LABORATOIRE HOSPITALIER UNIVERSITAIRE DE BRUXELLES
LHUB - ULB
UNIVERSITAIR LABORATORIUM BRUSSEL

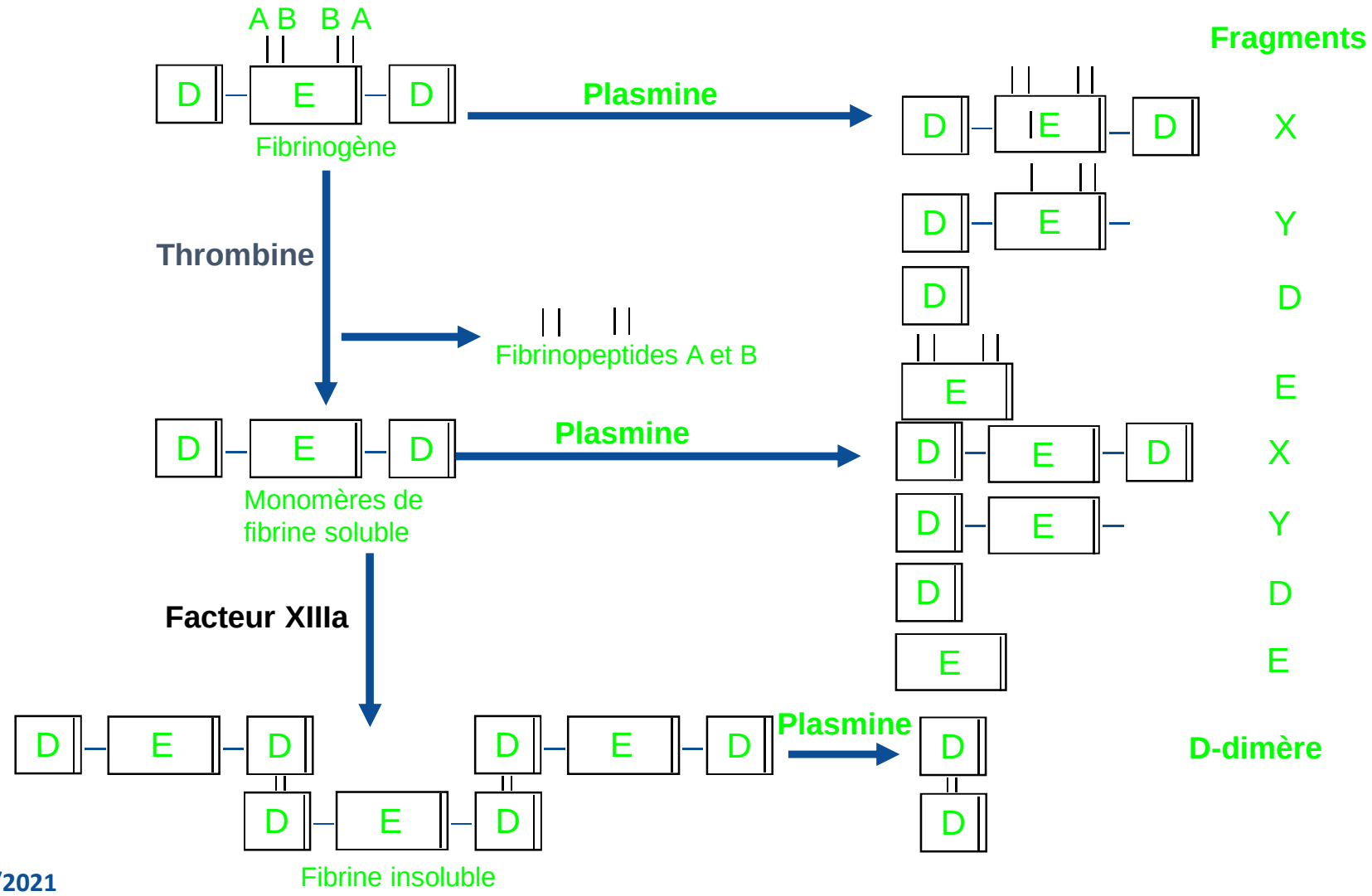
D-Dimères

04/10/2021

D-Dimères

Les D-dimères sont des produits de dégradation de la fibrine.

Ils sont formés à la fin de la cascade de la coagulation lorsque la fibrine est clivée par la plasmine


A B B A
D
E
D
Fibrinogène
Plasmine
Fragments
X
Y
D
E
Thrombine
Fibrinopeptides A et B
Monomères de
fibrine soluble
Plasmine
X
Y
D
E
Facteur XIIIa
Plasmine
D-dimère
Fibrine insoluble

Concentrations plasmatiques

- Faibles quantités détectables chez les individus en bonne santé (intervalle de référence ≠cut-off)
- Taux augmentent
  - avec âge
  - en cas de MTE
- Faible spécificité/MTE

Old age	Stroke
Neonatal period	Peripheral arteriopathy
Pregnancy	Aneurism
Hospitalization	Congestive cardiac failure
Disability	Hemolysis (falciform anemia)
Infection	Hemorrhage
Tumor	Acute respiratory distress syndrome
Recent surgery	Liver or renal disease
Trauma, burns	Inflammatory bowel disease
DIC	Thrombolytic therapy
VTE	Aortic dissection
Ischemic cardiopathy	

Concentrations plasmatiques

- La majorité des patients atteints de MTE ont des D-Dimères élevés
  - Taux varie avec le degré d'importance de la thrombose (thrombose proximale><distale, EP massive)
  - Taux chute au fur et à mesure du délai par rapport à la survenue de la thrombose (thrombose ancienne=> D-Dimères négatifs)
  - Chute rapidement après instauration de l'anticoagulation
    - 24h après traitement par héparine, le taux chute de ± 25%

→ Le test d'autant plus sensible que la thrombose est importante, que les symptômes sont survenus depuis moins d'une semaine.

Le test doit est réalisé avant la mise sous anticoagulant

Indications cliniques

- Diagnostic d'exclusion de l'embolie pulmonaire (EP) et de la thrombose veineuse (VTE) en association avec un pré-test de probabilité clinique.

