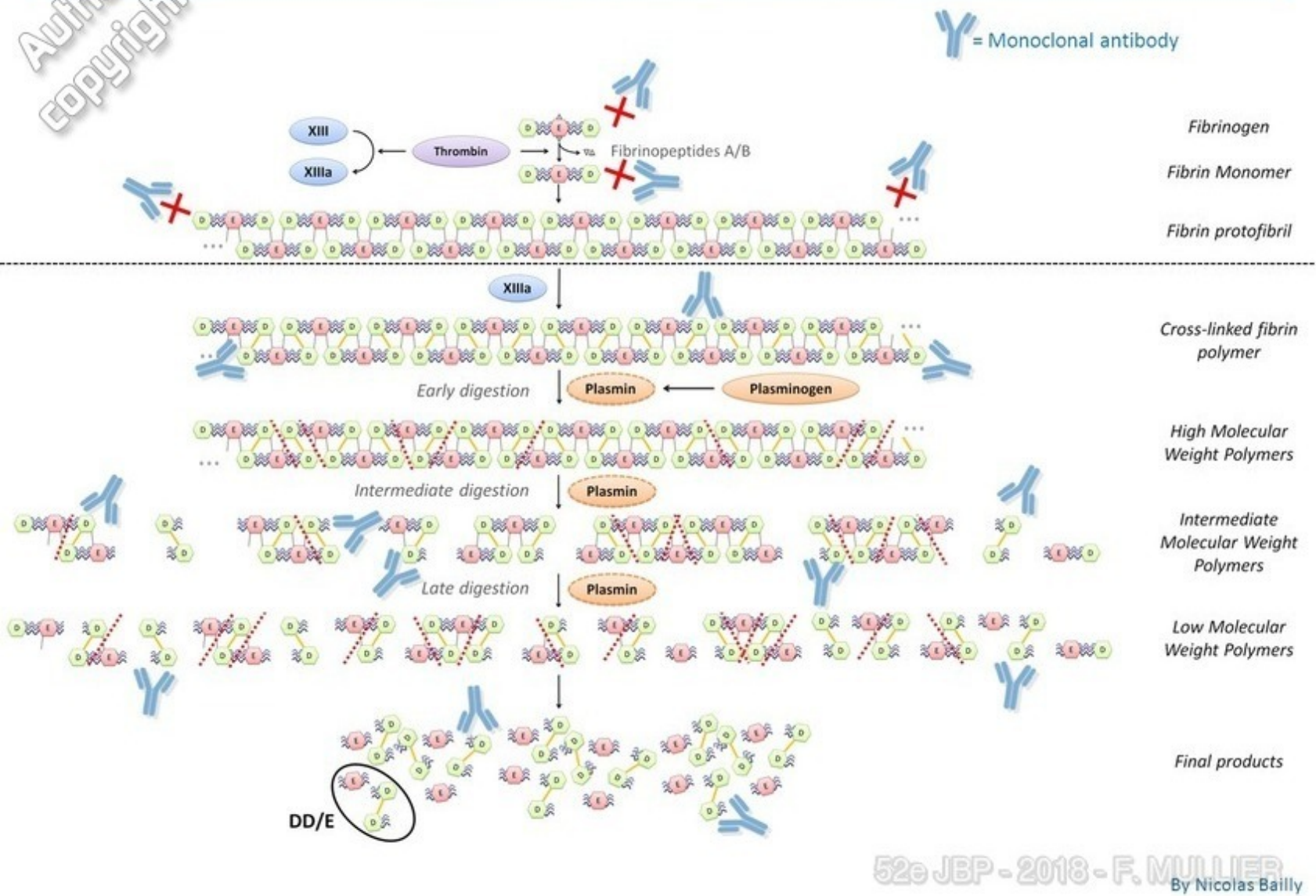
D-D-D-DE

ED-D-D-DE

* Assumed sizes for monomolecular core constituents: E [—●—], 50 kDa; D [—(D)—], 95 kDa; Y [—●—(D)—], 145 kDa; X [—(D)—●—(D)—], 240 kDa

Figure 13.1 Macromolecular fragments from plasmic digests of cross-linked fibrin. From reference 15.

Inter-laboratory variations



By Nicolas Bailly

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- **Leading sources of inter-laboratory variability**

1. Use of different monoclonal antibodies with different specificity towards D-dimer epitopes (>20 differents)
2. Heterogeneity of fragments derived from plasmin digestion of cross-linked fibrin (from LMWF to HMWF)
3. Lack of international certified internal control or calibrators
4. Use of different units or clinical cut-offs

➔ D-dimer assays standardization is a quite challenging, if not an impossible target

➔ Less stringent harmonization procedures have been proposed

Meijer et al. Thromb Haemost. 2006 Mar;95(3):567-72
Reber and Moerloose. Quality in Laboratory Hemostasis and Thrombosis. Standardization of D-dimer Testing. 2013: p. 136-146
Nieuwenhuizen. Thromb Haemost. 1997 May;77(5):1031-3
Dempfe et al. Thromb Haemost. 2001 Apr;85(4):671-8

Harmonization

- **Fourth attempt in 2007**
- Three calibrators and two test samples were delivered to more than 500 laboratories participating to the UKNEQAS external quality survey, using 9 different D-dimer techniques
- Individual laboratory results of calibrators were plotted against the median results obtained with all D-dimer immunoassays. The individual regression line was used to convert data generated on the two test samples into harmonized results.
- This approach was effective to improve the between-center agreement after calibration, with significant improvement of inter-laboratory variability (**from 25.9% to 11.6% and from 22.4% to 7.7% for FEU; from 55.3% to 21.6% and from 40.8% to 11.6% for data reported in DDU**)

Meijer et al. Thromb Haemost. 2006 Mar;95(3):567-72
Reber and Moerloose. Quality in Laboratory Hemostasis and Thrombosis. Standardization of D-dimer Testing. 2013: p. 136-146

3. Postanalytical variables

Different D-dimer units

- Two different units

	Definition	Preparation of calibrators	Molecular weight
FEU	Compare the mass of D-dimer of that of fibrinogen	Plasmin degradation of purified fibrinogen clotted in the presence of factor XIII	340 kD
DDU	The mass of the estimated weight of D-dimer	Composed of purified D-dimer	195 kD

Rem: different units according to the type of calibrators used

D-dimer Unit (DDU): 195 kDa

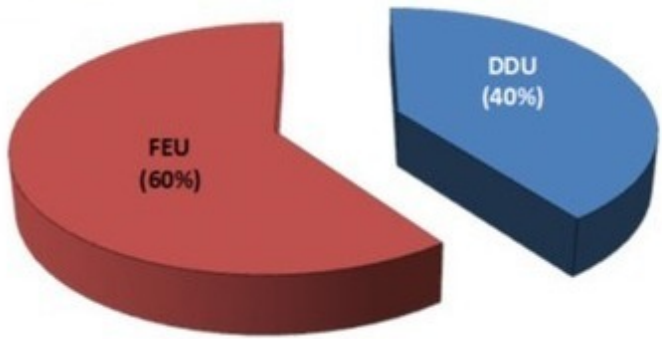
Fibrinogen Equivalent Units (FEU): 340 kDa

