Societat Catalana d'Hematologia i Hemoteràpia

L'Acadèmia

TROMBOC@T Working Group

JORNADA DIA MUNDIAL DE LA TROMBOSIS
13 OCTUBRE 2016

Trombosis Venosa
Utilidad del Dímero D: contras
Duración de la anticoagulación en ETEV

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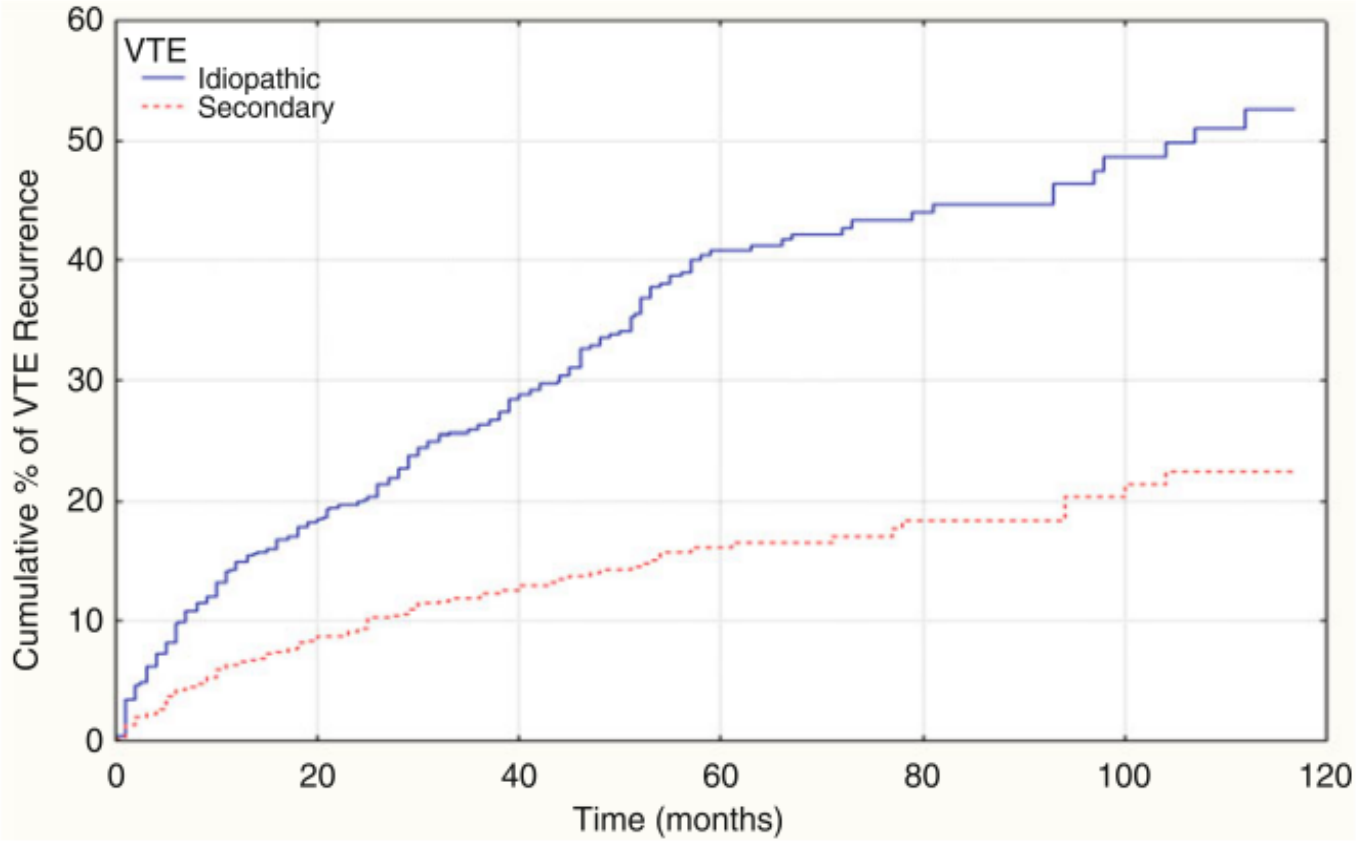