- Identification des patients à risque de récurrence d'EP et VTE après un traitement anticoagulant.

- *(Diagnostic et monitoring de la coagulation intravasculaire disséminée -DIC)*

Tests disponibles au laboratoire

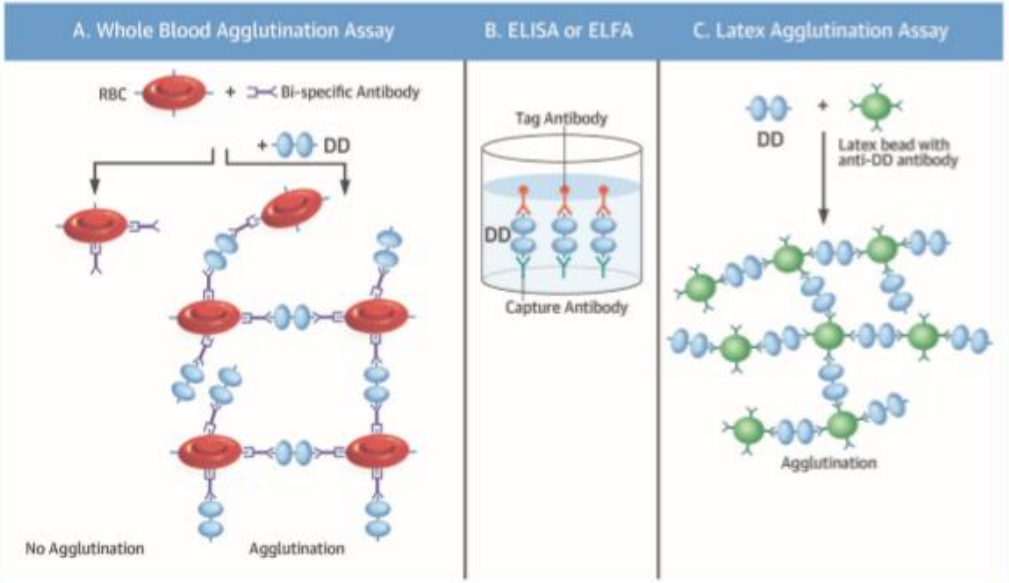
Il existe toute une série de tests disponibles sur le marché: mais le test est non standardisé (valeurs non comparables d'un laboratoire à l'autre)

Deux catégories:

- Tests de haute sensibilité: 95% ou plus mais faible spécificité (± 40/45%)
- Tests de sensibilité modérée (80-94%), mais meilleure spécificité (±70%)

D-dimères: Principes de mesure et test disponibles

CENTRAL ILLUSTRATION Diagnostic Assays for D-Dimer Quantification



Weitz, J.I. et al. J Am Coll Cardiol. 2017;70(19):2411-20.

(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.

TABLE 1 Performance Characteristics of Commercially Available D-Dimer Assays for Detection of VTE

Assay	Sensitivity, % (95% CI)	Specificity, % (95% CI)	Negative Predictive Value, % (95% CI)
Whole blood			
SimplyRed	75 (63–87)	83 (77–89)	89 (82–97)
ELISA			
Asserachrome	95 (83–98)	45 (29–65)	97 (95–100)
Instant IA	87 (59–96)	65 (43–81)	91 (84–93)
ELFA			
Vidas	96 (88–99)	57 (54–61)	99 (98–100)
Latex			
Tina-quant	95 (78–100)	61 (55–67)	99 (97–100)
STA-Liatest	95 (78–100)	48 (42–55)	99 (96–100)

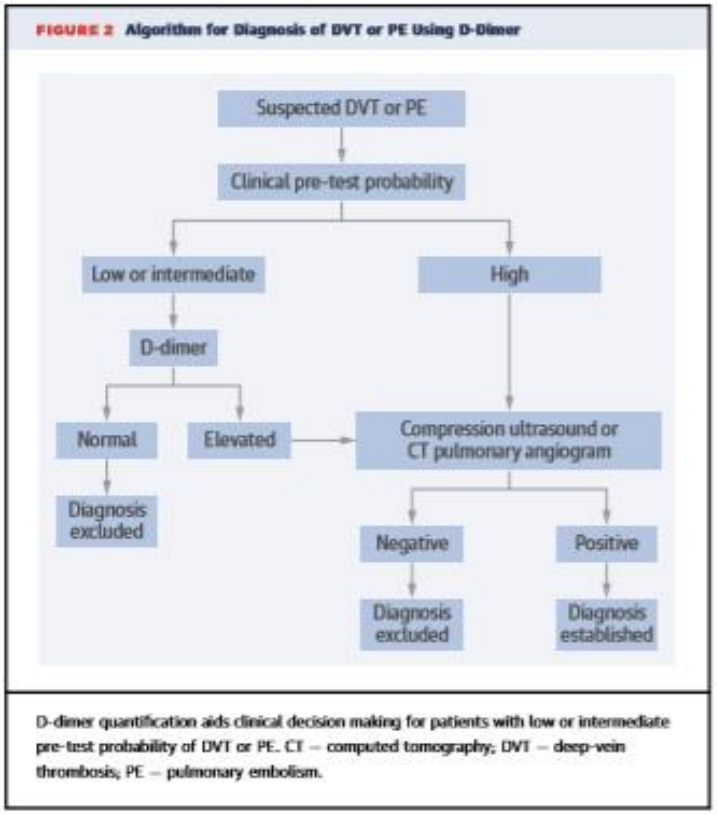
Adapted from Di Nisio et al. (14) and manufacturers' data. Sensitivity, specificity, and negative predictive value can vary depending on the prevalence of VTE in the study's population.

CI = confidence interval; ELFA = enzyme-linked immunofluorescence assay; ELISA = enzyme-linked immunosorbent assay; VTE = venous thromboembolism.

LABORATOIRE HOSPITALIER UNIVERSITAIRE DE BRUXELLES
LHUB - ULB
UNIVERSITAIR LABORATORIUM BRUSSEL

Diagnostic d'exclusion de l'embolie pulmonaire (EP) et de la thrombose veineuse (VTE) en association avec un pré-test de probabilité clinique.

