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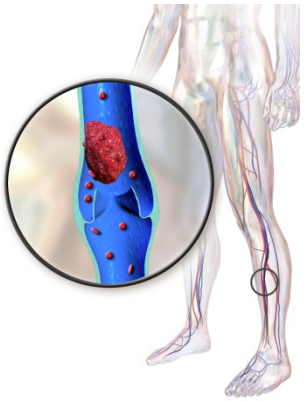
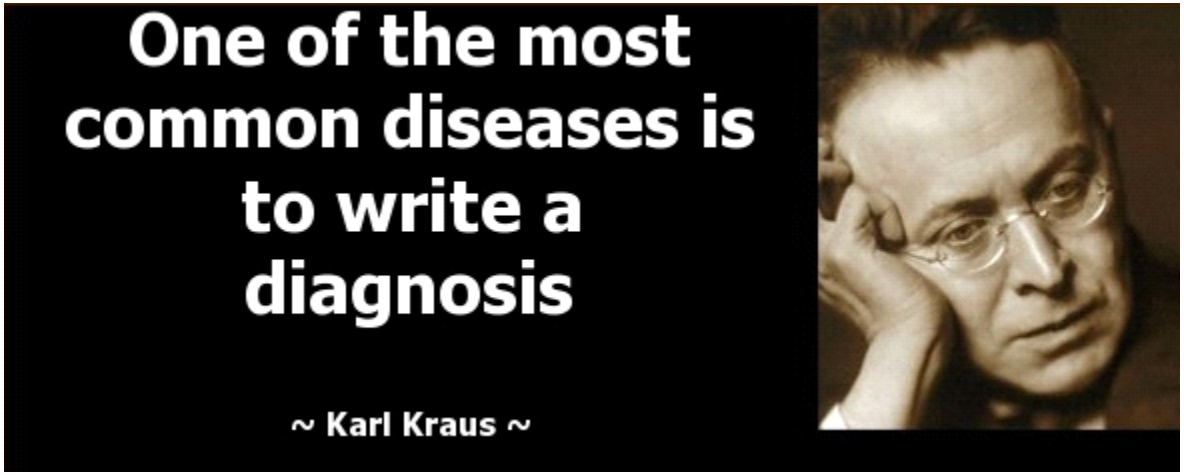


Diagnostics in venous thromboembolism: from origin to future prospects

Giuseppe Lippi

University of Verona

DIAGNOSTIC OF VENOUS THROMBOEMBOLISM

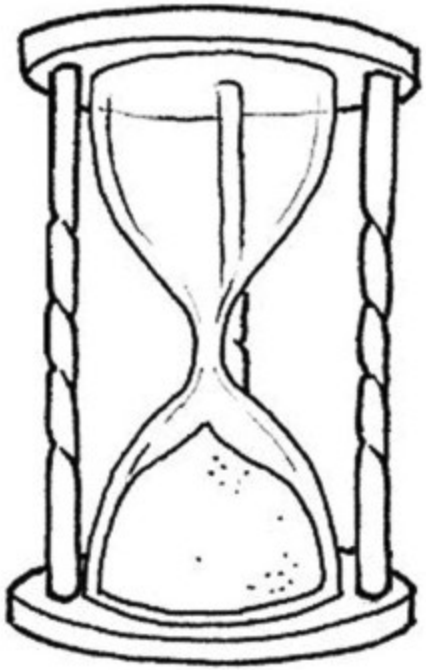


… especially if only based on laboratory testing

Semin Thromb Hemost

Diagnostics in Venous Thromboembolism: From Origin to Future Prospects

Giuseppe Lippi, MD[1] Elisa Danese, PhD[2] Emmanuel J. Favaloro, PhD FFSc (RCPA)[3]
Martina Montagnana, MD[2] Massimo Franchini, MD[4]



Pulmonary Embolism
Deep Vein Thrombosis

1939: Pulmonary angiography

1942: Venography

1964: Ventilation/perfusion lung scintigraphy

1965: Doppler ultrasonography

1970: Pulsed-wave Doppler ultrasonography

1972: Fibrinogen degradation products

1972: Impedance plethysmography

1978: Computed Tomography angiography

1985: Color Doppler

1994: Computed Tomography venography

1983: D-dimer

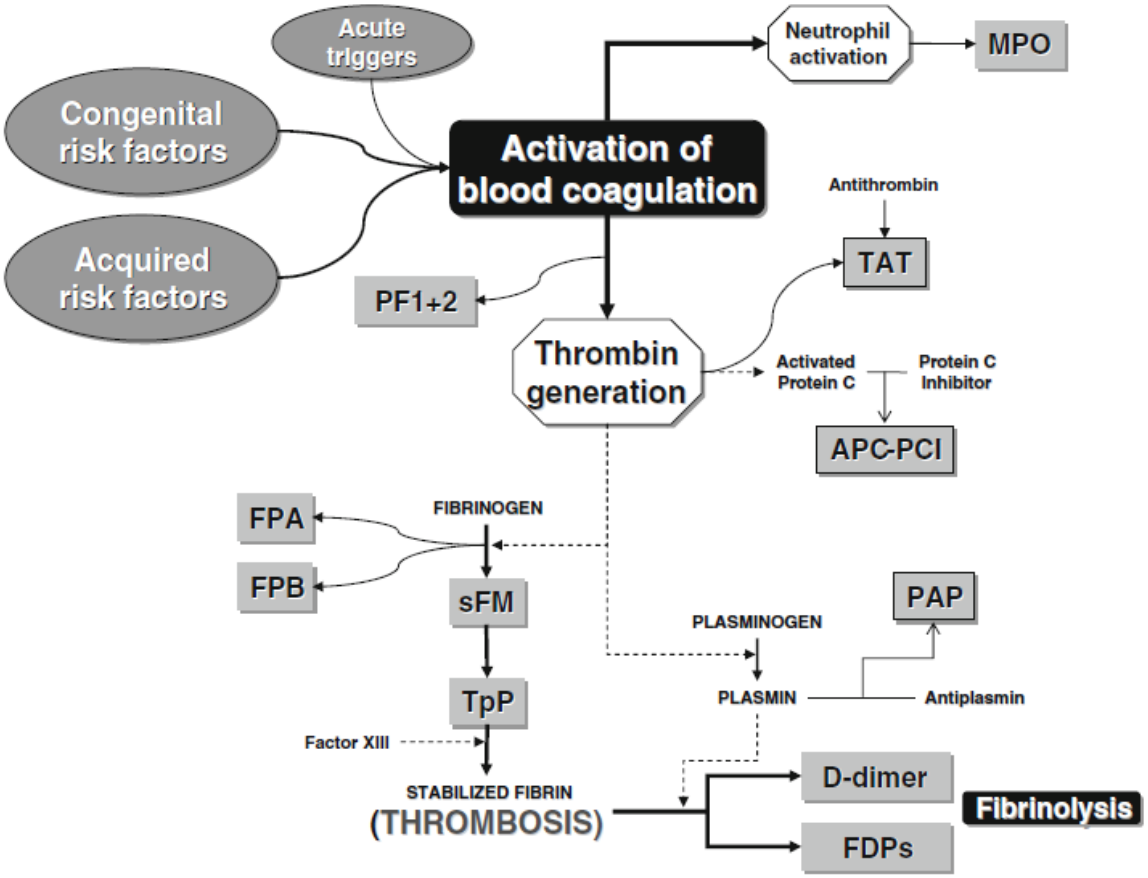
1997: Magnetic resonance imaging angiography

Laboratory Diagnostics of venous thromboembolism

J Thromb Thrombolysis (2010) 30:459–471
DOI 10.1007/s11239-010-0460-x

Biochemical markers for the diagnosis of venous thromboembolism: the past, present and future

Giuseppe Lippi · Gianfranco Cervellin · Massimo Franchini · Emmanuel J. Favaloro



J Thromb Thrombolysis (2010) 30:459–471
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Biochemical markers for the diagnosis of venous thromboembolism: the past, present and future

Giuseppe Lippi · Gianfranco Cervellin · Massimo Franchini · Emmanuel J. Favaloro

D-dimer outperforms all other putative biomarkers

Table 1 Summary of some key findings from the literature

References	Patient cohort	Biochemical markers studied	Sensitivity (%)	Specificity (%)	NPV (%)	PPV (%)	Comments
[27]	116 consecutive patients referred to an angiology unit for a clinically suspected DVT	DD, TAT and PF1 + 2					DD, displayed best characteristics, with high sensitivity (94%) and a high NPV (95%). The TAT and PF1 + 2 were far less sensitive and provided NPV ranging between 78 and 85%
[28]	85 consecutive patients with suspected PE	DD by ELISA	96	42	96	49	DD by ELISA yielded slightly better performance than both DD by latex and total FDP
		DD by latex	93	29	89	43	
		Total FDP	96	26	93	42	
[29]	55 patients presenting to the emergency department	DD	95	43	94	49	The performance of DD, TpP and TAT was better than that of PF1 + 2
		TpP	100	54	100	56	
		PF1 + 2	80	51	82	49	
		TAT	100	40	100	49	
[30]	135 consecutive out-patients referred to the vascular laboratory because of suspected DVT of the lower limb	DD	100	78	100	74	The AUCs were 0.93 for DD, 0.77 for FP1 + 2, 0.83 for TAT, 0.60 for VCAM-1 and 0.81 for P-Selectin. Overall best performance, therefore, was for DD
		FP1 + 2	100	11	100	40	
		TAT	100	18	100	42	
		VCAM-1	100	0	100	18	
		P-selectin	100	19	100	45	
[32]	74 consecutive patients with clinically suspected DVT	DD	95	46	89	66	DD yielded best overall performance
		TAT	82	66	73	77	
		PF1 + 2	59	77	74	63	
		TpP	67	77	76	67	
		VWF	69	54	63	61	
[33]	231 in- and out-patients with clinically suspected DVT	sFM	97–99	6–12	90–93	34–36	The resulting AUC were 0.58 to 0.69 for sFM and 0.77 for DD. DD therefore yielded best overall performance
		DD	96	27	93	40	
[36]	159 patients undergoing hip surgery under antithrombotic Prophylaxis	DD	100	9	100	44	DD and PF1 + 2 performance better than that of TAT
		PF1 + 2	100	6	100	44	
		TAT	54	52	60	46	

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Biochemical markers for the diagnosis of venous thromboembolism: the past, present and future