Fig. 1 Cumulative incidence of recurrent VTE after the first episode of DVT and/or PE. The incidence of recurrent VTE after discontinuing anticoagulation is twice as high in patients with idiopathic than in those with secondary VTE

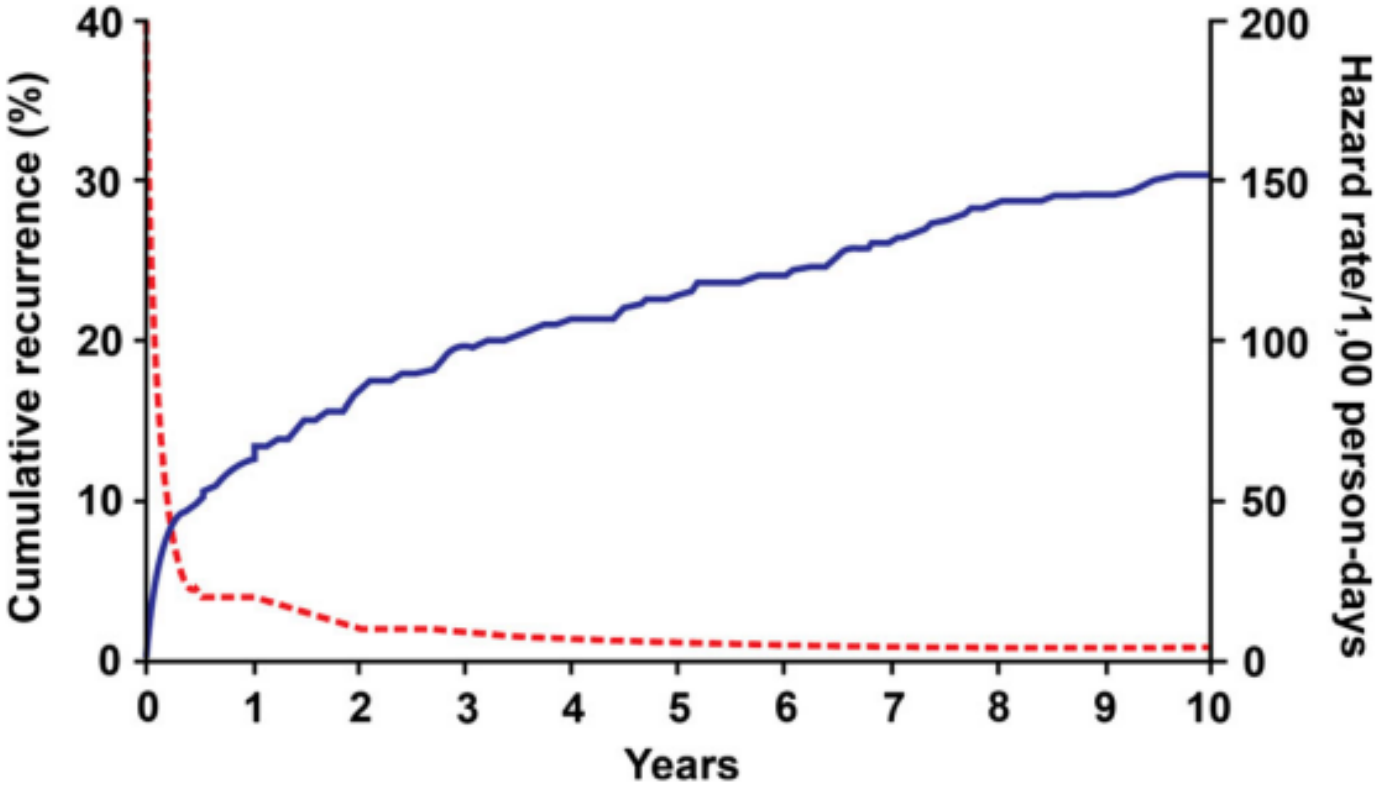

Fig. 4 Cumulative incidence of first venous thromboembolism recurrence (*continuous line*), and the hazard of first recurrence per 1000 person-days (*dotted line*) [32]