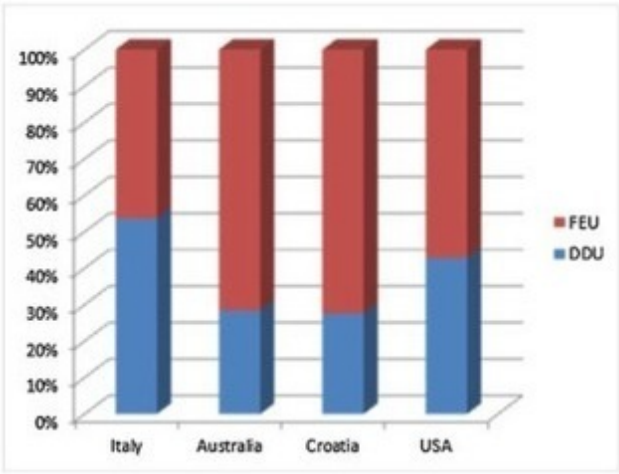
Results of D-dimer testing obtained with different methods should not be directly compared nor used interchangeably

Olson et al. Arch Pathol Lab Med. 2013 Aug;137(8):1030-8
Lippi et al. Semin Thromb Hemost. 2015 Apr;41(3):287-93

Different D-dimer units

- International survey on D-dimer reporting: a call for standardization
- 409 responses across the world





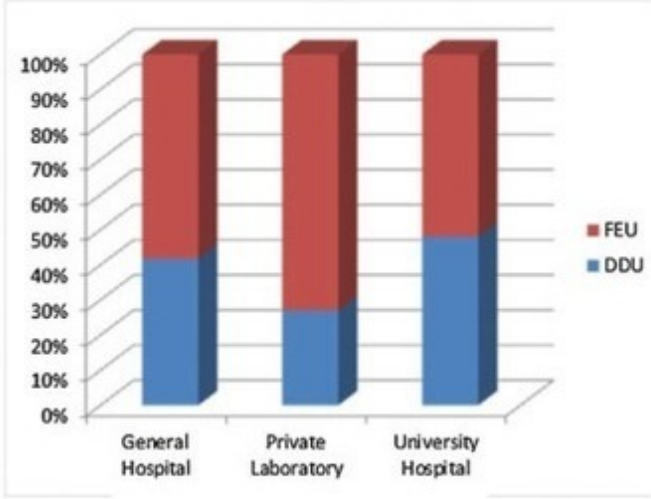
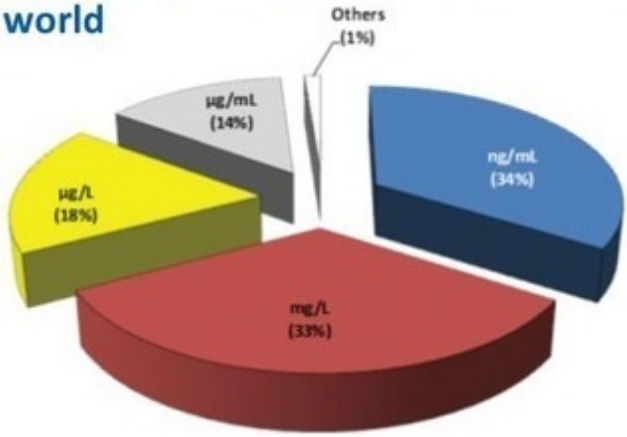


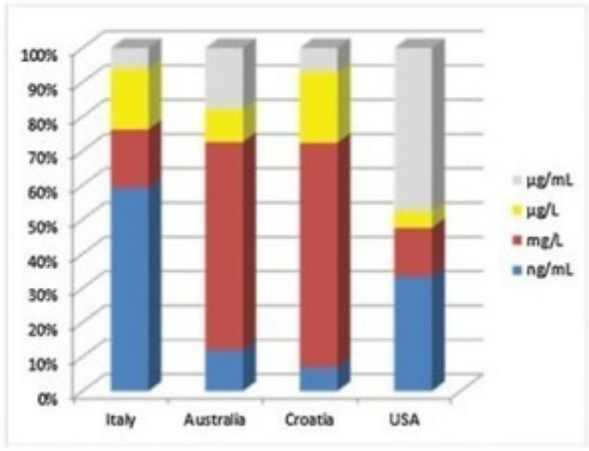
Fig. 3 Use of DDU or FEU for D-dimer reporting among respondents to the survey. DDU, D-dimer unit; FEU, fibrinogen-equivalent unit.

Lippi et al. Semin Thromb Hemost. 2015 Apr;41(3):287-93

Different D-dimer units

- International survey on D-dimer reporting: a call for standardization
- 409 responses across the world





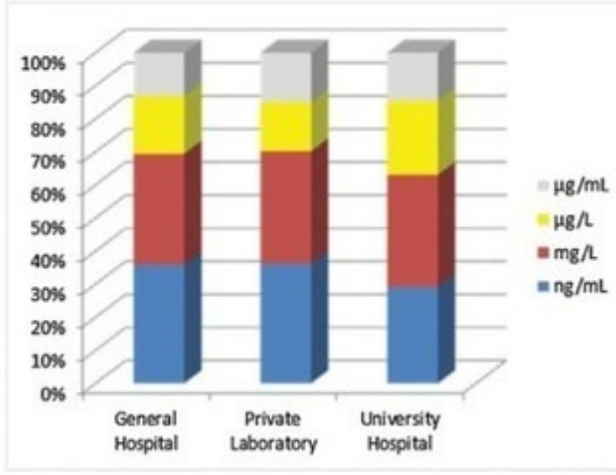


Fig. 4 Use of different measure units for D-dimer reporting among respondents to the survey.

Lippi et al. Semin Thromb Hemost. 2015 Apr;41(3):287-93

Different D-dimer units

- Survey performed by the College of American Pathologists (CAP)

	ng/mL, No.	g/L, No.	g/mL, No.	mg/L, No.	Total
DDU	379	12	39	125	555
FEU	304	19	336	143	802
Total	683	31	375	268	1357

"At least 14 combinations for D-dimer measurement coexist"

*"Among the measure units that can be adopted, "**µg/L**" (or "**ng/mL**") is probably the unit that best approximates the **International System (IS)** and is also recommended by the Italian Consensus document"*

"Some laboratories did not even acknowledge the type of measure unit they are using (8% of laboratories in the CAP survey)"

Table 3 Interconversion of D-dimer values into SI units.

FEU=DDU×2
µg/L FEU=mg/L FEU×1000
µg/L FEU=µg/mL FEU×1000
µg/L FEU=ng/mL FEU

Olson et al. Arch Pathol Lab Med. 2013 Aug;137(8):1030-8
Lippi et al. Semin Thromb Hemost. 2015 Apr;41(3):287-93

Turnaround time

- **Consensus document of AcEMC, CISMEL, SIBioC, and SIMeL**
  - A recommended overall **TAT <1h**
  - Impossible with manual ELISAs
  - Faster centrifugation process, PTS, reliable POC analyzers, wide range of linearity (up to 5,000 µg/L FEU), …
  - In a European study, **81%** of participants declared to measure D-dimer **24h per day**

Lippi et al. Semin Thromb Hemost. 2015 Apr;41(3):287-93
Spannagl et al. Blood Coagul Fibrinolysis. 2005 Sep;16(6):439-43