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References	Patient cohort	Biochemical markers studied	Sensitivity (%)	Specificity (%)	NPV (%)	PPV (%)	Comments
[40]	Systematic review of MEDLINE and EMBASE databases up to March 2005 and identifying studies reporting on the diagnostic accuracy of DD test in patients with suspected DVT of the lower extremities or PE	DVT:					Only the ELFA, microplate ELISA and latex quantitative assay were characterized by low negative likelihood ratios for DVT (0.09, 0.11, and 0.13, respectively) and PE (0.07, 0.10, and 0.10, respectively)
		ELFA	96	46			
		Microplate ELISA	94	53			
		Latex quantitative assay	93	53			
		Membrane ELISA	89	53			
		Latex semiquantitative assay	85	68			
		Whole-blood assay	83	71			
		Latex qualitative assay	69	99			
		PE:					
		ELFA	97	43			
		Microplate ELISA	95	50			
		Latex quantitative assay	95	50			
		Membrane ELISA	91	50			
		Latex semiquantitative assay	88	66			
		Whole-blood assay	87	69			
		Latex qualitative assay	75	99			

AUC area under the Roc Curve, *DD* D-dimer, *DVT* Deep venous thrombosis, *ELFA* Enzyme linked fluorescentv immunoassay, *ELISA* enzyme-linked immunosorbent assay, *FDPs* Fibrin/Fibrinogen degradation products, *NPV* negative predictive value, *PE* Pulmonary embolism, *PF1+2* Prothrombin fragments 1+2, *PPV* Positive predictive value, *sFM* Soluble fibrin monomers, *TAT* Thrombin-antithrombin complex, *TpP* Thrombus precursor protein, *VWF* von Willebrand Factor

JAMA, December 2, 1998—Vol 280, No. 21

Plasma D-Dimer in the Diagnosis of Deep Vein Thrombosis

Giuseppe Lippi, MD
Alessandra Mengoni, MD
Franco Manzato, MD

JAMA®
The Journal of the American Medical Association

Plasma **D-dimer** measurement has been shown to allow the rapid exclusion of about 30% of patients undergoing evaluations for DVT from other expensive, time-consuming, and more risky diagnostic procedures.

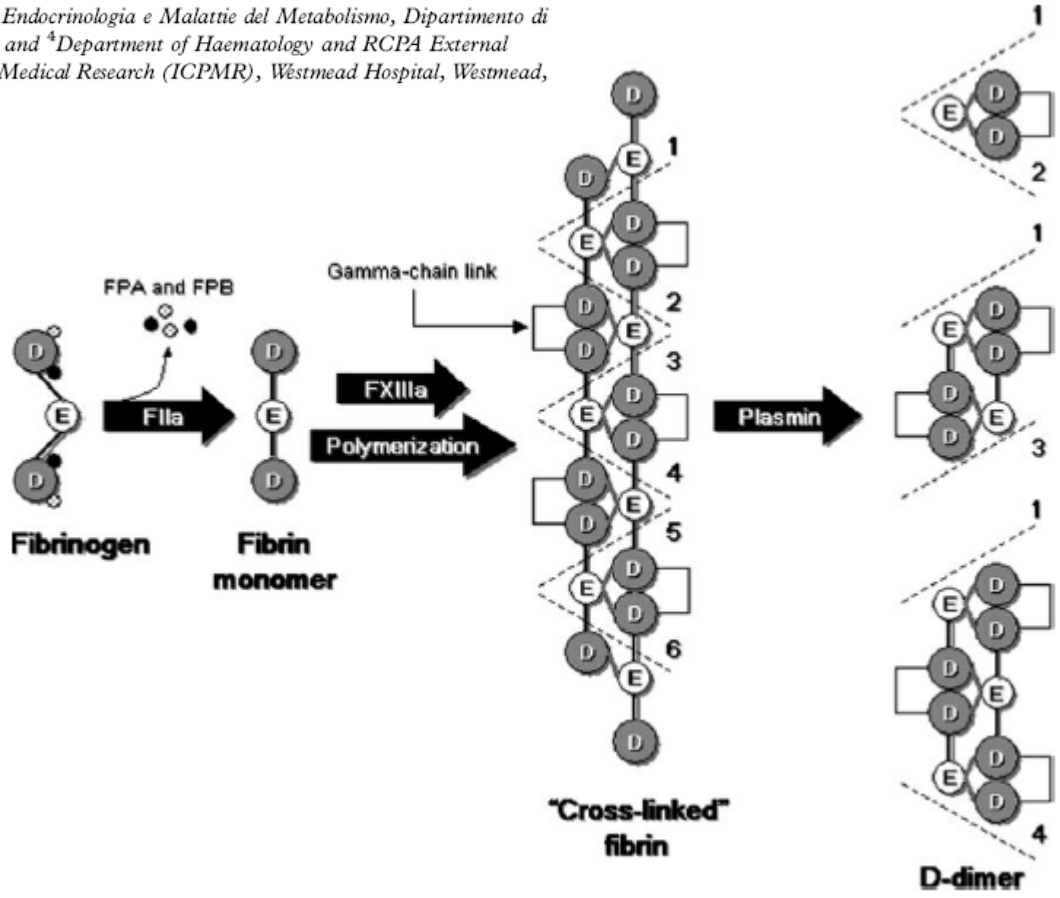
Annals of Medicine. 2008; 40: 594–605

REVIEW ARTICLE

Help me, Doctor! My D-dimer is raised

GIUSEPPE LIPPI[1], MASSIMO FRANCHINI[2], GIOVANNI TARGHER[3] & EMMANUEL J. FAVALORO[4]

[1]*Sezione di Chimica e Clinica, Dipartimento di Patologia, Università di Verona, Italy,* [2]*Servizio di Immunoematologia e Trasfusione, Azienda Ospedaliera di Verona, Italy,* [3]*Sezione di Endocrinologia e Malattie del Metabolismo, Dipartimento di Scienze Biomediche e Chirurgiche, Università di Verona, Italy, and* [4]*Department of Haematology and RCPA External Quality Assurance Program, Institute of Clinical Pathology and Medical Research (ICPMR), Westmead Hospital, Westmead, NSW, Australia*



Q J Med 2005; 98:513–527
doi:10.1093/qjmed/hci085

Variation in the diagnostic performance of D-dimer for suspected deep vein thrombosis

S. GOODACRE[1], F.C. SAMPSON[1], A.J. SUTTON[2], S. MASON[1] and F. MORRIS[3]

Table 2 Sensitivity and/or specificity for selected groups identified by meta-regression

Variable	Sensitivity	Heterogeneity *p*	Specificity	Heterogeneity *p*
Mixed patient selection	87% (86–88)	<0.001	50% (49–51)	<0.001
ED patients only	89% (87–91)	<0.001	62% (60–64)	<0.001
Out-patients only	94% (93–95)	<0.001	59% (58–60)	<0.001
Studies excluding pregnant patients	95% (93–97)	<0.001	57% (56–58)	<0.001
Studies excluding anticoagulated patients	93% (92–94)	<0.001	61% (60–62)	<0.001
Studies excluding patient with past history of thromboembolism	91% (90–93)	<0.001	65% (63–66)	<0.001
Studies excluding patients with a prolonged history	93% (92–94)	<0.001	54% (52–56)	<0.001
Consecutive patients recruited	91% (90–92)	<0.001	57% (56–58)	<0.001
Prospective study	90% (89–91)	<0.001	58% (57–59)	<0.001
Venographic reference standard	91% (90–92)	<0.001	62% (61–64)	<0.001
D-dimer measured blind to reference standard	90% (89–91)	<0.001	56% (55–57)	<0.001
Reference standard measured blind	90% (89–91)	<0.001	57% (56–58)	<0.001
D-dimer threshold derived from data	95% (94–96)	0.245	41% (39–44)	<0.001

Review: ELISA D-dimer is sensitive but not specific in diagnosing pulmonary embolism in an ambulatory clinical setting

Brown MD, Rowe BH, Reeves MJ, et al. The accuracy of the enzyme-linked immunosorbent assay D-dimer test in the diagnosis of pulmonary embolism: a meta-analysis. Ann Emerg Med 2002;40:133–44.

QUESTION: What is the accuracy of the enzyme linked immunosorbent assay (ELISA) D-dimer test in diagnosing pulmonary embolism (PE) in the emergency department or outpatient clinic?

Conclusion

The enzyme linked immunosorbent assay D-dimer test is highly sensitive but not specific in diagnosing pulmonary embolism in an ambulatory clinical setting.

*Test properties of enzyme linked immunosorbent assay D-dimer for pulmonary embolism in an ambulatory clinical setting**

Number of studies	Sensitivity (95% CI)	Specificity (CI)	+LR	–LR
11	95% (90 to 98)	45% (38 to 52)	1.73	0.11
9	94% (88 to 97)	45% (36 to 55)	1.71	0.13

*Diagnostic terms defined in glossary; LRs calculated using the pooled summary estimates of sensitivity and specificity reported by the author.

Annals of Medicine. 2008; 40: 594–605

REVIEW ARTICLE

Help me, Doctor! My D-dimer is raised

GIUSEPPE LIPPI[1], MASSIMO FRANCHINI[2], GIOVANNI TARGHER[3] & EMMANUEL J. FAVALORO[4]

[1]*Sezione di Chimica e Clinica, Dipartimento di Patologia, Università di Verona, Italy,* [2]*Servizio di Immunoematologia e Trasfusione, Azienda Ospedaliera di Verona, Italy,* [3]*Sezione di Endocrinologia e Malattie del Metabolismo, Dipartimento di Scienze Biomediche e Chirurgiche, Università di Verona, Italy, and* [4]*Department of Haematology and RCPA External Quality Assurance Program, Institute of Clinical Pathology and Medical Research (ICPMR), Westmead Hospital, Westmead, NSW, Australia*

Diagnostic algorithms, including **clinical assessment** and **D-dimer**, have been validated in several trials for diagnosing venous thromboembolism.

Wells Prediction Rule for Diagnosing Deep Venous Thrombosis: Clinical Evaluation Table Predicting Pretest Probability of Deep Vein Thrombosis

Medscape® www.medscape.com

Clinical Characteristic	Score
Active cancer (treatment ongoing, within previous 6 months, or palliative)	1
Paralysis, paresis, or recent plaster immobilization of the lower extremities	1
Recently bedridden >3 days or major surgery within 12 weeks requiring general or regional anesthesia	1
Localized tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Calf swelling 3 cm larger than asymptomatic side (measured 10 cm below tibial tuberosity)	1
Pitting edema confined to the symptomatic leg	1
Collateral superficial veins (nonvaricose)	1
Alternative diagnosis at least as likely as deep venous thrombosis	-2

Note: Clinical probability: low ≤0; intermediate 1-2; high ≥3. In patients with symptoms in both legs, the more symptomatic leg is used.