4 October 2021



D-Dimère < cut-off permet d'exclure EP et VTE chez patients avec score faible ou intermédiaire.
En présence d'un score élevé, les D-dimères ont une faible VPN -> imagerie en première intention.

Weitz et al 2017

Performance des tests

- Si la SENSIBILITE d'un test est égale à 98% et que sa SPECIFICITE est égale à 45%, pour un test quantitatif avec une valeur seuil de 500 ng/ml:
- Cela veut dire que, sur 100 patients avec MTE, 98 auront un test positif (98% de vrais positifs) et 2 auront un test négatif (2% de faux négatifs).
- Pour 100 patients qui n'ont pas de MTE, 45 auront un test négatif (45% de vrais négatifs) et 55 auront un test positif (55% de faux positifs).

Performance des tests

Le plus important est de déterminer

- Åquel est le % de vrais négatifs sur l'ensemble des tests négatifs (Valeur Prédictive Négative)
- Åquel est le % de vrais positifs sur l'ensemble des tests positifs (Valeur Prédictive Positive ou VPP)
- ÅPour ce faire, vous devez connaître la probabilité a priori ou pré-test de la MTE pour votre patient ou la prévalence de MTE dans une population de cas similaires.

Performance des tests

Prévalence de 25%
Sensibilité 98% et Spécificité 45%
n= 1000 patients

	TEST +	**test –**	
Embolie pulmonaire N=250	**245**	5	sensibilité 245/250= **98%**
Pas d'embolie pulmonaire N=750	412	**338**	spécificité 338/750= **45%**
	657	**343**	

VAL. PRED. POS = 245/657= **37%** **val.pred.nég** = 338/343= **97%**

Que se passe-t-il si la prévalence ou probabilité pré-test varie ?

Prévalence (Probabilité pré-test)	5%	25%	70%
Valeur prédictive positive	9%	37%	81%
Valeur prédictive négative	100%	98.5%	91%

EP: Probabilité clinique

Score de WELLS*	
Antécédents personnels d'EP ou TVP	+ 1,5
Chirurgie ou immobilisation <4 semaines	+ 1,5
Cancer actif	+ 1
Hémoptysie	+ 1
FC > 100/min	+ 1,5
Signes de TVP	+ 3
Diag. alternatif - probable que celui d'EP	+ 3
Score de Wells	
Probabilité clinique : ☐ ***faible (0-1)*** ☐ ***intermédiaire (2- 6)*** ☐ ***forte (≥ 7)***	

On définit 3 classes de probabilité clinique (prétest) associées à des prévalences distinctes d'EP.

- probabilité clinique faible: prévalence de l'EP < 10%
- probabilité clinique intermédiaire: prévalence de l'EP 30-40%%
- probabilité clinique forte: prévalence de l'EP >60-70%.

VTE: probabilité clinique

Cancer actif (dernier traitement ≤ 6 mois, ou palliatif)	+ 1
Paralysie, parésie ou plâtre d'un membre inférieur	+ 1
Alitement de plus de 3 jours ou chirurgie majeure de moins de 4 semaines	+ 1
Douleur sur un trajet veineux	+ 1
Œdème de tout le membre inférieur	+ 1
Circonférence du mollet atteint >3 cm par rapport au mollet controlatéral (mesuré 10 cm sous la tubérosité tibial antérieure)	+ 1
Œdème prenant le godet du côté symptomatique	+ 1
Circulation veineuse collatérale superficielle (veines non variqueuses)	+ 1
Diagnostic alternatif au moins aussi probable que le diagnostic de TVP	-2
score < 2 : probabilité faible score ≥ 2 : probable	

Score >3: forte

On définit 3 classes de probabilité clinique (prétest) associées à des prévalences distinctes d'EP.

- probabilité clinique faible: prévalence de la VTE < 10%
- probabilité clinique intermédiaire: prévalence de la VTE 30-40%
- probabilité clinique forte: prévalence de la VTE>60-70%.

Score de Wells et TVP

Table 1. Wells score for DVT clinical pretest probability

	Number of points	Proportion of patients	Prevalence of PE
Variables			
Active cancer (treatment ongoing or within previous 6 mo or palliative)	1		
Paralysis, paresis, or recent plaster immobilization of the lower extremities	1		
Recently bedridden >3 d or major surgery within 4 wks	1		
Localized tenderness along the distribution of the deep venous system	1		
Entire leg swollen	1		
Calf swelling 3 cm greater than on asymptomatic side (measured 10 cm below tibial tuberosity)	1		
Pitting edema confined to the symptomatic leg	1		
Dilated superficial veins (nonvaricose)	1		
Previous documented DVT (or PE)	1		
Alternative diagnosis as likely or greater than that of DVT	−2		
Score interpretation			
High probability*	≥3	10%	60%
Moderate probability*	1 or 2	30%	25%
Low probability†	≤0	60%	5%

*A score of ≥2 has been termed "DVT likely." This group makes up ~40% of patients and has a prevalence of DVT of ~33%.
†A score of ≤1 has been termed "DVT unlikely." This group makes up ~75% of patients and has a prevalence of DVT of ~10%. The original Wells DVT model was for a first suspected DVT and, therefore, did not include a score for previous VTE.