4. Clinical applications

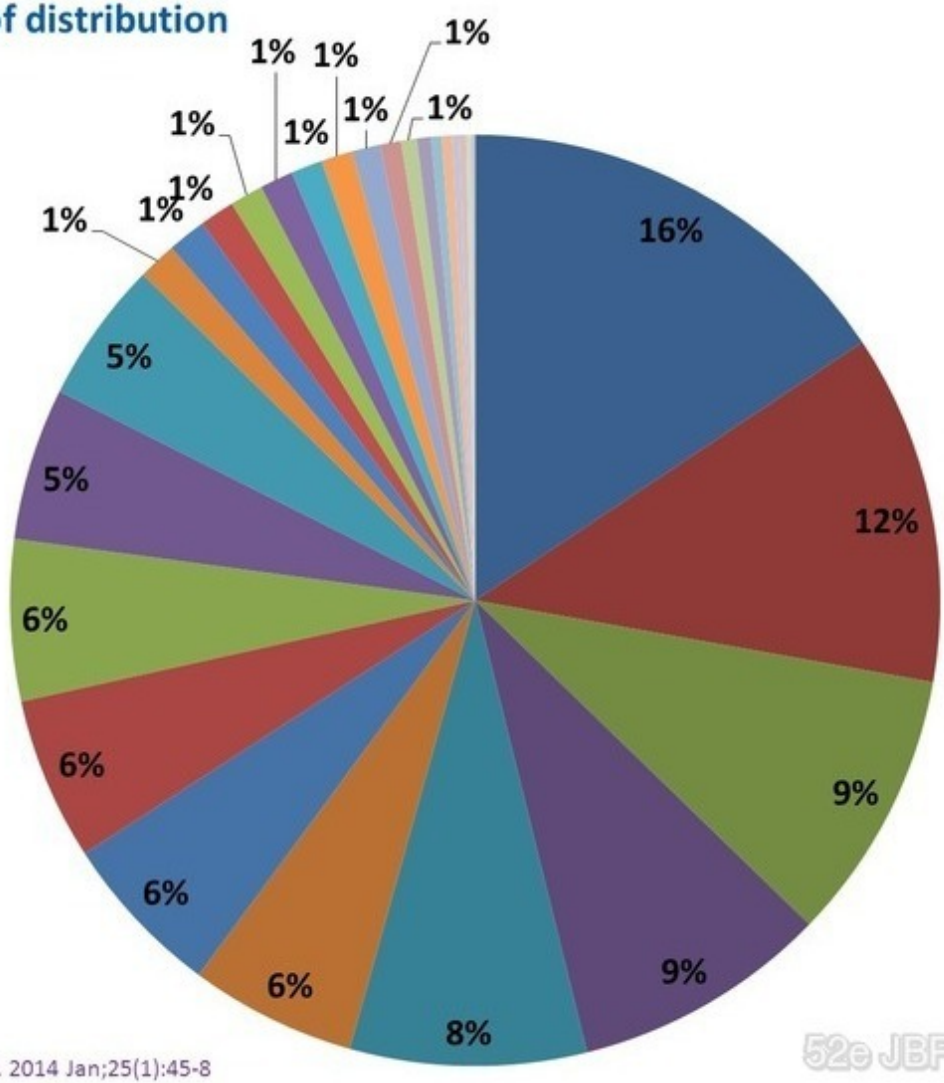
Clinical applications

1. Ruling out VTE (DVT/PE)
2. Prediction of recurrence of VTE
3. Diagnosis and monitoring of DIC
4. Excluding acute aortic dissection (AAD)
5. Predicting and managing thrombotic complications in patients with severe infections and sepsis
6. Prognostication of peripheral artery disease
7. Identification of vaso-occlusive crisis in sickle cell disease
8. Screening of intracardiac thrombus
9. Prediction of VTE in sleep apnea
10. Identifying patients with low probability of cerebral venous thrombosis (CVT)
11. Diagnosis of acute mesenteric ischemia (AMI)
12. Prediction of mortality, CV events and and cancer in patients with stable coronary disease
13. ....

Causes of D-dimer elevation

- Frequency of distribution

(n = 1,647)



Lippi et al. Eur J Interm Med. 2014 Jan;25(1):45-8

Performances of D-dimers

- Number needed to test

Table 5 Number needed to test (NNT) to rule out one PE in various medical situations

Author	Clinical conditions	NNT to rule out one PE
Perrier *et al.* [22]	Outpatients with suspected PE	3.3
Righini *et al.* [77]	High clinical probability	9.1
	Non-high clinical probability	2.2
Righini *et al.* [87]	Cancer	9.1
	No cancer	3.1
Le Gal *et al.* [78]	Previous VTE	6.3
	No previous VTE	3.1
Chabloz *et al.* [75]	Pregnancy before the 30th week	2.6
	Pregnancy between weeks 30 and 42	4
Righini *et al.* [79]	Elderly outpatients of more than 80 years	20
Miron *et al.* [50]	Inpatients (non-surgical patients)	30
	Inpatients (surgical patients)	Infinite*

The number NNT reflects the number of patients in whom DD measurement has to be performed to rule out one pulmonary embolism. These figures concern a high-sensitivity, low-specificity test. *No patient with negative DD result in this cohort.

Sensitivity/NPV high enough to safely rule out VTE

Clinical usefulness (proportion of patients in which VTE can be ruled out on the basis of a negative DD): greatly diminished → high NNT(10 or more).

M.Righini et al. J Thromb Haemost 2008; 6: 1059–71.

Performances of D-dimers for VTE exclusion

- **False-negative D-dimer results**
  - Small thrombus
  - Distal DVT
  - Isolated subsegmental PE
  - Anticoagulant therapy
  - D-dimer testing performed to early or late after the thrombosis
  - Severe infection, cancer
  - Hypofibrinolytic state

D-dimer as stand-alone test

Journal of Thrombosis and Haemostasis, **16**: 1–11 DOI: 10.1111/jth.14314

ORIGINAL ARTICLE

Safety of D-dimer testing as a stand-alone test for the exclusion of deep vein thrombosis as compared with other strategies

S. G. FRONAS,*† H. S. WIK,‡ A. E. A. DAHM,†§ C. T. JØRGENSEN,* J. GLEDITSCH,¶ N. RAOUF,* F. A. KLOK** and W. GHANIMA*†

*Department of Internal Medicine, Østfold Hospital Trust, Grålum; †Institute of Clinical Medicine, University of Oslo, Oslo; ‡Department of Hematology, Oslo University Hospital, Oslo; §Department of Hematology, Akershus University Hospital, Lørenskog; ¶Department of Radiology, Østfold Hospital Trust, Grålum, Norway; and **Department of Thrombosis and Hemostasis, Leiden University Medical Center, Leiden, the Netherlands

- 913 patients
- 298: negative D-dimer (STA-Liatest D-Di plus D-dimer)
- 1/298: DVT (failure rate:0,3% 95%CI:0.1-1.9%)
- Wells: (failure rate:0,0% 95%CI:0.1-1.8%) but 87 more CUS examinations

Fronas SG et al. J Thromb Haemost 2018

©Clinical Prediction Rules: current practice

- **70.3%** of clinicians used pre-test probability scores
- **10%** could exclude or confirm DVT only based on D-dimer test results
- Moreover, a significant number of clinicians still order D-dimer testing in patients with high VTE probability, whilst others order imaging testing in case of low pre-test probability

Received: 28 February 2017 | Accepted: 2 May 2017
DOI: 10.1002/rth2.12008

BRIEF REPORT

WILEY rpth | isth

Cost-minimization analysis of venous thromboembolism diagnosis: Comparison of standalone imaging with a strategy incorporating D-dimer for exclusion of venous thromboembolism