32. Heit JA, Mohr DN, Silverstein MD, Petterson TM, O'Fallon WM, Melton LJ 3rd (2000) Predictors of recurrence after deep vein thrombosis and pulmonary embolism: a population-based cohort study. Arch Intern Med 160:761–768

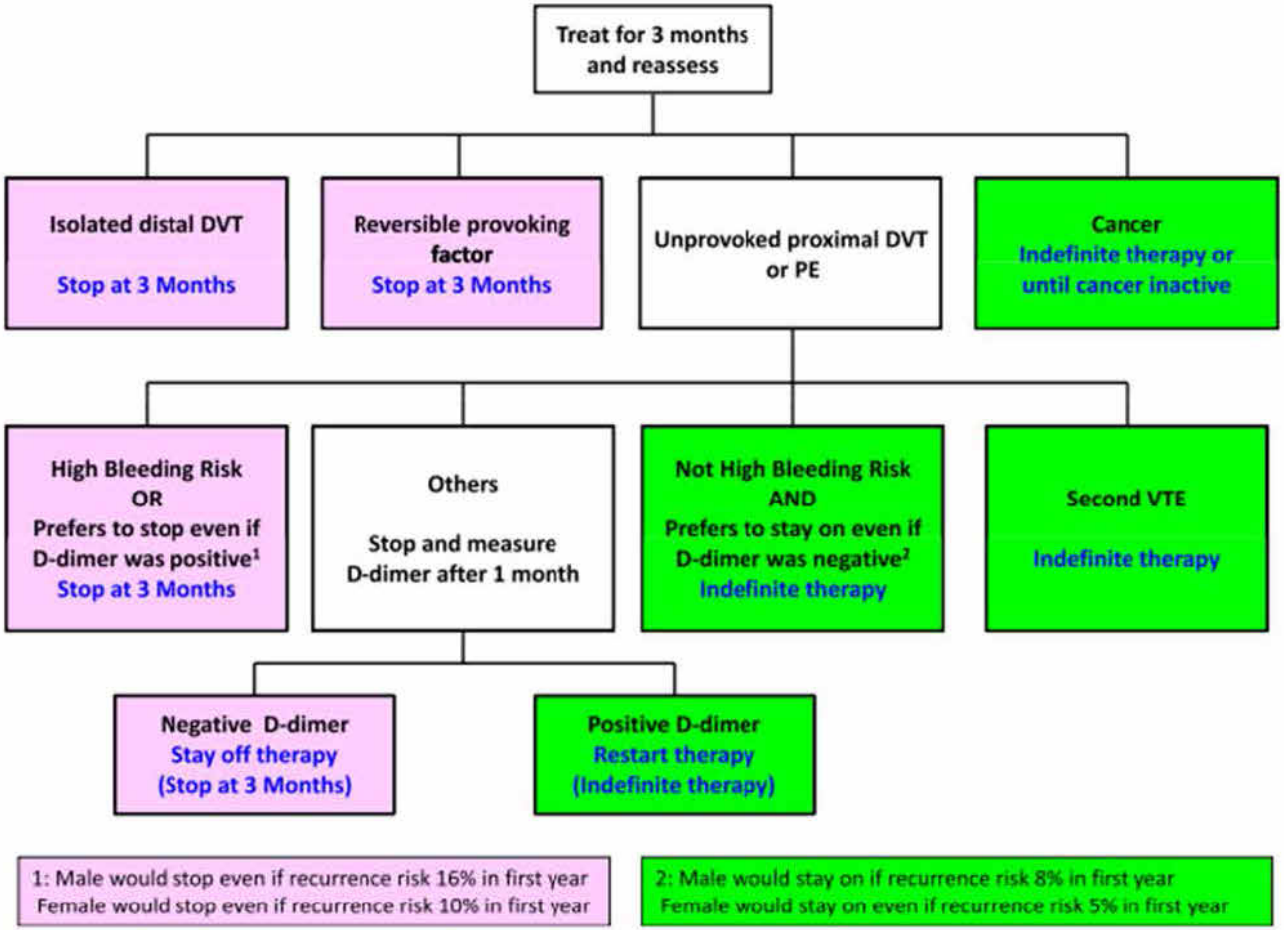

Figure 1. Patients with VTE who should be treated for 3 months and who should be treated indefinitely. Use of D-dimer testing to guide treatment decisions in patients with a first unprovoked proximal DVT or PE is optional. If D-dimer is not used, the decision is based on risk of bleeding and patient preference (estimated risk of recurrence in the first year of 12% for men and 8% for women).