Score de Wells et EP

Table 2. Wells score for PE clinical pretest probability

	Number of points	Proportion of patients	Prevalence of PE
Variables			
Clinically suspected DVT	3		
Alternative diagnosis is less likely than PE	3		
Heart rate >100 beats/min	1.5		
Immobilization or surgery in previous 4-wk period	1.5		
History of VTE	1.5		
Hemoptysis	1		
Malignancy or treatment of it in previous 6-mo period	1		
Score interpretation			
High probability*	≥6.5	10%	60%
Moderate probability*	4.5-6.0	30%	25%
Low probability†	≤4.0	60%	5%

*A score of ≥4.5 (moderate and high probability groups combined) has been termed "PE likely." This group makes up ~40% of patients and has a prevalence of PE of ~33%.
†Is also termed "PE unlikely." In the original derivation of the Wells PE model, patients were required to have a score of ≤1.5 to be categorized as low probability, but a score of ≤4 has subsequently been used for low probability.[8,9]

D-Dimères: Valeurs seuils de positivité

- Traditionnellement déterminées par le fabricant
- ≠ de la valeur supérieure de l'intervalle de référence usuel pour ce test
- Fixé à un niveau bas pour augmenter la sensibilité et diminuer le risque de rater les patients atteints de MTE: 500 ng/ml (traditionnel)

2 modifications testées pour augmenter la spécificité du test

- Ajustement en fonction du niveau du pré-test de probabilité clinique
  - Faible prévalence de la MTE en cas de faible probabilité du score clinique *(Linkins et al, 2013)*
- Valeur cut-off ajustée à l'âge *(ADJUST-PE study, 2014)*

Valeurs seuils ajustées au pré-test de probabilité clinique

- Cette approche «ajustée au pré-test» de l'interprétation des D-dimères a été validée de manière prospective chez les patients suspectés de MTE *(Linkins et al, 2013)* et
- récemment pour l'EP *(NEJM dec 2019)*
- seuil de D-dimère, 1000 ng / mL pour exclure la MTE chez les patients avec un pré-test faible car ils ont une faible prévalence de la maladie.
- Le seuil de D-dimère de 500 ng / mL chez les patients avec un pré-test modéré est conservé

Selective D-dimer testing for diagnosis of a first suspected episode of deep venous thrombosis: a randomized trial.

Linkins LA[1], Bates SM, Lang E, Kahn SR, Douketis JD, Julian J, Parpia S, Gross P, Weitz JI, Spencer FA, Lee AY, O'Donnell MJ, Crowther MA, Chan HH, Lim W, Schulman S, Ginsberg JS, Kearon C.

BACKGROUND: D-Dimer testing is sensitive but not specific for diagnosing deep venous thrombosis (DVT). Changing the use of testing and the threshold level for a positive test result on the basis of risk for DVT might improve the tradeoff between sensitivity and specificity and reduce the need for testing.

OBJECTIVE: To determine whether using a selective D-dimer testing strategy based on clinical pretest probability (C-PTP) for DVT is safe and reduces diagnostic testing compared with using a single D-dimer threshold for all patients.

DESIGN: Randomized, multicenter, controlled trial. Patients were allocated using a central automated system. Ultrasonographers and study adjudicators but not other study personnel were blinded to trial allocation. (ClinicalTrials.gov: NCT00157677)

SETTING: 5 Canadian hospitals.

PATIENTS: Consecutive symptomatic patients with a first episode of suspected DVT.

INTERVENTION: Selective testing (n = 860), defined as D-dimer testing for outpatients with low or moderate C-PTP (DVT excluded at D-dimer levels <1.0 µg/mL [low C-PTP] or <0.5 µg/mL [moderate C-PTP]) and venous ultrasonography without D-dimer testing for outpatients with high C-PTP and inpatients, or uniform testing (n = 863), defined as D-dimer testing for all participants (DVT excluded at D-dimer levels <0.5 µg/mL).

MEASUREMENTS: The proportion of patients not diagnosed with DVT during initial testing who had symptomatic venous thromboembolism during 3-month follow-up and the proportion of patients undergoing D-dimer testing and ultrasonography.

RESULTS: The incidence of symptomatic venous thromboembolism at 3 months was 0.5% in both study groups (difference, 0.0 percentage point [95% CI, -0.8 to 0.8 percentage points]). Selective testing reduced the proportion of patients who required D-dimer testing by 21.8 percentage points (CI, 19.1 to 24.8 percentage points). It reduced the proportion who required ultrasonography by 7.6 percentage points (CI, 2.9 to 12.2 percentage points) overall and by 21.0 percentage points (CI, 14.2 to 27.6 percentage points) in outpatients with low C-PTP.

LIMITATION: Results may not be generalizable to all D-dimer assays or patients with previous DVT, study personnel were not blinded, and the trial was stopped prematurely.

CONCLUSION: A selective D-dimer testing strategy seems as safe as and more efficient than having everyone undergo D-dimer testing when diagnosing a first episode of suspected DVT.

BACKGROUND

Retrospective analyses suggest that pulmonary embolism is ruled out by a D-dimer level of less than 1000 ng per milliliter in patients with a low clinical pretest probability (C-PTP) and by a D-dimer level of less than 500 ng per milliliter in patients with a moderate C-PTP.

METHODS

We performed a prospective study in which pulmonary embolism was considered to be ruled out without further testing in outpatients with a low C-PTP and a D-dimer level of less than 1000 ng per milliliter or with a moderate C-PTP and a D-dimer level of less than 500 ng per milliliter. All other patients underwent chest imaging (usually computed tomographic pulmonary angiography). If pulmonary embolism was not diagnosed, patients did not receive anticoagulant therapy. All patients were followed for 3 months to detect venous thromboembolism.

RESULTS

A total of 2017 patients were enrolled and evaluated, of whom 7.4% had pulmonary embolism on initial diagnostic testing. Of the 1325 patients who had a low C-PTP (1285 patients) or moderate C-PTP (40 patients) and a negative D-dimer test (i.e., <1000 or <500 ng per milliliter, respectively), none had venous thromboembolism during follow-up (95% confidence interval [CI], 0.00 to 0.29%). These included 315 patients who had a low C-PTP and a D-dimer level of 500 to 999 ng per milliliter (95% CI, 0.00 to 1.20%). Of all 1863 patients who did not receive a diagnosis of pulmonary embolism initially and did not receive anticoagulant therapy, 1 patient (0.05%; 95% CI, 0.01 to 0.30) had venous thromboembolism. Our diagnostic strategy resulted in the use of chest imaging in 34.3% of patients, whereas a strategy in which pulmonary embolism is considered to be ruled out with a low C-PTP and a D-dimer level of less than 500 ng per milliliter would result in the use of chest imaging in 51.9% (difference, –17.6 percentage points; 95% CI, –19.2 to –15.9).