Reprinted from The Lancet, Vol 350, Wells PS, Anderson DR, Bormanis J, et al. Value of assessment of pretest probability of deep-vein thrombosis in clinical management, pp 1795-1798,

European Heart Journal (2014) **35**, 3033–3080

2014 ESC Guidelines on the diagnosis and management of acute pulmonary embolism

The Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC)

Table 3 Clinical characteristics of patients with suspected PE in the emergency department (adapted from Pollack et *al.* (2011)).[82]

Feature	PE confirmed (*n* = 1880)	PE not confirmed (*n* = 528)
Dyspnoea	50%	51%
Pleuritic chest pain	39%	28%
Cough	23%	23%
Substernal chest pain	15%	17%
Fever	10%	10%
Haemoptysis	8%	4%
Syncope	6%	6%
Unilateral leg pain	6%	5%
Signs of DVT (unilateral extremity swelling)	24%	18%

Thromb Haemost 2008; 99: 1134–1136

Cardiac biomarkers in pulmonary embolism

Giuseppe Lippi[1], Emmanuel J. Favaloro[2]

[1]Sezione di Chimica e Clinica, Dipartimento di Patologia, Università di Verona, Italy; [2]Department of Haematology, Westmead Hospital, Westmead, New South Wales, Australia

Table 1: Differential diagnosis of pulmonary embolism (PE).

Anemia
Angina pectoris
Aortic stenosis
Atrial fibrillation
Cardiogenic shock
Chronic obstructive pulmonary disease
Cor pulmonale
Costochondritis
Emphysema
Herpes zoster
Mitral stenosis
Musculoskeletal pain
Myocardial ischemia and infarction
Myocarditis
Pericarditis
Pleuritis
Pneumonia
Pneumothorax
Rib fracture
Shock (septic, distributive, haemorrhagic)
Syncope
Toxic shock syndrome

European Heart Journal (2014) 35, 3033–3080

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Items	Clinical decision rule points	
Wells rule	**Original version[95]**	**Simplified version[107]**
Previous PE or DVT	1.5	1
Heart rate ≥100 b.p.m.	1.5	1
Surgery or immobilization within the past four weeks	1.5	1
Haemoptysis	1	1
Active cancer	1	1
Clinical signs of DVT	3	1
Alternative diagnosis less likely than PE	3	1
Clinical probability		
Three-level score		
Low	0–1	N/A
Intermediate	2–6	N/A
High	≥7	N/A
Two-level score		
PE unlikely	0–4	0–1
PE likely	≥5	≥2
Revised Geneva score	**Original version[93]**	**Simplified version[108]**
Previous PE or DVT	3	1
Heart rate 75–94 b.p.m. ≥95 b.p.m.	 3 5	 1 2
Surgery or fracture within the past month	2	1
Haemoptysis	2	1
Active cancer	2	1
Unilateral lower limb pain	3	1
Pain on lower limb deep venous palpation and unilateral oedema	4	1
Age >65 years	1	1
Clinical probability		
Three-level score		
Low	0–3	0–1
Intermediate	4–10	2–4
High	≥11	≥5
Two-level score		
PE unlikely	0–5	0–2
PE likely	≥6	≥3

Practical issues

What about harmonization?

How should we use it?

Measurement uncertainty?

Measure unit?

Age-dependent reference values?

Practical issues

What about harmonization?

How should we use it?

Measurement uncertainty?

Measure unit?

Age-dependent reference values?

Standardization issues

- *D-dimer exists in plasma as a complex variety of cross-linked fibrin derivatives of molecular weight in excess of $2x10^6$ daltons, and rarely as free D-dimer.*
- *Commercially available D-dimer kits differ in reactivity toward D-dimer, implying an international standard may be challenging.*
- *Standardization of D-dimer assays has been under review of the Fibrinogen and DIC sub-committee of the International Society on thrombosis and Haemostasis (ISTH) for several years.*

RIMeL / IJLaM 2005; 1

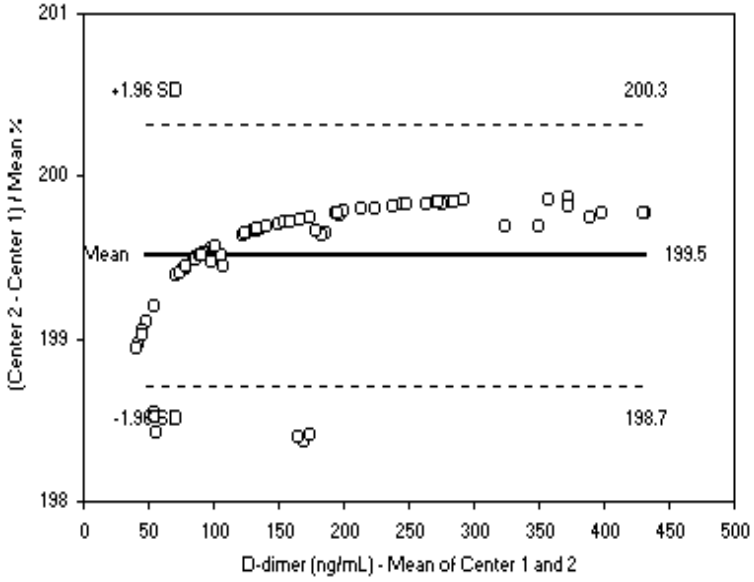
Articolo originale

Variability of coagulation testing between two separate laboratories: implications for diagnosis and therapeutic monitoring

G. Lippi[a,c], D. Giavarina[b], M.R. Carta[b], G. Poli[a], M. Montagnana[a], G.L. Salvagno[a], G. Soffiati[b], G.C. Guidi[a,c]

[a] Istituto di Chimica Microscopia Clinica, Dipartimento di Scienze Morfologico-Biomediche, Università degli Studi di Verona, Verona
[b] Laboratorio di Chimica clinica ed Ematologia, Ospedale S. Bortolo, Vicenza
[c] CISMEL. Comitato Italiano per la Standardizzazione dei Metodi Ematologici e di Laboratorio

Accordingly, the percentage of patients outside the reference range (150-400 mg/dL for fibrinogen) or exceeding the relative diagnostic thresholds (<500 µg/L for Vidas d-dimer and <400 g/L for Liatest D-DI) was significantly different for fibrinogen (46.4% versus 32.1%, *P*<0.001), but not for d-dimer (15.5% versus 20.2%, *P*=0.24).



Thromb Haemost 2006; 95: 567–72

A model for the harmonisation of test results of different quantitative D-dimer methods

Piet Meijer[1,2], Frits Haverkate[1], Cornelis Kluft[2], Philippe de Moerloose[3], Bert Verbruggen[4], Michael Spannagl[5, 6]

Table 5: The coefficient of variation (%) for the method-specific consensus values of all methods included before and after harmonisation for the 5 different plasma samples.

Sample	Overall median value (ng/ml)	Before	After
A	252	91.0	18.2
B	425	92.3	7.4
C	736	86.8	6.1
D	1733	83.6	5.9
E	2816	82.3	1.5

Thrombosis Research 137 (2016) 219–220

Harmonisation of D-dimer — A call for action

Colin Longstaff
Biotherapeutics, Haemostasis Section, National Institute for Biological Standards and Control, South Mimms EN63QG, UK

Dorothy Adcock
Laboratory Corporation of America® Holdings, Englewood, CO, USA

John D. Olson
Department of Pathology, South Texas Reference Laboratories, University of Texas Health Science Center, San Antonio, TX, USA

Ian Jennings, Steve Kitchen
United Kingdom National External Quality Assessment Scheme for Blood Coagulation (Blood Coagulation), Sheffield, UK

Nicola Mutch
Institute of Medical Sciences, University of Aberdeen, Aberdeen, UK

Piet Meijer
ECAT Foundation (External quality Control for Assays and Tests), The Netherlands
Diagnostic Haemostasis Laboratory, Institute of Clinical Pathology and Medical Research (ICPMR), Australia

Emmanuel J. Favaloro
Westmead Hospital, Westmead, NSW, Australia

Giuseppe Lippi
Laboratory of Clinical Chemistry and Hematology, Academic Hospital of Parma, Italy

Jecko Thachil*
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E-mail address: jecko.thachil@cmft.nhs.uk.

A possible solution to these issues is to:

- use a large number of samples from different clinical settings
- to produce a stable freeze dried reference preparation
- containing a high D-dimer concentration of heterogeneous species.

- This material could be diluted to generate a range of D-dimer values and
- constructing a consensus reference line for different commercial assays.

Practical issues

What about harmonization?

How should we use it?

Measurement uncertainty?

Measure unit?

Age-dependent reference values?

Documenti *CISMEL*

LINEE GUIDA SULL'IMPIEGO CLINICO DEL D-DIMERO

Cristina Legnani, Gualtiero Palareti, **Domenico Prisco, per il Sottocomitato Emostasi del *CISMEL***.

U.O. di Angiologia e Malattie della Coagulazione, Policlinico S. Orsola-Malpighi, Bologna; * Dip. di Area Critica Medico-chirurgica, Centro Trombosi, Azienda Ospedaliera Universitaria Careggi, Firenze.

** P.M. Mannucci (Milano), *Coordinatore*; A. Tripodi (Milano), *Segretario*; N. Ciavarella (Bari); G. Lippi (Verona); C. Manotti (Parma); G. Palareti (Bologna); D. Prisco (Firenze); F. Rodeghiero (Vicenza).