Karan Verma MSc, MBA[1] | Cristina Legnani PhD[2] | Gualtiero Palareti MD[3]

TABLE 2 Cost calculator demonstrating the cost-minimization analysis

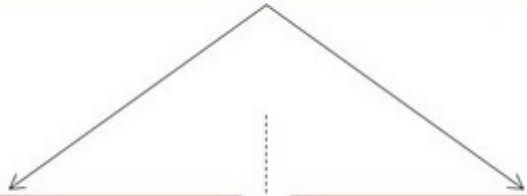
Tests	PE	DVT	VTE
Cost: D-dimer	$14	$14	
Cost of PE imaging: eg CTPA	$648		
Cost of DVT imaging: eg CUS		$184	
VTE prevalence distribution	30%	70%	100%
Before using a VTE Diagnostic Strategy			
Suspected patients using D-dimer tests (Low/Moderate PTP)	0%	0%	
Suspected patients excluded (Low/Moderate PTP & negative D-dimer)	0%	0%	
Suspected patients using imaging tests	100%	100%	
Total diagnostic test cost per suspected VTE patient (Before)	$648	$184	$323
After using a VTE diagnostic strategy			
Suspected patients using D-dimer tests (Low/Moderate PTP)	93%	80%	
Suspected patients excluded (Low/Moderate PTP & negative D-dimer)	40%	30%	
Suspected patients using imaging tests	60%	70%	
Total diagnostic test cost per suspected VTE patient (After)	$404	$140	$219
Average savings per suspected VTE patient when a VTE diagnostic strategy is applied	$244	$44	$104
Cost reduction	38%	24%	32%
Assuming 5000 suspected VTE Patients/Hospital/Year	1500	3500	5000
Total savings	$365 324	$153 372	$518 695

PE, pulmonary embolism; CTPA, computed tomography pulmonary angiography; DVT, deep venous thrombosis; CUS, compression ultrasonography; VTE, venous thromboembolism; PTP, pretest probability.

Kristoffersen et al. Thromb Res. 2017 Nov;159:19-23
Kristoffersen et al. Thromb Res. 2016 Jun;142:1-7

Recommended clinical performances for VTE exclusion

	FDA	CLSI
Sensitivity	≥95% (with lower limit of CI ≥90%)	≥97% (with lower limit of CI ≥90%)
Negative predictive value	≥97% (with lower limit of CI ≥95%)	≥98% (with lower limit of CI ≥95%)



High sensitivity (>95%)
Low specificity (<40%)

- ELFAs
- Microplate ELISAs
- Latex based-assays (2nd generation)

Moderate sensitivity (80-94)
High specificity (up to 70%)

- Whole blood agglutination assays
- Latex semi-quantitative or qualitative assays

Di Nisio et al. J Thromb Haemost. 2007 Feb;5(2):296-304
FDA and CLSI recommendations

Recommended cut-offs?

- Verification with a min. of 200 subjects (British Guidelines)
- Cut-offs validated in prospective studies (e.g., Vidas®, AxSYM®, STA-Liatest®)
- Otherwise, comparison with validated assays is encouraged

➔ The CAP survey showed that 488 laboratories out of 1,506 in USA were using cut-off values higher than those recommended by the literature or by the manufacturer

➔ A European survey also highlighted that 24% and 55% of participants used lower or higher cut-offs than those recommended, respectively

British Committee for standards in Haematology guidelines
Olson et al. Arch Pathol Lab Med. 2013 Aug;137(8):1030-8
Reber and Moerloose. Quality in Laboratory Hemostasis and Thrombosis. Standardization of D-dimer Testing. 2013: p. 136-146

Recommended cut-offs?

- Cut-offs validated in prospective studies (e.g., Vidas®, AxSYM®, STA-Liatest®)

- DIET study: international multicenter prospective non randomized non interventional management study

	VPN	Sensibilité	Spécificité
DiET TVP (N=980 patients)	**100%**	**100%**	**55,2%**
IC 95%	*(95,8 - 100%)*	*(99,3 - 100%)*	*(LB: 51,9%)*
DiET EP (N=1130 patients)	**99,7%**	**97,0%**	**75,5%**
IC 95%	*(99,2 - 100%)*	*(91,6 - 99,4%)*	*(72,8 - 78,1 %)*
Exigences FDA	≥ 97 % *IC 95% ≥ 95%*	≥ 95% *IC95% ≥ 90%*	-

Exclusion DVT: >80, pregnancy, postop, cancer, anticoagulation started 24h or more before measurement of D-dimer

Exclusion PE: "patients with bone fracture or surgery with generalanesthesia longer than 30 min within the previous month,disseminated malignancy or active cancer, sepsis, severe infection, pneumonia within the previous month, pregnancyor postpartum within the previous month, and ongoing anticoagulant drug treatment (at curative or prophylactic dose) started 24 h or more before the D-dimer level is measured were excluded".

C.Aguilar et al. Blood Coagulation Fibrinolysis 2018;29:562-566
G.Pernod et al. Blood Coagulation Fibrinolysis 2017;28:254-260

Clinical algorithm in the exclusion of the thromboembolic disease: Clinical Prediction Rules

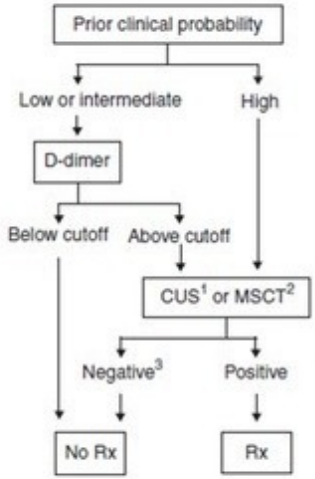


Fig. 1. Place of D-dimer measurement in a contemporary diagnostic algorithm for suspected deep vein thrombosis (DVT) or pulmonary embolism (PE).
[1]CUS (lower limb venous compression ultrasonography) in a case of suspected DVT.
[2]MSCT (multi-slice helical computed tomography) in a case of suspected PE.
[3]In a case of negative CUS or MSCT and high prior clinical probability, consider additional imaging, for example venography (suspected DVT) or lung ventilation/perfusion scintigraphy or pulmonary angiography (suspected PE).
Rx stays for treatment; D-dimer refers to highly sensitive D-dimer assays. If less sensitive assays are used, a negative test result rules out DVT or PE only in patients with low (or unlikely) clinical probability.

Righini et al. J Thromb Haemost. 2008 Jul;6(7):1059-71

Clinical Prediction Rules

Table 2 Most commonly used clinical prediction rules for suspected PE

Wells score [105]		Geneva score [106]		Revised Geneva score [107]	
Items	Score	Items	Score	Items	Score
Previous PE or DVT	1.5	Previous PE or DVT	2	Age > 65 years	1
Heart rate > 100	1.5	Heart rate >100	1	Previous DVT or PE	3
Recent surgery or immobilization	1.5	Recent surgery	3	Surgery or fracture within 1 month	2
Clinical signs of DVT	3	Age		Active malignancy	2
Alternative diagnosis less likely than PE	3	60–79	1	Unilateral lower limb pain	3
Hemoptysis	1	≥80	2	Hemoptysis	2
Cancer	1	Arterial blood gases		Heart rate	
		CO2 (kPa)		75–94	3
		<4.8	2	≥95	5
		4.8–5.19	1	Pain on lower limb deep vein palpation and unilateral edema	4
		O_2 (kPa)			
		<6.5	4		
		6.5–7.99	3		
		8–9.49	2		
		9.5–10.99	1		
		Chest X-ray			
		Atelectasia	1		
		Elevated hemidiaphragm	1		
Clinical probability		*Clinical probability*		*Clinical probability*	
Low	<2	Low	0–4	Low	0–3
Intermediate	2–6	Intermediate	5–8	Intermediate	4–10
High	>6	High	≥9	High	≥11
Dichotomized [71]					
PE unlikely	≤4				
PE likely	>4				

Righini et al. J Thromb Haemost. 2008 Jul;6(7):1059-71

Clinical Prediction Rules

Suspicion of pulmonary embolism: simplified Geneva score

Table 1 The Geneva score.