CONCLUSIONS

A combination of a low C-PTP and a D-dimer level of less than 1000 ng per milliliter identified a group of patients at low risk for pulmonary embolism during follow-up. (Funded by the Canadian Institutes of Health Research and others; PEGeD ClinicalTrials.gov number, NCT02483442.)

The NEW ENGLAND JOURNAL *of* MEDICINE

ORIGINAL ARTICLE

Diagnosis of Pulmonary Embolism with D-Dimer Adjusted to Clinical Probability

N ENGL J MED 381;22 NEJM.ORG NOVEMBER 28, 2019

Valeurs seuils ajustées à l’ âge

- Il a également été proposé d'utiliser un seuil de dimère de 500 ng / mL pour exclure la MTE chez les patients de 50 ans ou moins
- Un seuil égal à l'âge du patient X 10 (par exemple, 750 mg / L ou ng/ml à 75 ans) chez ceux de plus de 50 ans, augmenteront la spécificité de test du D-dimère sans compromettre la sensibilité
- Cette approche «ajustée en fonction de l'âge» de l'interprétation du D-dimère a été validée de manière prospective chez les patients suspects d'EP.

IMPORTANCE D-dimer measurement is an important step in the diagnostic strategy of clinically suspected acute pulmonary embolism (PE), but its clinical usefulness is limited in elderly patients.

OBJECTIVE To prospectively validate whether an age-adjusted D-dimer cutoff, defined as age × 10 in patients 50 years or older, is associated with an increased diagnostic yield of D-dimer in elderly patients with suspected PE.

DESIGN, SETTINGS, AND PATIENTS A multicenter, multinational, prospective management outcome study in 19 centers in Belgium, France, the Netherlands, and Switzerland between January 1, 2010, and February 28, 2013.

INTERVENTIONS All consecutive outpatients who presented to the emergency department with clinically suspected PE were assessed by a sequential diagnostic strategy based on the clinical probability assessed using either the simplified, revised Geneva score or the 2-level Wells score for PE; highly sensitive D-dimer measurement; and computed tomography pulmonary angiography (CTPA). Patients with a D-dimer value between the conventional cutoff of 500 µg/L and their age-adjusted cutoff did not undergo CTPA and were left untreated and formally followed-up for a 3-month period.

MAIN OUTCOMES AND MEASURES The primary outcome was the failure rate of the diagnostic strategy, defined as adjudicated thromboembolic events during the 3-month follow-up period among patients not treated with anticoagulants on the basis of a negative age-adjusted D-dimer cutoff result.

RESULTS Of the 3346 patients with suspected PE included, the prevalence of PE was 19%. Among the 2898 patients with a nonhigh or an unlikely clinical probability, 817 patients (28.2%) had a D-dimer level lower than 500 µg/L (95% CI, 26.6%-29.9%) and 337 patients (11.6%) had a D-dimer between 500 µg/L and their age-adjusted cutoff (95% CI, 10.5%-12.9%). 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%]). Among the 766 patients 75 years or older, of whom 673 had a nonhigh clinical probability, using the age-adjusted cutoff instead of the 500 µg/L cutoff increased the proportion of patients in whom PE could be excluded on the basis of D-dimer from 43 of 673 patients (6.4% [95% CI, 4.8%-8.5%]) to 200 of 673 patients (29.7% [95% CI, 26.4%-33.3%]), without any additional false-negative findings.

CONCLUSIONS AND RELEVANCE Compared with a fixed D-dimer cutoff of 500 µg/L, the combination of pretest clinical probability assessment with age-adjusted D-dimer cutoff was associated with a larger number of patients in whom PE could be considered ruled out with a low likelihood of subsequent clinical venous thromboembolism.

Original Investigation

Age-Adjusted D-Dimer Cutoff Levels to Rule Out Pulmonary Embolism

The ADJUST-PE Study

JAMA March 19, 2014 Volume 311, Number 11

Table: Summary of Findings

	Pre-Implementation	Post-Implementation
Total No. of D-dimer tests	422	290
Positive D-dimer	273 (64.6%)	65 (22.4%)
Positive D-dimer and VTE confirmed	21 (5%)	25 (9%)
Negative D-dimer	149 (35.4%)	225 (77.6%)
Negative D-dimer and VTE confirmed	2	0

Conclusion: Proportion of patients with positive D-dimer results had significantly reduced using age-adjusted reporting. Total number of VTE cases was comparable between the two periods but diagnostic yield from radiological investigations increased from 11% to 22% following introduction of age-adjusted assay. Our audit did not reveal any VTE diagnosis being missed with new reporting method in negative D-dimer group. From our experience, clinical utility of D-dimer was enhanced following introduction of age-adjusted assay with subsequent increase in its specificity and reduction in radiological investigations requested to out-rule VTE. The new method also prevents patients from having unnecessary investigations with potential cost-saving benefits. The study did not find any evidence of compromising clinical efficacy in out-ruling VTE.

Sarah Kelliher, MBBS,Pearce Sharon, MSc,Breda Melvin, MSc,Su Wai Maung, MD, Review of Clinical Utility of Age-Adjusted D-Dimer Assay, Blood, 2019,

Review of Clinical Utility of Age-Adjusted D-Dimer Assay

Clinical Pre-Test Probability Adjusted vs. Age Adjusted D-dimer Interpretation Strategy For DVT Diagnosis: A Diagnostic Individual Patient Data Meta-Analysis

Sameer Parpia[1,2], Sarah Takach Lapner[3], Roger Schutgens[4], Johan Elf[5], Geert-Jan Geersing[4], Clive Kearon[6,7]

doi: 10.1111/jth.14718 , JTH 2020

ESSENTIALS

- It is uncertain which of the clinical pre-test probability adjusted or age-adjusted D-dimer interpretation is better at ruling out DVT
- Diagnostic individual patient data meta-analysis was conducted
- Both interpretations have similar NPVs and specificity
- Both interpretations have superior specificity and utility compared with the stand alone D-dimer interpretation

LABORATOIRE HOSPITALIER UNIVERSITAIRE DE BRUXELLES
LHUB - ULB
UNIVERSITAIR LABORATORIUM BRUSSEL

Identification des patients à risque de récurrence d'EP et VTE après un traitement anticoagulant.