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Figura 1. Flow-chart schematica che rappresenta la determinazione del D-dimero come approccio iniziale per escludere una TEV

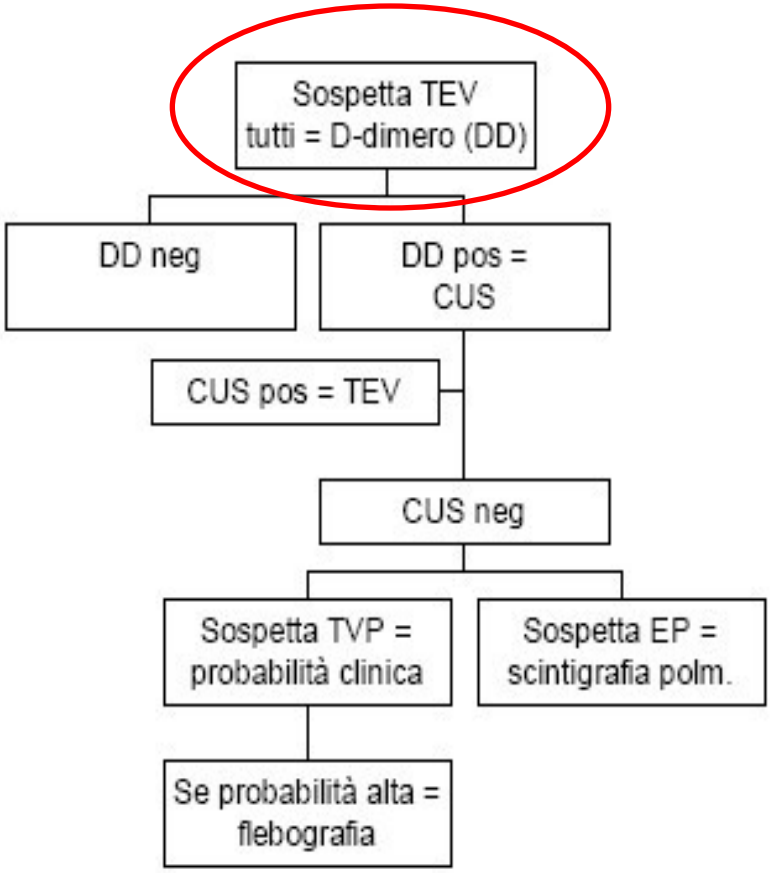

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Figura 2. Flow-chart schematica che rappresenta il ruolo della determinazione del D-dimero dopo un primo accertamento specifico per TVP risultato negativo

Documenti *CISMEL*

LINEE GUIDA SULL'IMPIEGO CLINICO DEL D-DIMERO

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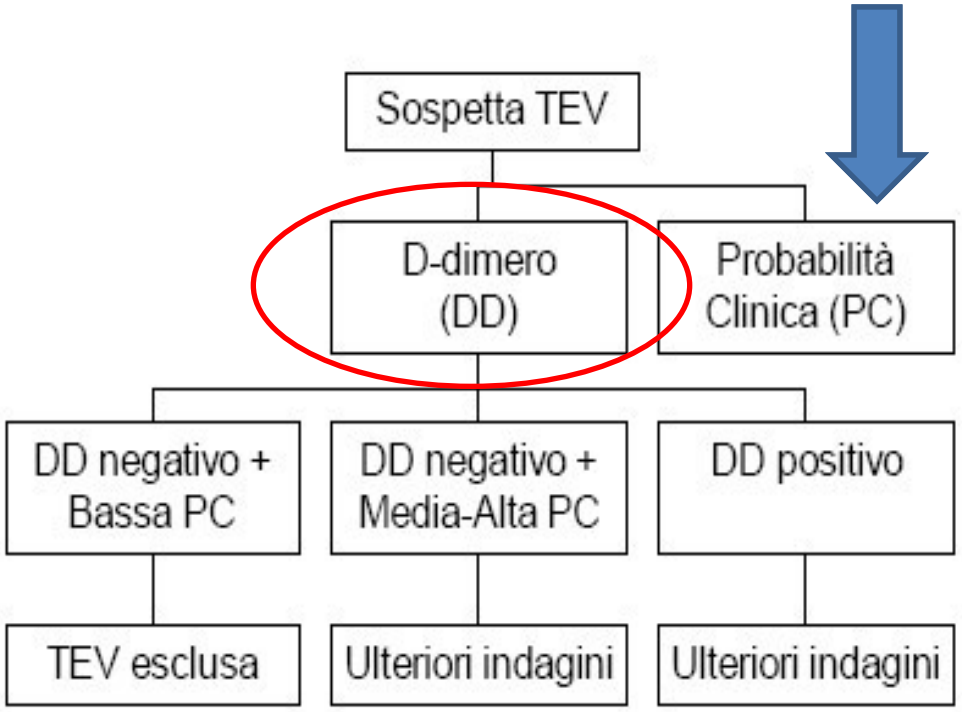
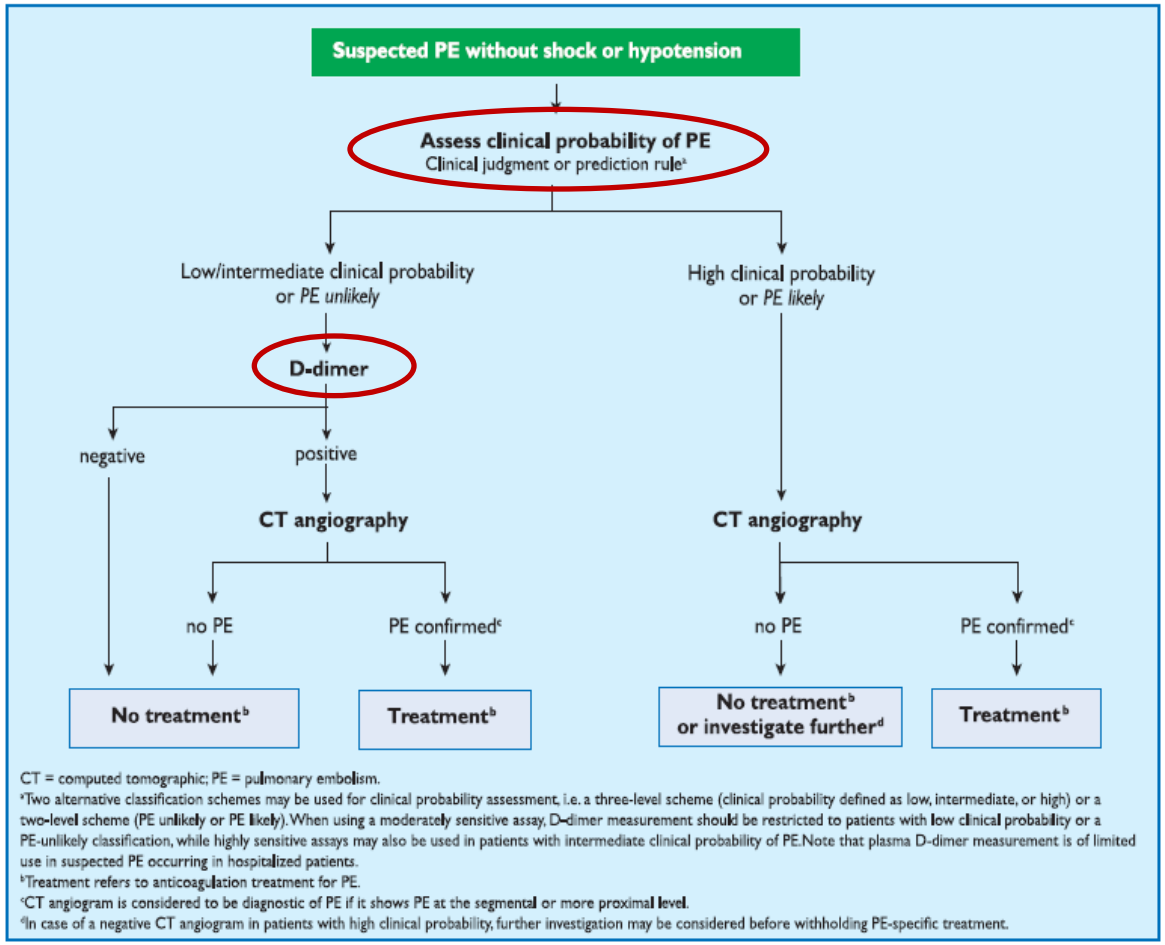
Figura 3. Flow-chart schematica che rappresenta il ruolo della determinazione del D-dimero integrata con la valutazione della probabilità clinica e con ulteriori accertamenti specifici (se indicati)



European Heart Journal (2014) **35**, 3033–3080

2014 ESC Guidelines on the diagnosis and management of acute pulmonary embolism

The Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC)



CT = computed tomographic; PE = pulmonary embolism.

[a]Two alternative classification schemes may be used for clinical probability assessment, i.e. a three-level scheme (clinical probability defined as low, intermediate, or high) or a two-level scheme (PE unlikely or PE likely). When using a moderately sensitive assay, D-dimer measurement should be restricted to patients with low clinical probability or a PE-unlikely classification, while highly sensitive assays may also be used in patients with intermediate clinical probability of PE. Note that plasma D-dimer measurement is of limited use in suspected PE occurring in hospitalized patients.

[b]Treatment refers to anticoagulation treatment for PE.

[c]CT angiogram is considered to be diagnostic of PE if it shows PE at the segmental or more proximal level.

[d]In case of a negative CT angiogram in patients with high clinical probability, further investigation may be considered before withholding PE-specific treatment.

DOI 10.1515/cclm-2013-0706 — Clin Chem Lab Med 2014; 52(5): 621–628

Giuseppe Lippi*, Gianfranco Cervellin, Ivo Casagranda, Benedetto Morelli, Sophie Testa and Armando Tripodi

D-dimer testing for suspected venous thromboembolism in the emergency department. Consensus document of AcEMC, CISMEL, SIBioC, and SIMeL