Items	Points	
Geneva score	Original version	Simplified version
Age > 65 years	1	1
Previous DVT or PE	3	1
Surgery or fracture within 1 month	2	1
Active malignancy	2	1
Unilateral lower limb pain	3	1
Hemoptysis	2	1
Heart rate		
75–94 beats per minute	3	1
≥ 95 beats per minute	5	2
Pain on lower limb deep vein palpation and unilateral edema	4	1
Clinical probability		
Low	0–3	0–1
Intermediate	4–10	2–4
High	≥ 11	≥ 5

DVT, deep vein thrombosis; PE, pulmonary embolism.

Robert-Ebadi et al. J Thromb Haemost 2017; 15: 1764-69.

Clinical Prediction Rules

Suspicion of pulmonary embolism: simplified Geneva score

Table 5 Diagnostic performance of the simplified Geneva score associated with the age-adjusted D-dimer cut-off.

Simplified Geneva score (SGS)	Low (n = 608)		Intermediate (n = 980)	
Diagnostic management				
D-dimer cut-off	500 μg L^{-1}	Age-adjusted	500 μg L^{-1}	Age-adjusted
Negative D-dimer test, n (%)	298 (49%)	343 (56%)	192 (20%)	310 (32%)
Increase in the yield of the D-dimer test		+45 (+7.5%)		+118 (+12%)
Positive D-dimer, need for CTPA, n (%)	310 (51%)	265 (44%)	788 (80%)	670 (68%)
Follow-up in patients with negative D-dimer test, n (%)				
Anticoagulation during follow-up	2 (0.6%)	2 (1.6%)	1 (0.5%)	6 (1.9%)
Non-VTE death	1 (0.3%)	1 (0.3%)	1 (0.5%)	2 (0.6%)
Lost to follow-up	1 (0.3%)	1 (0.3%)	3 (1.6%)	3 (1.0%)
3-month TE risk, 95% CI	0/294 (0%, 0.0–1.3%)	0/339 (0%, 0.0–1.1%)	0/187 (0%, 0.0–2.0%)	0/299 (0%, 0.0–1.3%)

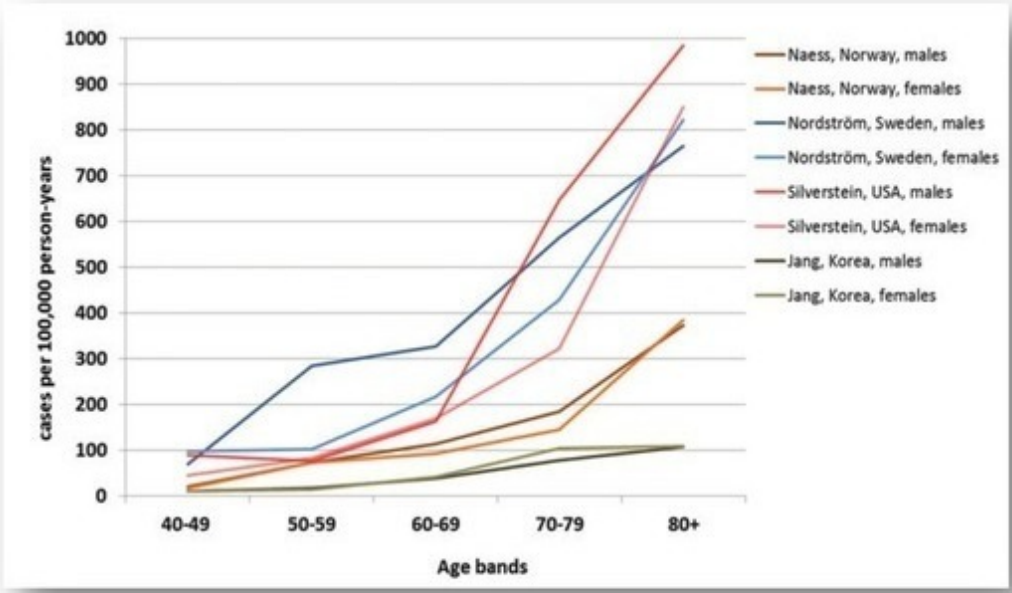
CTPA, computed tomography pulmonary angiography; VTE, venous thromboembolic event; TE, thromboembolic event; CI, confidence interval.

None of the patients considered as not having PE based on a low or intermediate SGS and negative D-dimer had a recurrent thromboembolic event during the 3-month follow-up.

Conclusions: The use of SGS has similar efficiency and safety to the GS in excluding PE in association with the D-dimer test.

Robert-Ebadi et al. J Thromb Haemost 2017; 15: 1764-69.

Age specific cut-offs



- **The incidence of VTE is known to increase sharply with age**
- **D-dimer values tend to increase with ageing**
  - 60% of older patients have D-dimer values higher than classical cut-offs

➔ **A high rate of these patients with low clinical score would undergone unnecessary imaging testing!**

Mazzolai et al. Eur Heart J. 2017 Feb 17. doi: 10.1093/eurheartj/ehx003
Deitelzweig et al. Am J Hematol. 2011 Feb;86(2):217-20
Spyropoulos et al. J Manag Care Pharm. 2007 Jul-Aug;13(6):475-86

Age specific cut-offs

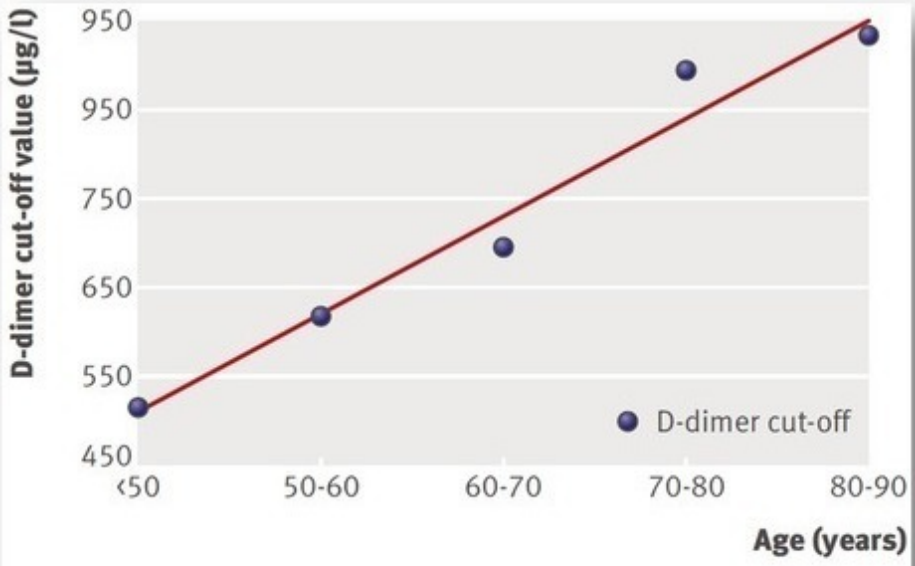


Fig 1 | Optimal cut-off values for D-dimer test for pulmonary embolism by age in patients with an unlikely clinical probability of pulmonary embolism (sensitivity set at 100%)

- **[age-adjusted cut-off, µg/L FEU] = [age, years]) x 10**
  - These cut-offs would enable to a substantially increase in the PPV without significantly impairing the NPV (and is cost-effective)

Douma et al. BMJ. 2010 Mar 30;340:c1475

Validation of age adjusted cut-off

Exclusion of pulmonary embolism: adjust-PE study

- 3346 patients with suspected PE
- 2895 patients with non high probability
- 817 (28,2%) with Ddimers < 500 µg/L
- 337 (11,6%) with Ddimers between 500 µg/L and the age-adjusted cut-off
- The 3-month failure rate in patients with a D-dimer level higher than 500 µg/L but below the age-adjusted cutoff was 1 of 331 patients (0.3% [95% CI, 0.1%-1.7%]).