4 October 2021

Quelle est la durée optimale de l'anticoagulation après un premier épisode de MTE idiopathique?

- Anticoagulation:
  - Diminue le risque de récidive
  - Augmente le risque de saignement
- Comment identifier les patients à haut risque de récurrence?
- Idéalement : biomarqueur spécifique qui permettrait d'exclure la récidive
- D-dimère dosés au moment de l'arrêt du traitement: prédictif d'une récidive?

D-Dimères et prédiction du risque de VTE récurrente

Risque de récidive après une MTE idiopathique

- Å 10% après 1 an
- Å 50% après 5ans

ÅD_Dimères élevés après 3 mois de traitement chez les patients avec un premier épisode de MTE idiopathique

- ÅRisque de récidive: plus de X2 / D-Dimères normaux

Méta-analyse portant sur 7 études

Risque annuel de récurrence chez ces patients

- 3.5 %/ an: pour patients avec D-dimères < cut-off
- 8.9%/an : pour patients avec D-dimères > cut-off

Verhovsek M, Douketis JD, Yi Q, et al. Systematic review: D-dimer to predict recurrent disease after stopping anticoagulant therapy for unprovoked venous thromboembolism. Ann Intern Med 2008;149:481–90.

CLINICAL TRIALS AND OBSERVATIONS

D-dimer to guide the duration of anticoagulation in patients with venous thromboembolism: a management study

Gualtiero Palareti,[1] Benilde Cosmi,[1] Cristina Legnani,[1] Emilia Antonucci,[2] Valeria De Micheli,[3] Angelo Ghirarduzzi,[4] Daniela Poli,[2] Sophie Testa,[5] Alberto Tosetto,[6] Vittorio Pengo,[7] and Paolo Prandoni,[8] on behalf of the DULCIS (D-dimer and ULtrasonography in Combination Italian Study) Investigators

[1]Angiology and Blood Coagulation, University Hospital of Bologna, Bologna, Italy; [2]Thrombosis Centre, Department Heart and Vessels, University Hospital of Florence, Florence, Italy; [3]Haemostasis and Thrombosis Centre, Hospital of Lecco, Lecco, Italy; [4]Internal Medicine, ASMN-IRCCS-Reggio Emilia, Reggio nell'Emilia, Italy; [5]Haemostasis and Thrombosis Centre, Hospital of Cremona, Cremona, Italy; [6]Haematology and Thrombosis Centre, Hospital of Vicenza, Vicenza, Italy; and [7]Department of Cardiothoracic and Vascular Sciences and [8]Internal Medicine, Department of Medical and Surgical Sciences, University Hospital of Padua, Padua, Italy

Key Points

- The duration of anticoagulation after VTE is uncertain; this management study intended to identify patients with low/high recurrence risk.
- Patients with persistently negative D-dimers after stopping standard therapy have a low recurrence risk and can stop anticoagulation.

The optimal duration of anticoagulation in patients with venous thromboembolism (VTE) is uncertain. We investigated whether persistently negative D-dimers in patients with vein recanalization or stable thrombotic burden can identify subjects at low recurrence risk. Outpatients with a first VTE (unprovoked or associated with weak risk factors) were eligible after at least 3 months (12 in those with residual thrombosis) of anticoagulation. They received serial D-dimer measurements using commercial assays with predefined age/sex-specific cutoffs and were followed for up to 2 years. Of 1010 patients, anticoagulation was stopped in 528 (52.3%) with persistently negative D-dimer who subsequently experienced 25 recurrences (3.0% pt-y; 95% confidence interval [CI], 2.0-4.4%). Of the remaining 482 patients, 373 resumed anticoagulation and 109 refused it. Recurrent VTE developed in 15 patients (8.8% pt-y; 95% CI, 5.0-14.1) of the latter group and in 4 of the former (0.7% pt-y; 95% CI, 0.2-1.7; hazard ratio = 2.92; 95% CI, 1.87-9.72; $P = .0006$). Major bleeding occurred in 14 patients (2.3% pt-y; 95% CI, 1.3-3.9) who resumed anticoagulation. Serial D-dimer measurement is suitable in clinical practice for the identification of VTE patients in whom anticoagulation can be safely discontinued. This study was registered at clinicaltrials.gov as #NCT00954395.
(*Blood*. 2014;124(2):196-203)

BLOOD, 10 JULY 2014 x
VOLUME 124, NUMBER 2

Patients after 12 mo VKA, to repeat D-dimer testing after 15 to 18 days (T15), 25 to 35 (T30),55 to 65 (T60), and 85 to 95 (T90) days from T0. Patients were recommended to resume anticoagulation at the first positive D-dimer result.

Age and sex specific cutoff values were calculated for risk of recurrence and used in the tests, instead of those recommended by the manufacturers for VTE exclusion.