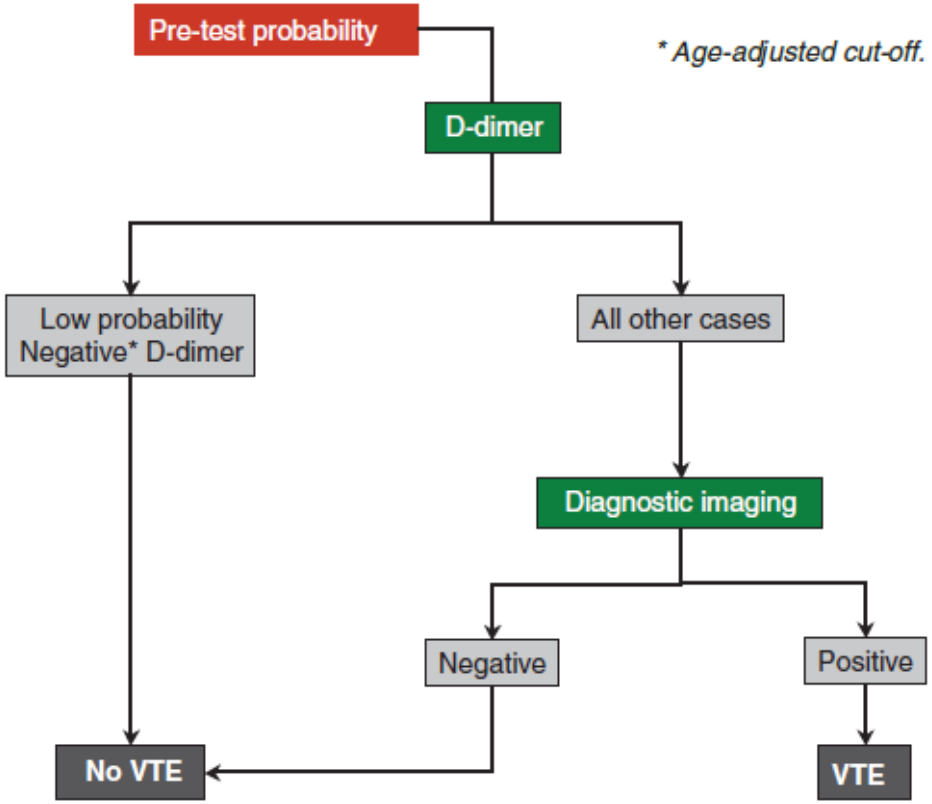
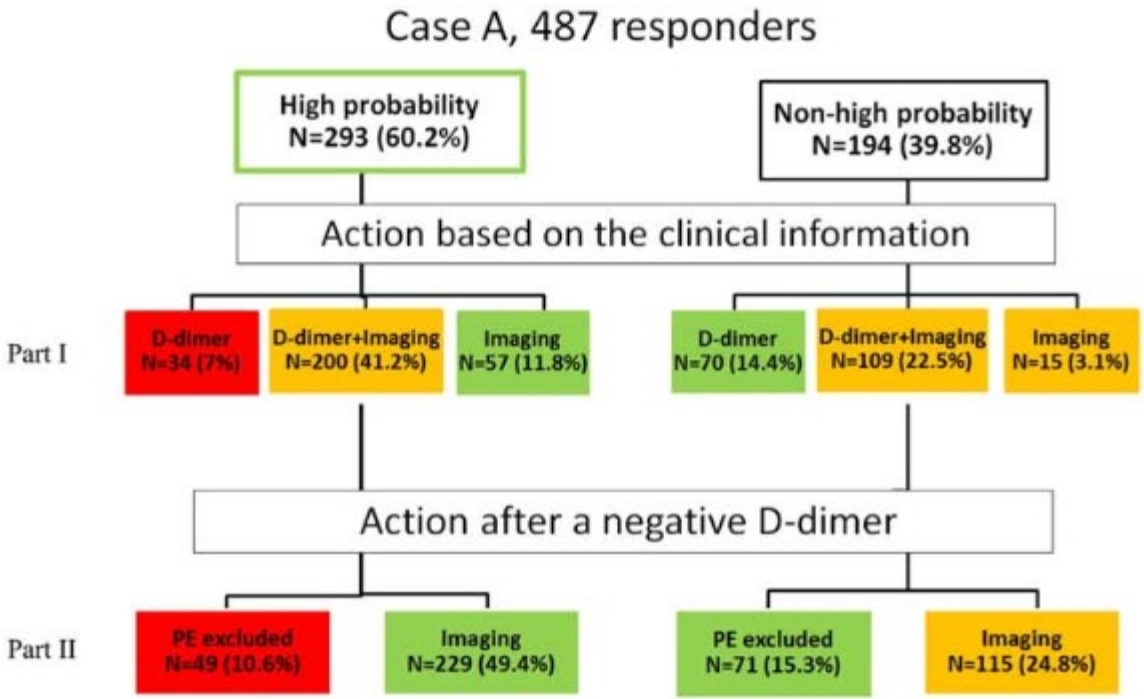


Figure 2 Diagnostic algorithm for patients admitted to the ED with suspected VTE.

Thrombosis Research 142 (2016) 1–7

Is D-dimer used according to clinical algorithms in the diagnostic work-up of patients with suspicion of venous thromboembolism? A study in six European countries

Ann Helen Kristoffersen [a,b,*], Eva Ajzner [c], Dunja Rogic [d], Eser Y. Sozmen [e], Paolo Carraro [f], Ana Paula Faria [g], Joseph Watine [h], Piet Meijer [i], Sverre Sandberg [a,b,j],
On behalf of the joint Working Group on Postanalytical Phase (WG-POST) of the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) and European Organisation for External Quality Assurance Providers in Laboratory Medicine (EQALM)



Thrombosis Research 142 (2016) 1–7

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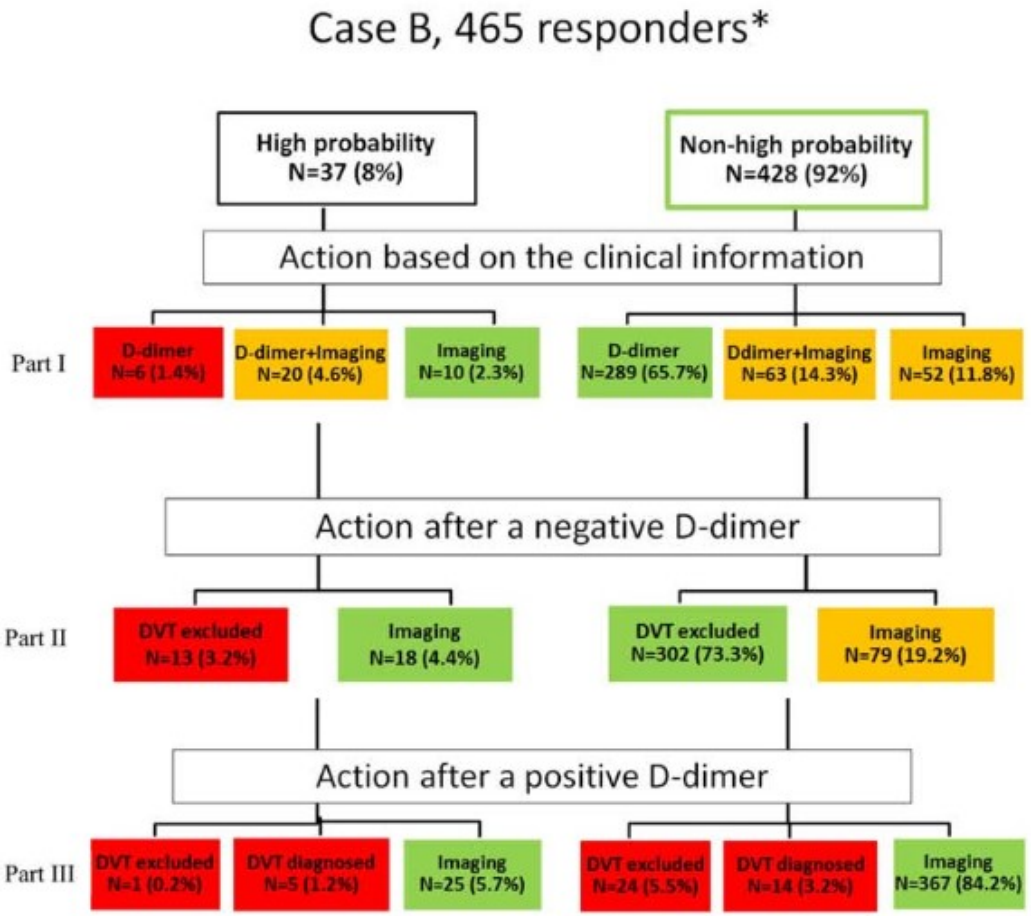

Practical issues

What about harmonization?

How should we use it?

Range or specific value?

Measurement uncertainty?

Age-dependent reference values?

ELSEVIER

The Journal of Emergency Medicine, Vol. xx, No. x, pp. xxx, 2009

0736-4679/09 $–see front matter

☐ D-DIMER MEASUREMENT AND LABORATORY FEEDBACK

Giuseppe Lippi, MD
Emmanuel J. Favaloro, PHD

- **Time elapsed since the thrombotic event.**

  D-dimer has a half life of ~6 hours with normal renal function. Patients with stabilised clots not undergoing active fibrin deposition and plasmin activation, may not give detectable D-dimer.

- **The initial size of the clot.**

  The larger the clot size, the higher the expected level of circulating D-dimer.

- **The rate of fibrinolysis.**

  Blood fibrinolysis is a regulated process in dynamic balance. Should any component be compromised (deficiency or dysfunction), the rate of fibrinolysis will be altered.

- **Alternative fibrin sites.**

  Fibrin may be present at alternative sites other than that suspected (atherosclerotic lesions, extravascular fibrin deposits, cancers can be encapsulated in a fibrin sheath, etc.).

- **Differing antibody specificity.**

  D-dimer assays are not alike - Depending on the commercial source, different antibodies have differing specificities for fibrinogen, fibrin and derivatives. There are still FDP assays calling themselves “D-dimer specific”.

Practical issues

What about harmonization?

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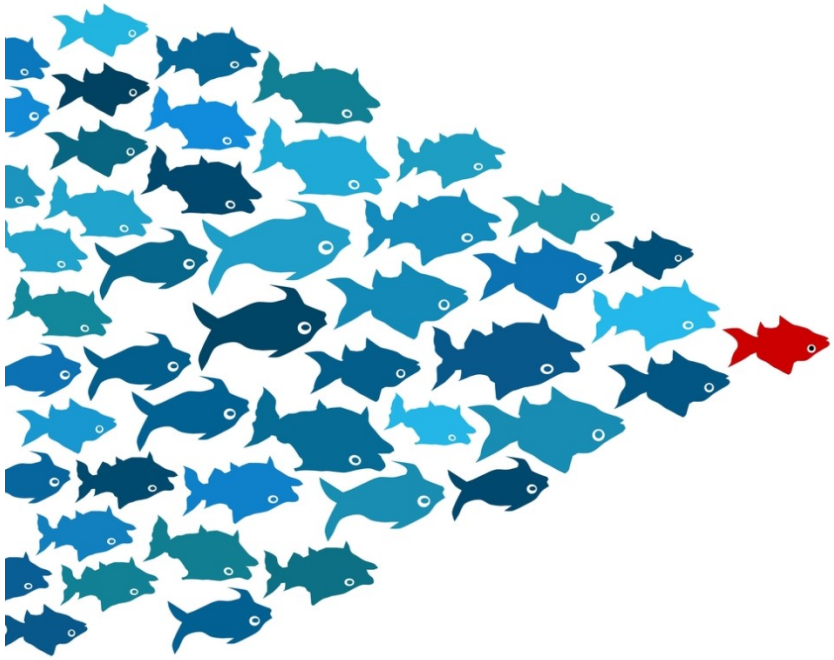
Measure unit?

Age-dependent reference values?

Semin Thromb Hemost 2015;41:287–293.

International Survey on D-Dimer Test Reporting: A Call for Standardization

Giuseppe Lippi, MD[1] Armando Tripodi, PhD[2,3] Ana-Maria Simundic, PhD[4]
Emmanuel J. Favaloro, PhD, FFSc (RCPA)[5]



Semin Thromb Hemost 2015;41:287–293.