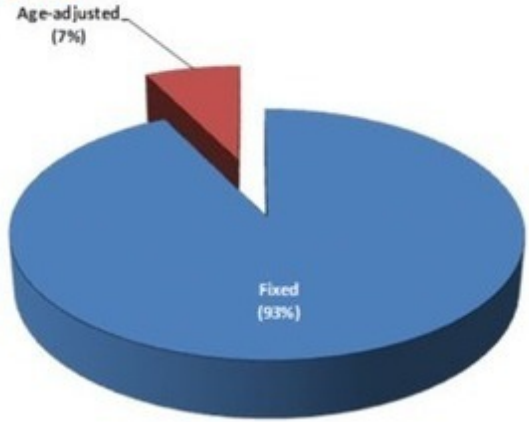
M.Righini et al. JAMA 2014 Mar 19;311(11):1117-24.

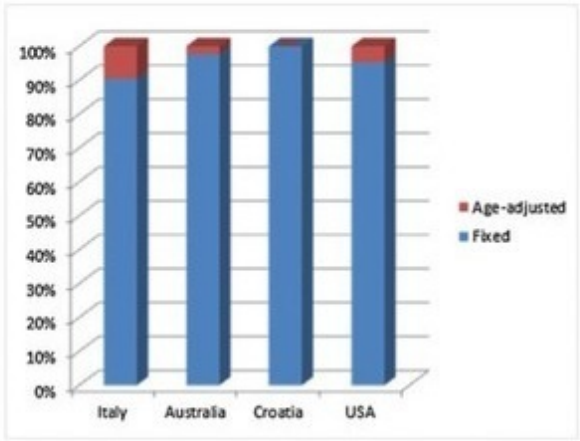
2014 ESC guidelines in the diagnosis and management of acute pulmonary embolism: Age-adjusted cut-off if > 50 y

Eur Heart J. 2014 Nov 14;35(43):3033-69 .

Age specific cut-offs

- International survey on D-dimer reporting: a call for standardization
- 409 responses across the world





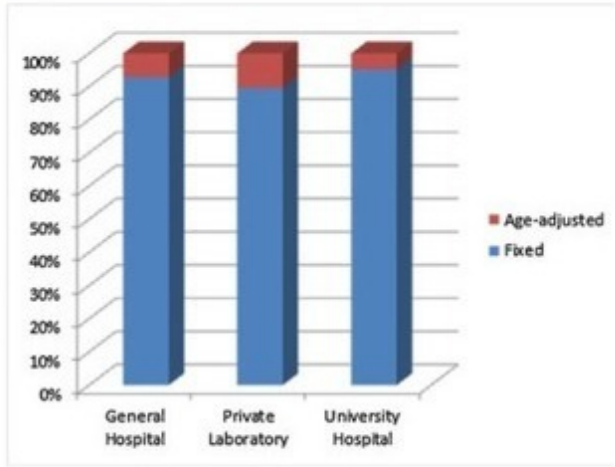
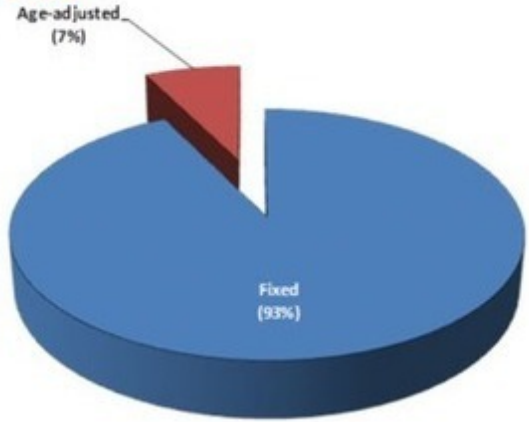


Fig. 5 Use of fixed or age-adjusted cutoff for D-dimer reporting among respondents to the survey.

Lippi et al. Semin Thromb Hemost. 2015 Apr;41(3):287-93

Age specific cut-offs

- International survey on D-dimer reporting: a call for standardization
- 409 responses across the world



"Along with the 14 different combinations of D-dimer units, the use of age-adjusted cut-off complicated further the clinical decision making due to the ***nearly 30 different possibilities for reporting D-dimer test results****"*

Other limitations: most studies with a limited number of commercially available kits « if a laboratory adopts or reports AADD cutoffs on an FDA-approved or –cleared D-dimer assay, it must demonstrate assay-specific evidence of clinical performance characteristics. If literature is not available to support AADD cutoffs for a specific assay, the laboratory must perform a validation that exceeds the resources of most institutions ».

Lippi et al. Semin Thromb Hemost. 2015 Apr;41(3):287-93
Goodwin et al. *Ann Intern Med.* 2017;166:361-363.

Clinical probability-adjusted cut-offs

- Higher cut-off in patients with low clinical probability (**1,000 µg/L FEU**)
- Conventional cut-off in patients with moderate clinical probability (**500 µg/L FEU**)

Table 2: Accuracy of age-adjusted and clinical probability-adjusted D-dimer interpretation strategies for VTE.

Accuracy parameter	Age-adjusted Strategy	Clinical probability -adjusted Strategy	Difference p-value
Sensitivity			
n/N	106/109	106/109	1.0
% (95 % CI)	97.3 (92.2, 99.1)	97.3 (92.2, 99.1)	
Specificity			
n/N	837/1540	922/1540	<0.001
% (95 % CI)	54.4 (51.9, 56.8)	59.9 (57.4, 62.3)	
Negative predictive value			
n/N	837/840	922/925	0.095
% (95 % CI)	99.64 (99.11, 99.86)	99.68 (99.19, 99.87)	
Negative results			
n/N	840/1649	925/1649	<0.001
% (95 % CI)	50.9 (48.5, 53.4)	56.1 (53.7, 58.5)	

Clinical probability adjusted better than age-adjusted?