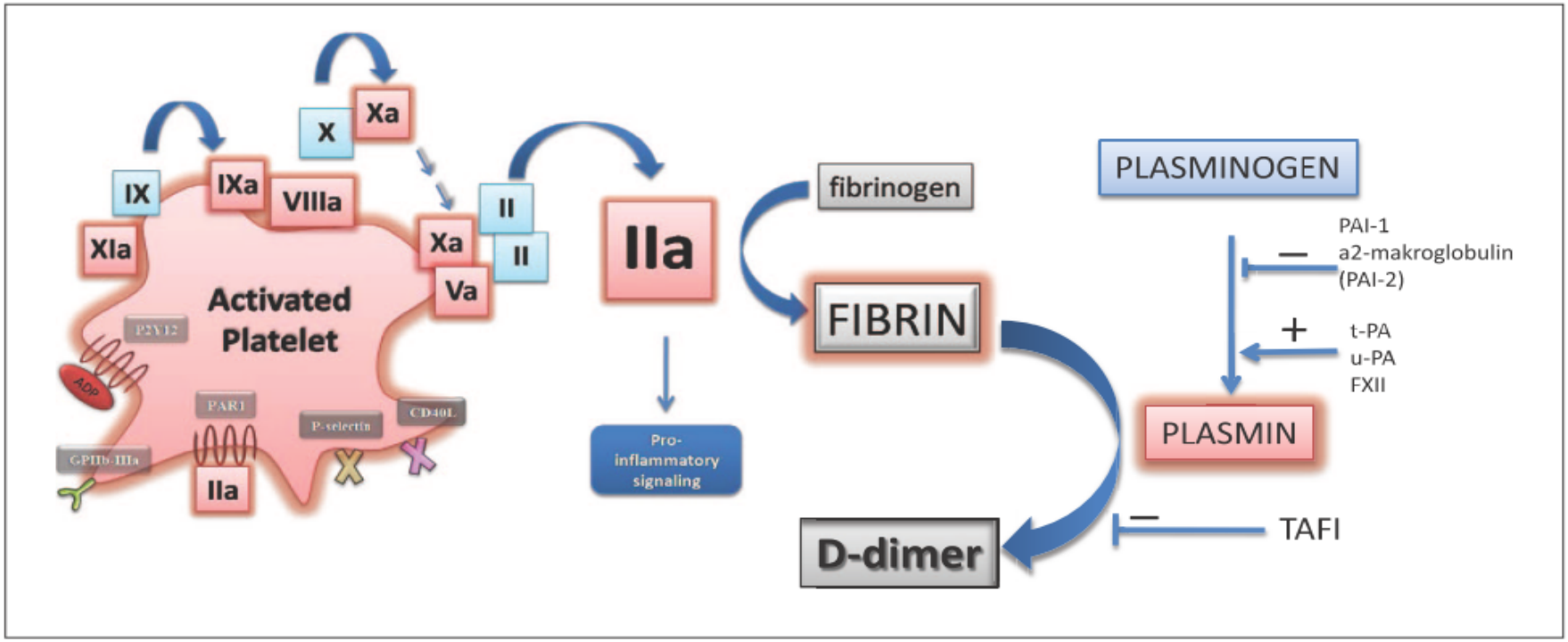

Figure 1. Pathophysiology of D-dimer formation.
The prothrombinase complex FXa+FVa generates large amounts of thrombin on the activated platelet surface during the propagation phase of coagulation. Thrombin then cleaves fibrinogen to fibrin and together with FXIII a stabilising fibrin network is formed. The proteolytic degradation of fibrin is performed by plasmin. Tissue plasminogen activator (tPA) and urokinase plasminogen activator (uPA) play essential roles in the conversion of plasminogen to plasmin. Plasminogen activator inhibitor (PAI)-1, a serine protease inhibitor, is an important inhibitor of the fibrinolytic system and rapidly forms complexes with tPA and uPA. PAI-1 is an acute phase protein and has large intraindividual variation. PAI-2 is only formed in the placenta during pregnancy. Thrombin activatable fibrinolysis inhibitor (TAFI) regulates fibrinolysis and is activated by thrombin and plasmin. Plasmin-driven TAFI activation ensures that TAFI is formed in close proximity to fibrin.

BIOMARCADOR

- criterio de validez
  - sensibilidad
  - especificidad
  - poder predictivo:
    - número de falsos positivos
    - falsos negativos
    - en un diagnóstico clínico

Dímero-D al diagnóstico de ETV

Sensibilidad: 98-100%

Especificidad: 35-39%

Valor predictivo negativo: 98-100% VPN alto

Valor predictivo positivo: 36-44%VPP bajo

CAUSAS: AUMENTO DEL DÍMERO D (NO ESPECÍFICO)

Tromboembolismo venoso (verdaderos positivos)
- **Embolia pulmonar**
- **Trombosis venosa profunda**

Otras causas (falsos positivos)