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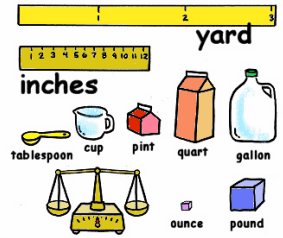

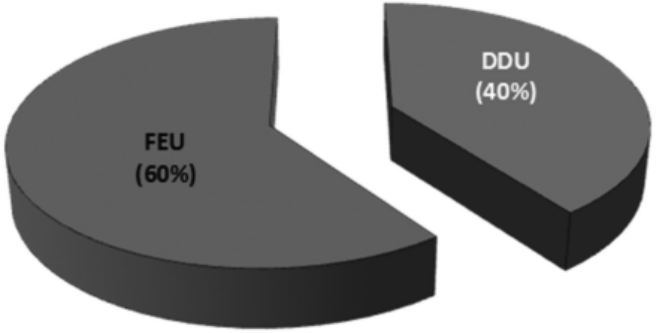

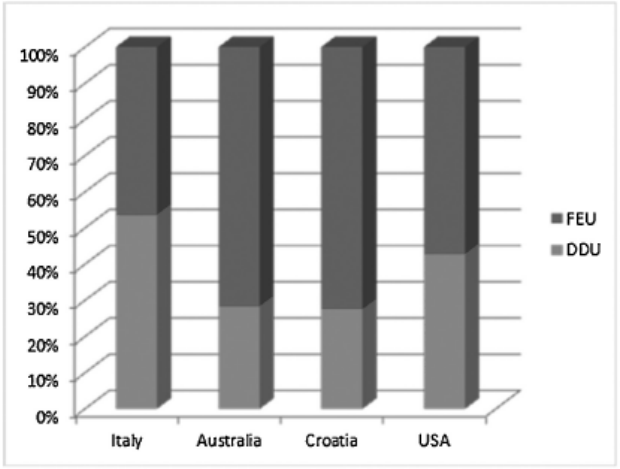

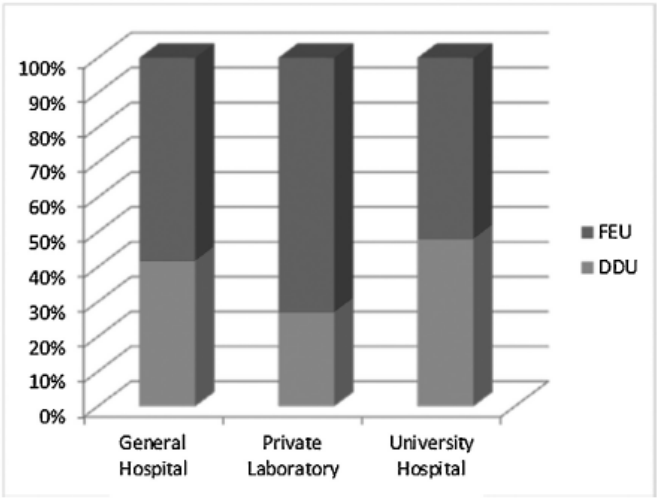

Fig. 3 Use of DDU or FEU for D-dimer reporting among respondents to the survey. DDU, D-dimer unit; FEU, fibrinogen-equivalent unit.

Semin Thromb Hemost 2015;41:287–293.

International Survey on D-Dimer Test Reporting: A Call for Standardization

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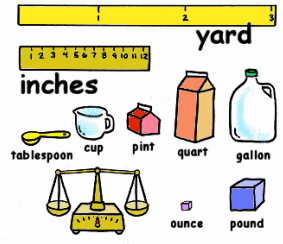

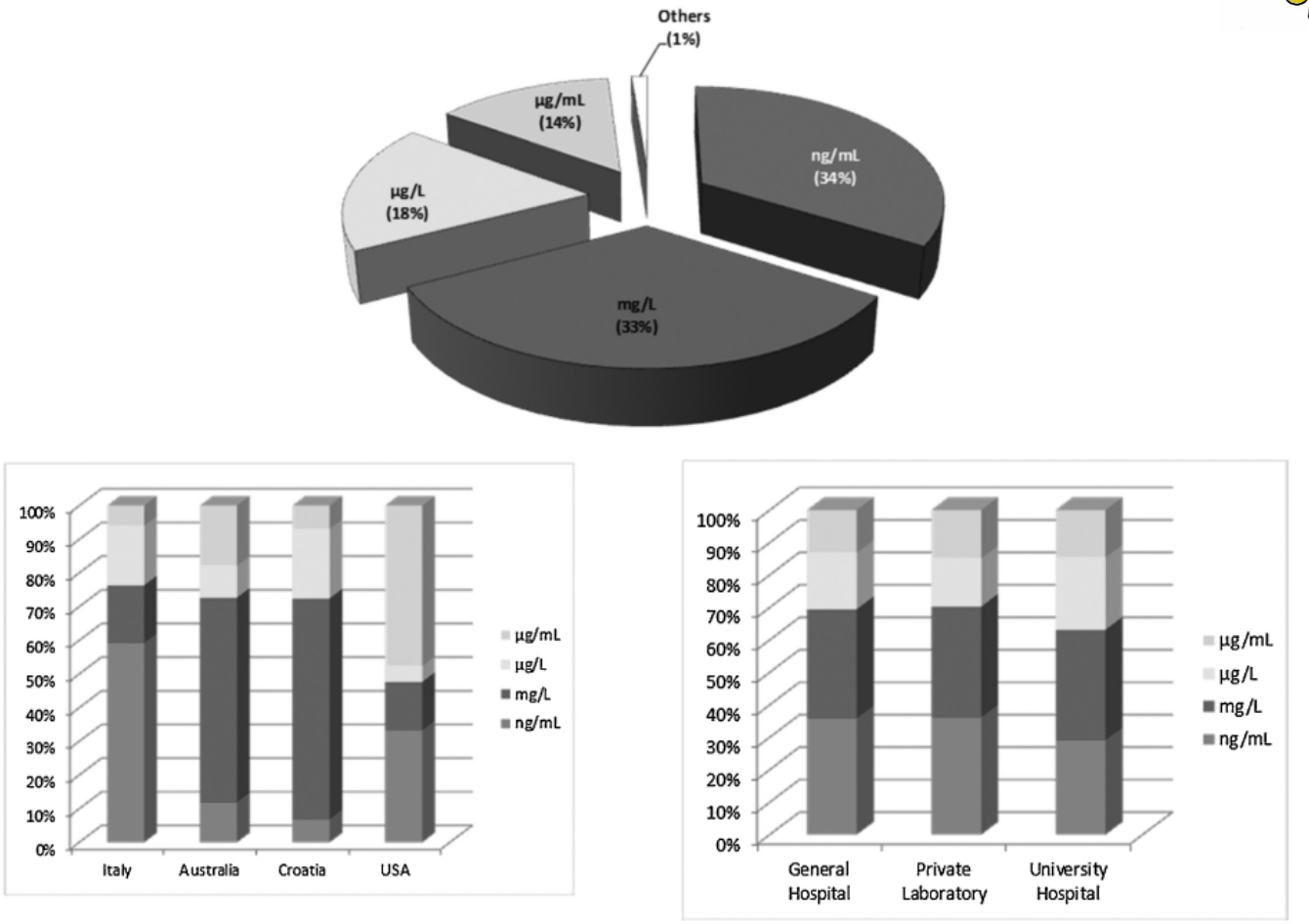

Fig. 4 Use of different measure units for D-dimer reporting among respondents to the survey.

Semin Thromb Hemost 2015;41:287–293.

International Survey on D-Dimer Test Reporting: A Call for Standardization

Giuseppe Lippi, MD[1] Armando Tripodi, PhD[2,3] Ana-Maria Simundic, PhD[4]
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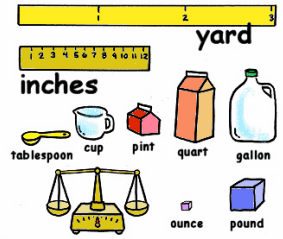


SUMMARY RECOMMENDATIONS

- The unit of measurement which is probably more in line with the International System (SI) is "**µg/L**," which is also essentially the same as "ng/mL."

Practical issues

What about harmonization?

How should we use it?

Measurement uncertainty?

Measure unit?

Age-dependent reference values?

Semin Thromb Hemost 2014;40:621–633.

Aging Hemostasis: Changes to Laboratory Markers of Hemostasis As We Age—A Narrative Review

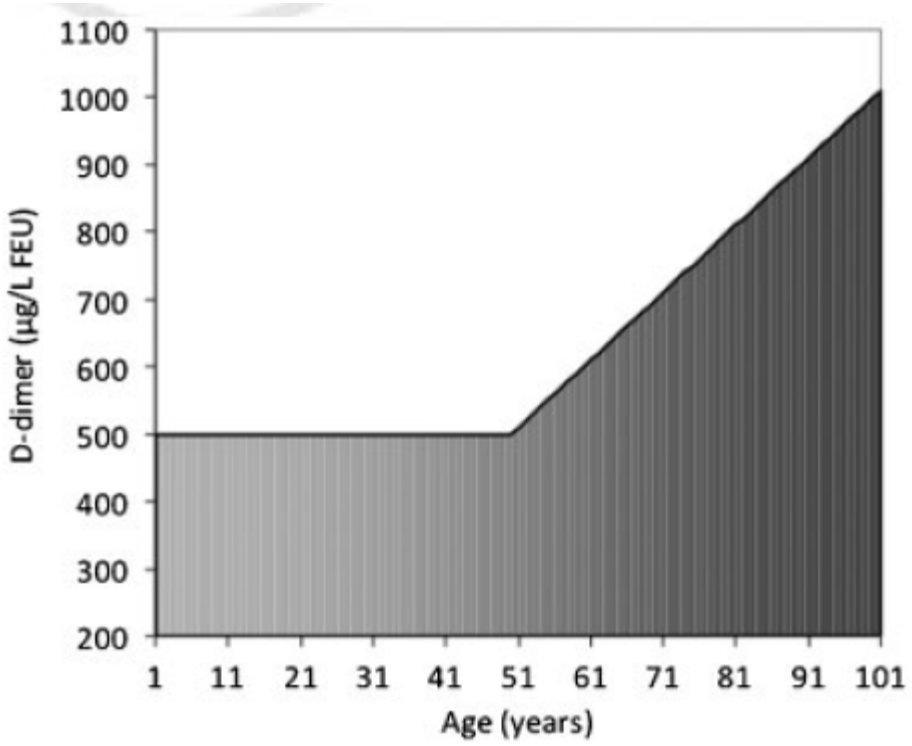
Emmanuel J. Favaloro, PhD, FFSc (FRCPA)[1] Massimo Franchini, MD[2] Giuseppe Lippi, MD[3]

System affected	Marker affected	References
Coagulation system proteins (secondary hemostasis)	Fibrinogen ↑	18–20
	Factor II =	27, 40
	Factor V ↑	27
	Factor VII ↑	24, 27, 32, 33
	Factor VIII ↑	24–27
	Factor IX ↑	27, 46
	Factor X =	27
	Factor XI ↑	27
	Factor XII =;↑	27, 45
	Factor XIII ↑	47
Markers of coagulation activation ↑	Prothrombin fragments 1 + 2, fibrinopeptide A, activated factor VII, activation peptides of factor IX and X, thrombin–antithrombin complex	40–44
Anticoagulant proteins	Antithrombin (sex difference): ↑ ; ↓ Protein C =; ↑ Protein S =; ↑ Tissue factor pathway inhibitor ↑ Heparin cofactor II ↓	26, 36, 40, 43, 55–61, 63–65
Fibrinolysis markers	Plasminogen =; ↓ (gender)	55, 66
	Euglobulin lysis time↑	67, 68
	Plasminogen Activator Inhibitor (PAI-1) ↑	73–75
	Plasmin-antiplasmin complex ↑; Fibrin degradation products/ D-dimers ↑; Thrombin activatable fibrinolysis inhibitor↑	9, 43, 76, 77
Thrombin generation ↑		90–94
Primary hemostasis and platelet function	von Willebrand factor ↑	26, 50–51
	platelet activation ↑	103–112
	PFA-100 closure time ↓	10, 114, 116

Semin Thromb Hemost 2014;40:634–639.