Takach Lapner et al. Thromb Haemost. 2017 Oct 5;117(10):1937-1943

Clinical probability-adjusted cut-offs: The YEARS algorithm

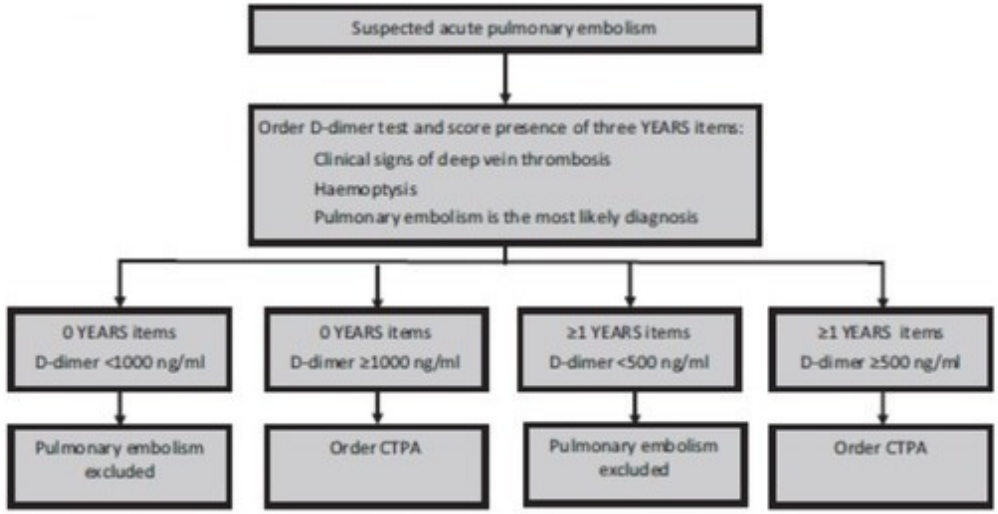


Fig 2. YEARS algorithm. CTPA, computed tomography pulmonary angiography.

- CTPA was not indicated in 48% of patients with the YEARS algorithm, with a failure rate of 0,61%, compared with 34% of patients if a fixed D-dimer cut off of 500 ng/ml and the Wells' criteria were utilised
- Shorter visit time and reduced cost

Van der Hulle T et al. Lancet 2017;390:289-297
Akikhan R, Roberts H. British Journal of Heamatology 2018;183:165-167
Van der Pol LM et al. British Journal of Haematology 2018 Nov:183(4):629-635
Van der Pol LM et al. J Thromb Haemost 2017; 15(12):2317-2324
Van der Pol LM et al. J Thromb Haemost 2018;16(4):725-733
Van der Pol LM et al. Thromb Haemost 2018;118(3):547-552

Summary of consensus indications for D-dimer testing in the ED in patients with suspected VTE

Table 5 Summary of consensus indications for D-dimer testing in the ED in patients with suspected VTE.

- D-dimer should not be used as a stand-alone test to exclude or confirm VTE.
- D-dimer testing should be used in the setting of a validated diagnostic algorithm, entailing assessment of clinical pretest probability.
- Use imaging testing according to guidelines.
- Draw blood using 3.2% (i.e., 105–109 mM) buffered sodium citrate.
- Straight-needled venipuncture for collecting blood for D-dimer testing is preferred.
- Use certified, quantitative immunoassays.
- Methods with high diagnostic sensitivity and acceptable diagnostic specificity is preferred.
- Measuring range and linearity of the method between 50 and 5000 μg/L.
- Imprecision at diagnostic cutoff ≤10%.
- Check for potential analytical errors and interference.
- Overall TAT <60 min.
- Do not repeat a request of D-dimer testing earlier than 6–8 h.
- Report final result in μg/L of FEU.
- Use clinically validated cutoffs (usually 500 μg/L FEU) in patients younger than 50 years.
- Use age-adjusted cutoffs in patients aged 50 years or older, as follows: (age-adjusted cutoff, μg/L FEU)=(age, years)×10.
- Specificity of D-dimer testing is remarkably decreased by a variety of clinical conditions other than VTE.
- Test results obtained with different methods should not be directly compared.
- Avoid testing patients presenting to the ED with hypofibrinolysis too early or too late after thrombosis or during anticoagulant therapy.

Lippi G et al. Clin Chem Lab Med 2014; 52(5): 621-628

Prediction of recurrence of VTE

- **1-year follow up after a first VTE episode**
  - Risk of recurrence in men = 9.5%
  - Risk of recurrence in women = 5.3%
- **3-year follow up after a first VTE episode**
  - Risk of recurrence in men = 19.7%
  - Risk of recurrence in women = 9.1%
- D-dimer value is a significant predictor of VTE
  - Risk x2 if > diagnostic cut-off after 3-months of anticoagulant therapy

➔ **D-dimer testing should be performed in all patients with clinical suspicion of recurrent VTE**

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Douketis et al. BMJ 2011 Feb 24;342:d813

Prediction of recurrence of VTE: DASH score

DASH score	
Feature	**Score**
Abnormal D-dimer *(measured one month after stopping anticoagulation)*	+2
Age ≤ 50	+1
Male	+1
Hormonal therapy at onset of VTE *(among women)*	−2
Probability	
Low	≤ 1
High	> 1

DASH: D-dimer, Age, Sex, Hormones

D-Dimères

Age

Sexe

Traitement **H**ormonal

- A DASH score ≤ 1 had a cumulative recurrence risk at 1 year of 3.6%, as predicted by the model (n=827)
- 66% of the participants candidate for AC suspension (DASH score ≤ 1)

A.Tosetto J Thromb Haemost 2017

Prediction of recurrence of VTE: scores

Table 5 Predictors included in final model

Model	HERDOO2	Vienna	DASH
Predictors included			
D-dimer	X	X	X
Age	X	–	X
Sex	–	X	X
BMI	X	–	–
Post-thrombotic signs	X	–	–
Site of index event	–	X	–
Hormone therapy	–	–	X

BMI, body mass index.

- « ***Should the anticoagulant treatment be discontinued or resumed after the usual 3-month period???*** »
  - Lack validation in interventional studies
  - Other D-dimer assays? (Vidas®, Liatest®).
  - Appropriate timing of D-dimer monitoring? 3 weeks? 2 months? after stopping anticoagulant therapy

Ensor et al. BMJ Open. 2016 May 6;6(5):e011190

Prediction of recurrence of VTE: scores

Table 5 Predictors included in final model

Model	HERDOO2	Vienna	DASH
Predictors included			
D-dimer	X	X	X
Age	X	–	X
Sex	–	X	X
BMI	X	–	–
Post-thrombotic signs	X	–	–
Site of index event	–	X	–
Hormone therapy	–	–	X

BMI, body mass index.

- « ***Should the anticoagulant treatment be discontinued or resumed after the usual 3-month period???*** »
  - Other D-dimer assays?

  NO!

Thrombosis Research 169 (2018) 82–86

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journal homepage: www.elsevier.com/locate/thromres

Full Length Article

"HERDOO2" clinical decision rule to guide duration of anticoagulation in women with unprovoked venous thromboembolism. Can I use any D-Dimer?

Marc A. Rodger*, Gregoire Le Gal, Nicole J. Langlois, Barron Gin, Ranjeeta Mallick, Antonio Giulivi, Marisa Freedman, Michael J. Kovacs, for the REVERSE II investigators

The Ottawa Hospital Research Institute, 501 Smyth Rd, Ottawa, ON K1H 8L6, Canada

Conclusion: The "HERDOO2 rule" is the only prospectively validated clinical decision rule that can be used to identify low-risk women with unprovoked venous thrombosis who can safely discontinue anticoagulants. An important implementation issue is whether any commercial DD assay can be used in the HERDOO2 rule, and at what cut-point. Our analysis shows that the HemosIL*, Innovance*, Liatest* and Tina-quant* DD assays should not be used in the "HERDOO2" rule due to poor concordance with the VIDAS* DD assay and unacceptable misclassification of women at high and low risk of recurrent venous thrombosis.