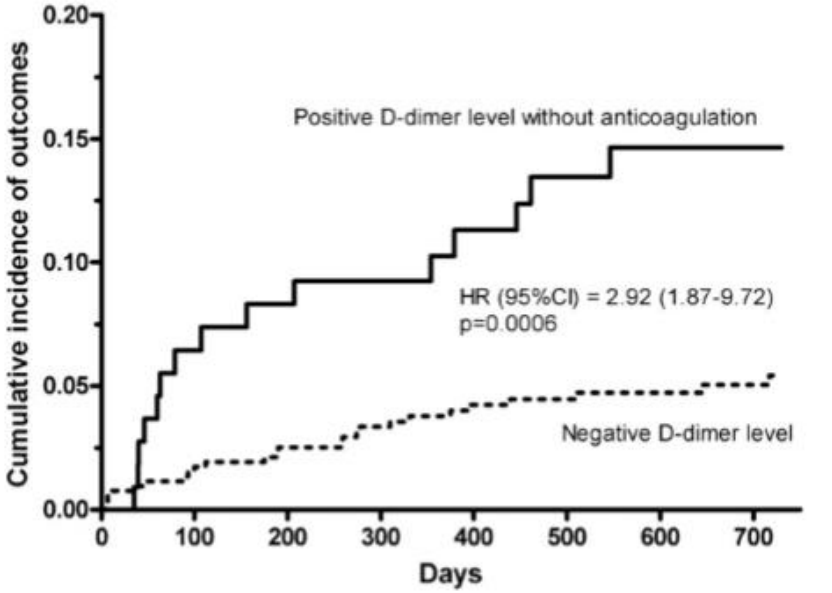


Figure 3. Kaplan-Meier cumulative event rates for the primary efficacy outcome in patients with persistently negative D-dimer results in whom anticoagulation was definitively stopped (dotted line) and in those with positive D-dimer results who refused to resume anticoagulation (continuous line).

RESEARCH ARTICLE

D-dimer levels during and after anticoagulation withdrawal in patients with venous thromboembolism treated with nonvitamin K anticoagulants

Cristina Legnani et al Plos one 2019

D-dimer levels were measured in 527 patients (ñcasesò) **during DOACs** treatment (T0) and after 15 (T15), 30 (T30), 60 (T60) and 90 (T90) days after their discontinuation and in **527** patients (ñcontrolsò) enrolled in the DULCIS study (**all treated with warfarin**), matched for sex, age (+/-3 y), type of D-dimer assay and site of venous thromboembolism. Both cases and controls received anticoagulant treatment after a first venous thromboembolism event that was unprovoked or associated with weak risk factors

The rate of positive D-dimer results was significantly **higher i**n cases than in controls at T0 (10.8% vs 5.1%, p = 0.002) and at T30 (18.8% vs 11.8%, p = 0.019), as well as at the other time-points, though not statistically significant

D-dimer levels during and after stopping an anticoagulant treatment for a venous thromboembolism episode differ between patients treated with a DOAC than in those treated with warfarin.
Specifically designed prospective studies are warranted to reassess the use of Ddimer as predictor of the risk of recurrent venous thromboembolism in patients treated with DOACs.

Conclusion

- Le dosage des D–dimères est un test largement utilisé lors d'une suspicion de MTE chez un patient ambulant.
- C'est un test rapide, automatisé, simple à réaliser.
- L'utilisation d'un test quantitatif a haute sensibilité (>95%) et haute valeur prédictive négative (97%) est recommandé
- Etant donné sa faible spécificité:
  - le test doit être combiné à **un score clinique dans le diagnostic d'exclusion de la MTE**.
  - La positivité du test n'est pas le seul facteur à considérer comme aide décisionnelle à la reprise d'un traitement anticoagulant après un premier épisode de MTE idiopathique

- DD à interpréter de manière délicate surtout dans certaines situations cliniques (personnes âgées, patients cancéreux, patients hospitalisés) .
- Le cut-off est essai dépendant et ne peut être extrapolé d'une étude à l'autre ou d'une situation clinique à l'autre si le test utilisé n'est pas le même.

Controverses..

- Quand tester les d-dimères après arrêt des anticoagulants?
  - 3 semaines, 2 mois, autre?
- Quel seuil utiliser?

Douketis J, Tosetto A, Marcucci M, et al. Patient-level meta-analysis: effect of measurement timing, threshold, and patient age on ability of D-dimer testing to assess recurrence risk after unprovoked venous thromboembolism. *Ann Intern Med*. 2010;153:523-531.

- D_Dimères négatifs après 3 mois d'anticoagulation
  - Ne prévoit pas un risque plus bas de récidive chez l'homme avec la même précision que chez la femme

Prédiction du risque de récurrence: recommandations?

- Associer le test à un score clinique *(DASH, HERDOO2, Vienna prediction model)*
- Une revue systématique récente a mis en lumière les limites de ces scores, l'absence de validation suffisante et l'impossibilité de les implémenter actuellement en routine clinique

Scores proposés pour estimer le risque de récidive après arrêt du traitement anticoagulant suite à un épisode de MTEV idiopathique			
Score	HERDOO2	Vienna	DASH
Predicteurs			
D-Dimer	X	X	X
Âge	X	-	X
Sexe	-	X	X
BMI	X	-	-
Syndrome post-thrombotique	X	-	-
Site de la thrombose	-	X	-
Hormonothérapie	-	-	X

Ensor et al J., Riley, R.D., Moore, D., Snell, K.I., Bayliss, S., Fitzmaurice, D. Systematic review of prognostic models for recurrent venous thromboembolism (VTE) post-treatment of first unprovoked VTE. Brit Med J Open, 2016, 6 (5): e011190.

Paramètres à prendre en compte pour identifier les patients candidats à une anticoagulation prolongée après une MTEV
Circonstances de survenue de la TVP/EP (Idiopathique versus circonstancielle)
Sévérité de l'accident thrombotique
Risques hémorragiques
Accidents thrombotiques antérieurs
Maladie inflammatoire chronique ou néoplasique sous-jacente
Antécédents familiaux / Thrombophilie (type et pénétrance au sein de la famille)
D-Dimères élevés après arrêt du traitement anticoagulant
Persistance de thrombi résiduels / hypertension artérielle pulmonaire résiduelle / maladie pulmonaire sous-jacente éventuelle
Qualité du traitement anticoagulant (AVK, AOD)
Préférences du patient
Compliance
Coût du traitement, remboursement

CIVD: Définition

- Syndrome acquis caractérisé par une activation anormale de la coagulation par le FT ou par une exposition aux endotoxines bactériennes dépassant les mécanismes régulateurs.

- Il en résulte :
  - Une génération excessive de thrombine
  - Une diminution de la concentration plasmatique de plusieurs facteurs de coagulation dont le fibrinogène
  - Le dépôt de fibrine dans la microcirculation
  - L'épuisement des facteurs pro et anticoagulants
  - L'activation du système fibrinolytique.