A Review of the Value of D-dimer Testing for Prediction of Recurrent Venous Thromboembolism with Increasing Age

Giuseppe Lippi, MD[1] Emmanuel J. Favaloro, PhD, FFSc (RCPA)[2] Gianfranco Cervellin, MD[3]



BMJ 2013;346:f2492 doi: 10.1136/bmj.f2492 (Published 3 May 2013)

Diagnostic accuracy of conventional or age adjusted D-dimer cut-off values in older patients with suspected venous thromboembolism: systematic review and meta-analysis

Henrike J Schouten *resident in geriatrics*[1 2], G J Geersing *general practitioner*[1], H L Koek *geriatrician*[2], Nicolaas P A Zuithoff *consultant in applied statistics*[1], Kristel J M Janssen *clinical epidemiologist*[3], Renée A Douma *resident internal medicine*[4], Johannes J M van Delden *professor of medical ethics*[1], Karel G M Moons *professor of clinical epidemiology*[1], Johannes B Reitsma *associate professor of clinical epidemiology*[1]

What this study adds

This systematic review and meta-analysis established a poor specificity (around 15%) of D-dimer testing with the conventional cut-off value in the eldest patients (>80 years)

The application of the age adjusted cut-off value increased the specificity of the D-dimer test to 35% in the eldest patients, while hardly affecting the sensitivity

Use of age adjusted D-dimer cut-off values would result in imaging examinations being correctly avoided in 30-54% of older patients with a non-high clinical probability of venous thromboembolism

Abstracts / Thrombosis Research 140S1 (2016) S168–S200

Excluding pulmonary embolism in cancer patients using the Wells rule and age-adjusted D-dimer testing: an individual patient data meta-analysis

N. van Es[1], T. van der Hulle[2], J. van Es[1], P.L. den Exter[2], R.A. Douma[1], R.J. Goekoop[3], I.C.M. Mos[2], J.G. Garcia[4], P.W. Kamphuisen[5], M.V. Huisman[2], F.A. Klok[2], H.R. Büller[1], P.M. Bossuyt[6]

Conclusions: Among cancer patients with clinically suspected PE, imaging and anticoagulant treatment can be withheld in 1 out of every 8 patients by the original Wells rule and age-adjusted D-dimer testing. The simplified Wells rule was neither efficient nor safe in this population.

Semin Thromb Hemost 2015;41:287–293.

International Survey on D-Dimer Test Reporting: A Call for Standardization

Giuseppe Lippi, MD[1] Armando Tripodi, PhD[2,3] Ana-Maria Simundic, PhD[4]
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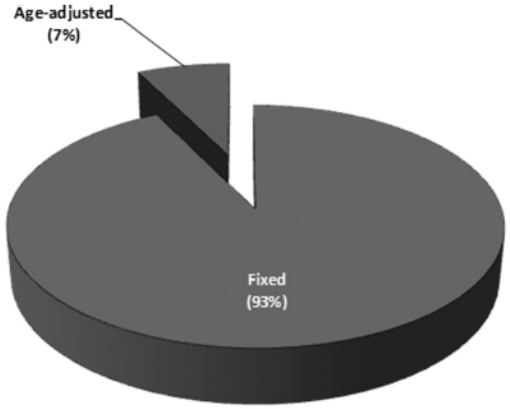
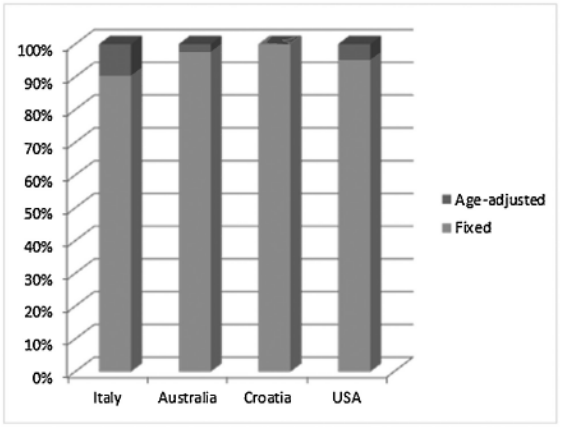




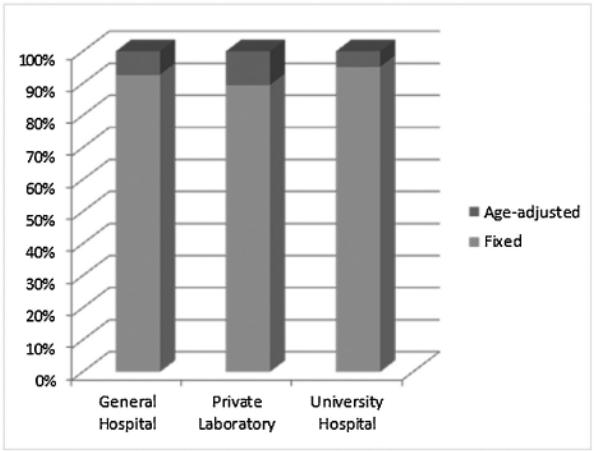


Fig. 5 Use of fixed or age-adjusted cutoff for D-dimer reporting among respondents to the survey.

Semin Thromb Hemost 2015;41:287–293.

International Survey on D-Dimer Test Reporting: A Call for Standardization

Giuseppe Lippi, MD[1] Armando Tripodi, PhD[2,3] Ana-Maria Simundic, PhD[4]
Emmanuel J. Favaloro, PhD, FFSc (RCPA)[5]

SUMMARY RECOMMENDATIONS

- The use of **age-adjusted cutoffs** should be further promoted for improving the clinical usefulness of D-dimer testing in elderly patients with non-high clinical probability.

Medical science has made such tremendous progress that there is hardly a healthy human left.

— Aldous Huxley —

Annals of Medicine. 2008; 40: 594–605

REVIEW ARTICLE

Help me, Doctor! My D-dimer is raised

GIUSEPPE LIPPI[1], MASSIMO FRANCHINI[2], GIOVANNI TARGHER[3] & EMMANUEL J. FAVALORO[4]

[1]*Sezione di Chimica e Clinica, Dipartimento di Patologia, Università di Verona, Italy,* [2]*Servizio di Immunoematologia e Trasfusione, Azienda Ospedaliera di Verona, Italy,* [3]*Sezione di Endocrinologia e Malattie del Metabolismo, Dipartimento di Scienze Biomediche e Chirurgiche, Università di Verona, Italy, and* [4]*Department of Haematology and RCPA External Quality Assurance Program, Institute of Clinical Pathology and Medical Research (ICPMR), Westmead Hospital, Westmead, NSW, Australia*

Table I. Physiological and pathophysiological sources of D-dimer elevation.

Physiological sources of D-dimer elevation:
Ageing (especially age >65 yrs)
Pregnancy
Recent injury, surgery or trauma
Pathophysiological sources of D-dimer elevation:
Venous thromboembolism
Deep vein thrombosis
Pulmonary embolism
Vein thrombosis in atypical sites (upper arms, mesenteric, cerebral)
Disseminated intravascular coagulation (DIC)
Arterial thrombosis
Acute coronary syndrome
Ischaemic stroke
Peripheral arteries occlusive disease (PAOD)
Intestinal ischaemia
Other vascular disorders
Alzheimer's disease
Acute aortic dissection (AAD)
Thrombosis of vascular accesses
Infections
Sepsis
Pneumonia
Malignancy
HELLP (syndrome) =hemolysis, elevated liver enzymes, low platelets (syndrome)
Liver disease
Sickle cell disease
Atrial fibrillation

European Journal of Internal Medicine 25 (2014) 45–48

Causes of elevated D-dimer in patients admitted to a large urban emergency department

Giuseppe Lippi [a,*], Laura Bonfanti [b], Carlotta Saccenti [b], Gianfranco Cervellin [b]

Final diagnosis	n	%
Infection	257	15.6
VTE	200	12.1
Syncope	155	9.4
Heart failure	146	8.9
Trauma	135	8.2
Cancer	95	5.8
Dyspnea	94	5.7
Cerebrovascular ischemia	93	5.6
ACS	92	5.6
COPD	87	5.3
Atrial fibrillation	81	4.9
Anemia	22	1.3
Cirrhosis	22	1.3
Subarachnoid hemorrhage	20	1.2
Abdominal aortic aneurysm	19	1.2
Superficial thrombosis	19	1.2
Acute renal failure	18	1.1
Cholecystitis	18	1.1
Peripheral occlusive disease	16	1.0
Lymphedema	12	0.7
Epilepsy	9	0.5
Intestinal ischemia	8	0.5
Arthritis	6	0.4
Hypertensive crisis	6	0.4
Baker's cyst	4	0.2
Renal colic	4	0.2
Recent surgery	3	0.2
Pancreatitis	2	0.1
Allergy	1	0.1
Amyloidosis	1	0.1
Gastric perforation	1	0.1
Inguinal hernia	1	0.1

Annals of Internal Medicine

D-Dimer Testing in Pregnancy: Clinically Useful, but at What Cost?

Giuseppe Lippi, MD
Martina Montagnana, MD

we calculated that the positive predictive value in the entire study population was 18% (this information was missing), whereas the specificity and the positive predictive value in women after 28 weeks of gestation were reduced to 49% and 9%, respectively.