Ensor et al. BMJ Open. 2016 May 6;6(5):e011190

Prediction of recurrence of VTE: scores

- D-dimer testing after 3 months of anticoagulant therapy for a first unprovoked VTE can guide decisions about duration of therapy, but should be used as part of a clinical decision model

- It is important to consider the risk of bleeding on anticoagulant therapy as well as the patient's personal preferences when making this important decision.

Linkins L-A, Takack Lapner S. Int J Lab Hem.2017;39(Suppl.1):98-103

Pregnancy

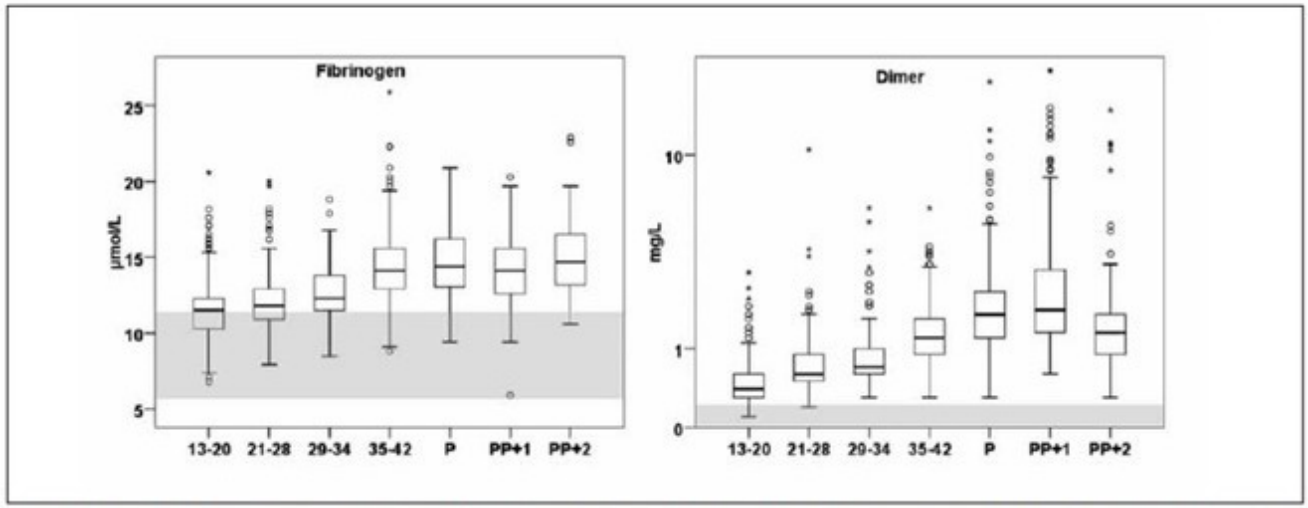

Figure 1: Box plot of gestational age-specific reference intervals for fibrinogen and fibrin D-dimer. Box plots represent the range of data from the 25th to the 75th percentile, while the bar in the middle of each box plot represents the median value. The "whiskers" extending from the box represent the range of values obtained excluding outliers. Circles and asterisks indicate outliers (1.5 x the interquartile range) and extreme values (3.0 x the interquartile range) outside the central box, respectively. The shaded area represents non-pregnant expected values accordingly to Stago or local recommendation.

Szecsi PB et al. Thromb Haemost 2010; 103: 718–727
Gutierez Garcia I. Scandinal Journal of Clinical and Laboratory Investigation 2018

Pregnancy

- D-dimer levels increased physiologically along the pregnancy and postpartum period. In a study including 1,343 pregnant women with D-dimer measurement using turbidimetry method (STALiatest), the rate of pregnant healthy women with a D-dimer test below the usual cut-off (500 µg/L) was 85%, 29% and 4.1% during the first, the second and the third trimester, respectively
- In postpartum, D-dimer returns to normal level around the 6th week
- In case of PE suspicion, since imaging tests may expose the mother and the fetus to radiation, the ability to rule-out PE on non-radiologic test is crucial.

Pregnancy

Annals of Internal Medicine

ORIGINAL RESEARCH

Diagnosis of Pulmonary Embolism During Pregnancy

A Multicenter Prospective Management Outcome Study

Marc Righini, MD; Helia Robert-Ebadi, MD; Antoine Elias, MD, PhD; Olivier Sanchez, MD, PhD; Emmanuelle Le Moigne, MD; Jeannot Schmidt, MD; Catherine Le Gall, MD; Jacques Cornuz, MD, PhD; Drahomir Aujesky, MD, MSc; Pierre-Marie Roy, MD, PhD; Céline Chauleur, MD, PhD; Olivier T. Rutschmann, MD; Pierre-Alexandre Poletti, MD; and Grégoire Le Gal, MD, PhD; for the CT-PE-Pregnancy Group*

Ann Intern Med. doi:10.7326/M18-1670 Annals.org

For author affiliations, see end of text.

This article was published at Annals.org on 23 October 2018.

* For members of the CT-PE-Pregnancy Group, see the Appendix (available at Annals.org).

- The proportion of women in whom PE could be ruled out on the basis of a negative D-dimer result was clinically significant in this setting given that chest imaging could be avoided in 11.6% of the included women.
- Also notable was that the proportion of negative D-dimer results decreased with increasing gestational age, but this remained significant and clinically useful at least during the first and second trimesters (25% and 11%, respectively).

Conclusion

- **Biomarker of activation of coagulation and fibrinolysis**
- **Preanalytical step: hemolysis!**
- **Mainly employed for the exclusion of VTE**
  - High sensitivity and NPV (≥95% and ≥97%, respectively)
  - Clinical Prediction Rules
  - Age-adjusted cut-offs (increased PPV) or clinically probability-adjusted cut-off
  - Still challenging in specific populations (i.e., pregnancy, cancer, renal failure)

➔ **Major efforts for a larger implementation of these recommendations**

- **Major drawback high inter-variability between immunoassays**
  - Different units
  - Different monoclonal antibodies
  - Broad mixture of degradation products of cross-linked fibrin
  - Lack of international certified internal control or calibrator

Aknowledgements

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- Pharm D Julien Favresse
- Professor Bernard Chatelain
- Professor Giuseppe Lippi
- Professor Pierre-Marie Roy
- Professor Hugo ten Cate
- PharmD SpLM Hugues Jacqmin
- Mrs Célia Devroye, Mrs Justine Baudar, Mrs Maité Guldenpfennig,
- Mr Nicolas Bailly

Soon in press

CRITICAL REVIEWS IN CLINICAL LABORATORY SCIENCES
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REVIEW ARTICLE

D-dimer: Preanalytical, analytical, postanalytical variables, and clinical applications

Julien Favresse[a], Giuseppe Lippi[b], Pierre-Marie Roy[c], Bernard Chatelain[a], Hugues Jacqmin[a], Hugo ten Cate[d] and François Mullier[a]

[a]CHU UCL Namur, Namur Thrombosis and Hemostasis Center, Hematology Laboratory, Université Catholique de Louvain, Yvoir, Belgium; [b]Section of Clinical Biochemistry, University Hospital of Verona, Verona, Italy; [c]Département de Médecine d'Urgence, CHU d'Angers, Institut MITOVASC, Université d'Angers, Angers, France; [d]Department of Internal Medicine, Cardiovascular Institute, Maastricht University Medical Center, Maastricht, the Netherlands

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