CIVD: facteurs déclenchants

Vascular Damage Leading to Release of Tissue Factor
Bacterial sepsis
Gram negative organisms
Meningococcus
Pneumococcus
Clostridia
Metabolic stress
Acidosis
Shock
Heat stroke
Release of Tissue Factor from Injured or Pathologic Tissue
Obstetrical complications
Placental abruption
Retained placenta/fetus
Placenta previa
Amniotic fluid embolus
Pre-eclampsia/eclampsia
Malignancies
Solid tumors, mucin-secreting adenocarcinomas
Acute promyelocytic leukemia
Severe burns

DIC

DIC = coagulation intravasculaire disséminée

« DIC is an acquired syndrome characterized by the intravascular activation of coagulation with loss of localization arisinf from different causes. It can originate from and cause damage to the microvasculature, which if sufficiently severe, can produce organ dysfunction. » *Taylor FB, Toh CH, Hoots WK, et al. Towards definition, clinical and laboratory criteria, and a scoring system for disseminated intravascular coagulation. Thromb Haemost 2001;86:1327–30.*

Différentes causes cliniques : sepsis, complications de la grossesse, malignité, ….

DIC : phénomène secondaire avec présence de signes cliniques et d'anomalies biologiques

CHU | UVC BRUGMANN

DIC

Score (DIC SSC ISTH)

Table 1 Scoring system for overt Disseminated Intravascular Coagulation (DIC)

1. Risk assessment: does the patient have an underlying disorder known to be associated with overt DIC?

   If yes: Proceed.

   If no: Do not use this algorithm.

2. Order global coagulation tests (platelet count, prothrombin time, fibrinogen, fibrin-related marker).

3. Score global coagulation test results.

- Platelet count
  (>100 = 0; <100 = 1; < 50 = 2)
- Elevated fibrin related marker (e.g. D-dimers; fibrin degradation products)
  (no increase = 0; moderate increase = 2; strong increase = 3)
- Prolonged prothrombin time
  (< 3 s = 0; > 3 but < 6 s = 1; > 6 s = 2)
- Fibrinogen level
  (>1.0 g L^{-1} = 0; < 1.0 g L^{-1} = 1)

5. Calculate score

If ≥ 5: compatible with overt DIC: repeat score daily

If < 5: suggestive (not affirmative) for non-overt DIC: repeat next 1–2 days.

Table 2 Scoring system for non-overt Disseminated Intravascular Coagulation (DIC)

1. Risk assessment: does the patient have an underlying disorder known to be associated with DIC?
   yes = 2, no = 0

2. Major criteria

Platelet Count	>100x10^9 l^{-1} = 0	<100x10^9 l^{-1} = 1
PT Prolongation	<3 s = 0	>3 s = 1
Fibrin related-markers	Normal = 0	Raised = 1

Rising = −1	Stable = 0	Falling = 1
Falling = −1	Stable = 0	Rising = 1
Falling = −1	Stable = 0	Rising = 1

3. Specific criteria

Antithrombin	Normal = −1	Low = 1
Protein C	Normal = −1	Low = 1
---------	Normal = −1	Abnormal = 1

4. Calculate score:

Taylor FB, Toh CH, Hoots WK, et al. Towards definition, clinical and laboratory criteria, and a scoring system for disseminated intravascular coagulation. Thromb Haemost 2001;86:1327–30.

DIC

Patients à l'USI avec choc septique

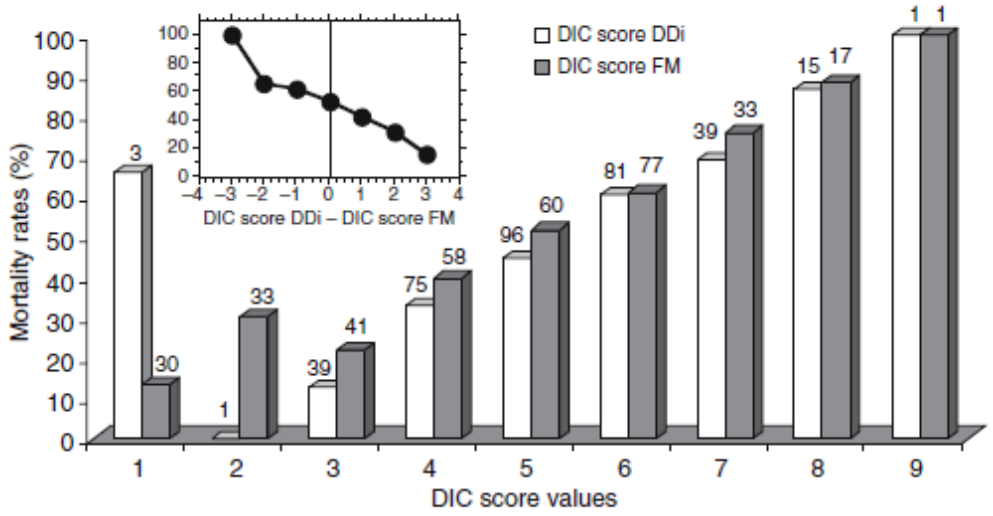


Fig. 1. Mortality rates according to the value of the disseminated intravascular coagulation (DIC) score using D-dimers (DIC score DDi) or using fibrin monomers (DIC score FM), and according to the individual value of the difference between the DIC score DDi value and the DIC score FM value. The number of patients associated with each DIC score value is given at the top of each bar.

Gris J-C, Faillie J-L, Cochery-Nouvellon E, et al. ISTH overt disseminated intravascular coagulation score in patients with septic shock: automated immunoturbidimetric soluble fibrin assay vs. D-dimer assay. J Thromb Haemost 2011;9:1252–5.

DIC - CIVD

- DD, comme marqueur de dégradation de la fibrine, à ne pas utiliser seul mais dans un score intégrant situation clinique et biologie.

- Le choix se fait souvent sur les DD dans la pratique courante car le test est rapide et facile à réaliser.

- Cependant les marqueurs précoces de dégradation de la fibrine, tels que les monomères de fibrine, sont des marqueurs plus précoces de l'activation de la coagulation.