Blood Coagulation and Fibrinolysis 2006, 17:87

Plasma D-dimer variation following elective orthopedic surgery

Giuseppe Lippi[a], Martina Montagnana[a], Dario Regis[b], Gino Viola[b] and Gian Cesare Guidi[a]

Table 1 Plasma D-dimer variations (ng/ml) in 37 patients undergoing elective orthopedic surgery

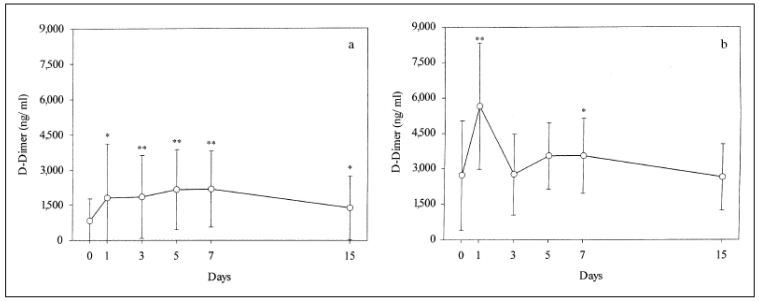
	3 h preoperative	4 h postoperative	72 h postoperative
All patients ($n = 37$)	781 ± 616	3943 ± 2736‡	2012 ± 1166‡
Hip arthroplasty ($n = 10$)	1114 ± 711	5235 ± 1965‡	2324 ± 1709‡
Knee arthroplasty ($n = 13$)	483 ± 483	2332 ± 1873‡	1628 ± 738‡
Lumbar spine surgical stabilization ($n = 14$)	847 ± 506	4685 ± 3151‡	2185 ± 878‡

Clin Exp Med (2001) 1:161–164

BRIEF DEFINITIVE REPORT

G. Lippi • G.F. Veraldi • M. Fraccaroli • F. Manzato • C. Cordiano • G. Guidi

Variation of plasma D-dimer following surgery: implications for prediction of postoperative venous thromboembolism



Increased D-dimer value and occult cancer in the absence of detectable thrombosis

Haematologica 2007; 92:(4)e53-e55

G. Lippi[1], M. Franchini[2], C. Biasiutti[3], G. Dellagiacoma[4], G.L. Salvagno[1], G.C. Guidi[1]*

Although screening for occult cancer in patients with unexplained high D-dimer is not supported by studies on its efficacy on the overall mortality, this diagnostic suspect may offer possible chances for anticipated diagnosis in specific patients with a very high D-dimer level which can not be explained otherwise and who have clues in their medical history suggesting possible malignancy.

Annals of Medicine. 2008; 40: 594–605

REVIEW ARTICLE

Help me, Doctor! My D-dimer is raised

GIUSEPPE LIPPI[1], MASSIMO FRANCHINI[2], GIOVANNI TARGHER[3] & EMMANUEL J. FAVALORO[4]

[1]*Sezione di Chimica e Clinica, Dipartimento di Patologia, Università di Verona, Italy,* [2]*Servizio di Immunoematologia e Trasfusione, Azienda Ospedaliera di Verona, Italy,* [3]*Sezione di Endocrinologia e Malattie del Metabolismo, Dipartimento di Scienze Biomediche e Chirurgiche, Università di Verona, Italy, and* [4]*Department of Haematology and RCPA External Quality Assurance Program, Institute of Clinical Pathology and Medical Research (ICPMR), Westmead Hospital, Westmead, NSW, Australia*

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Intestinal ischaemia
Other vascular disorders
Alzheimer's disease
Acute aortic dissection (AAD)
Thrombosis of vascular accesses
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Sepsis
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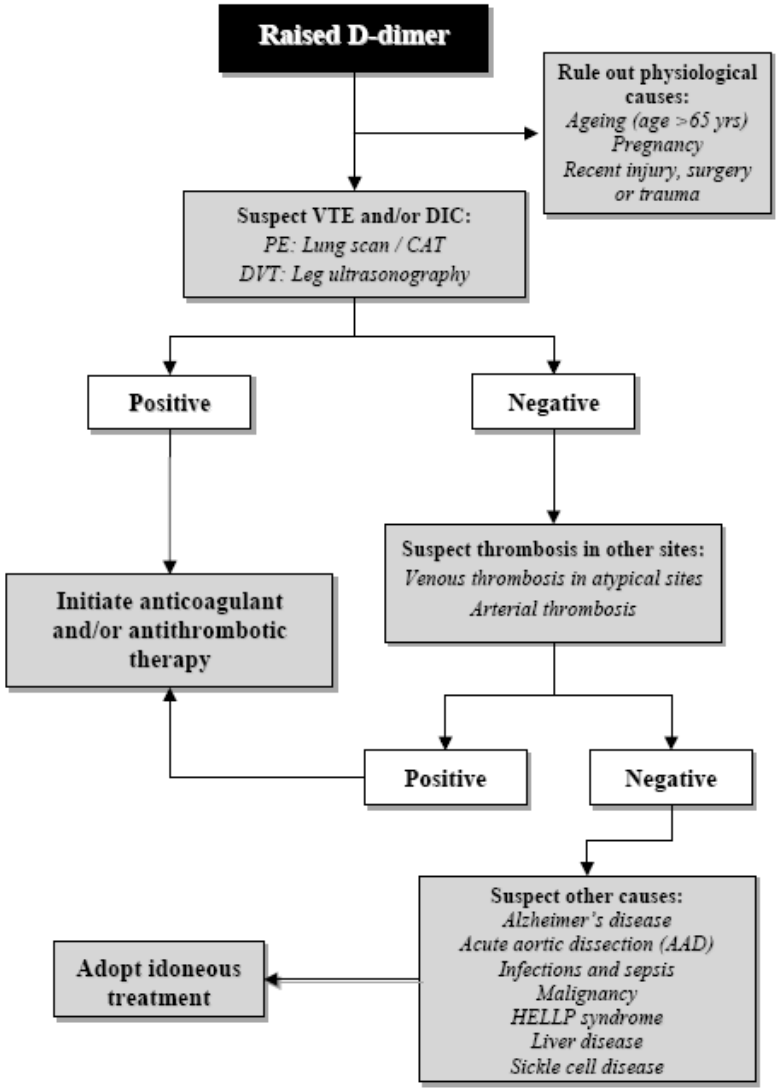
Sickle cell disease
Atrial fibrillation



Preanalytical variability

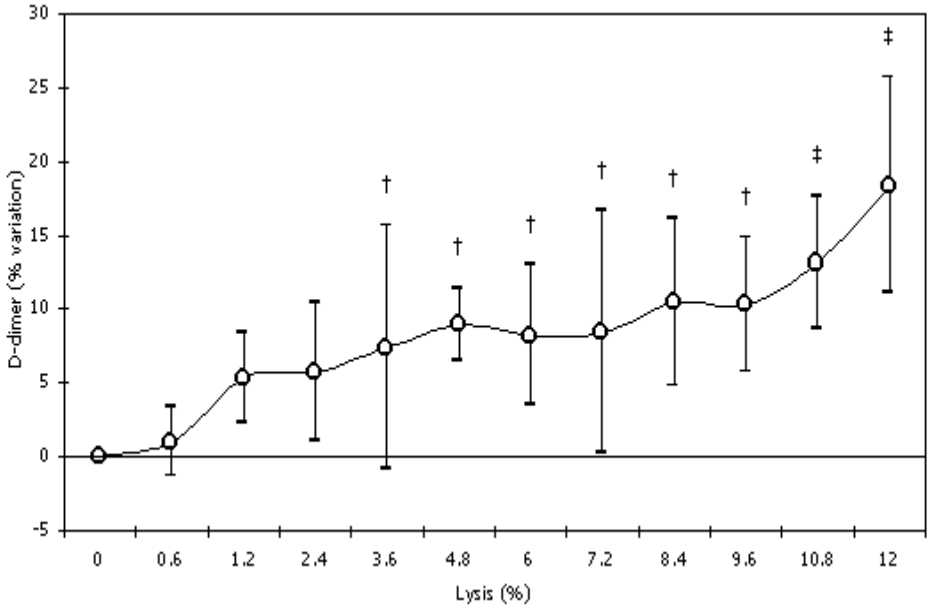
- Venipuncture
- Devices for specimen collection
- Final concentration of the anticoagulant
- Venous stasis
- Haemolysis

(*Arch Pathol Lab Med.* 2006;130:181–184)

Interference of Blood Cell Lysis on Routine Coagulation Testing

Giuseppe Lippi, MD; Martina Montagnana, MD; Gian Luca Salvagno, MD; Gian Cesare Guidi, MD

Conclusions. **-** Results of our investigation confirm that a moderate blood cells lysis, up to 1.2%, might influence the reliability of routine coagulation testing. As these interference in coagulation assays displays a wide interindividual bias, we do not recommend lysis correction and we suggest that the most appropriate corrective measure should be sample rerun.



CASE REPORT:

29/09/2010, sample collected at 8 AM
- D-dimer: 5380 ng/mL

29/09/2010, sample collected at 12 AM
- D-dimer: 285 ng/mL

EXPLANATION:
First Sample **HEMOLYZED!!!**

Semin Thromb Hemost

Diagnostics in Venous Thromboembolism: From Origin to Future Prospects

Giuseppe Lippi, MD[1] Elisa Danese, PhD[2] Emmanuel J. Favaloro, PhD FFSc (RCPA)[3]
Martina Montagnana, MD[2] Massimo Franchini, MD[4]

Table 1 Innovative techniques for diagnosing venous thromboembolism

1. Thrombus-targeted molecular imaging
a. Radioiodinated monoclonal antibodies
b. Small molecules with fibrin affinity
c. Nanoparticles
2. Infrared thermal imaging
3. Thrombin generation
4. Proteomics

EXPERT REVIEWS

Proteomic analysis of venous thromboembolism

Expert Rev. Proteomics 7(2), 275–282 (2010)

Giuseppe Lippi†, Emmanuel J Favaloro and Mario Plebani
†*Author for correspondence*
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ulippi@tin.it;
glippi@ao.pr.it

KEY ISSUES

- **Proteomics is a young field and there are only a handful of published examples applying proteomic analysis to venous thrombosis.**
- **Definition of a fingerprint profile might be useful to assess the individual thrombotic risk and evaluate proteosome modifications in patients with venous thromboembolism.**
- **The advent of high-throughput techniques might further help to understand the complex inter-relationships affecting the hemostatic balance.**
- **There are still some problems to be solved, namely the transfer of basic research applications to the clinical practice and the impact of preanalytical variability.**