- Cirugía reciente (1 semana antes)
- Infarto de miocardio
- Fibrilación auricular
- Infección o sepsis
- Cáncer
- Enfermedad sistémica concurrente
- Utilización del tratamiento anticoagulante oral
- Embarazo
- Hemorragia en curso
- Insuficiencia renal

DESVENTAJAS: CIRCUNSTANCIAS EN LAS CUALES DÍMERO D NO ES ÚTIL

Con tratamiento anticoagulante

Edad superior a 70 años

Post-cirugía

Cáncer

Schutgens (2002) Am J Med 112:617-21
Lippi (2001) Clin Exp Med 1(3):161-4

DÍMERO D

ACP recomienda en adultos con edad> 50 años ajustar el resultado por (I)

En estos pacientes se debe corregir el punto de corte o intervalo de normalidad(I)

(I)= Edad X 10 ng/ml

Dímero-D fue falsamente positivos en el 94% de los pacientes con TEV-negativa con la edad avanzada (60 años o más) insuficiencia renal y radiología de tórax anormal

Table 1. Diseases with elevated D-dimer.

- Acute myocardial infarction
- Peripheral arteriopathy
- Acute upper gastrointestinal haemorrhage, other haemorrhage
- Aortic dissection/aneurysm
- Acute respiratory distress syndrome
- Arterial or venous thromboembolism
- Fibrinolytic therapy
- Atrial fibrillation
- Consumptive coagulopathy – DIC
- Infection
- Malignancy
- Pregnancy
- Pre-eclampsia
- Sickle cell disease/haemolysis
- Stroke
- Superficial thrombophlebitis
- Trauma, burns
- Hospitalisation
- Old age
- Neonatal period
- Disability

DIC: disseminated intravascular coagulation.

Table 6. Analytically false positive or false negative D-dimer results.

- Identification errors
- Calibration bias
- Reagent deterioration
- Analyser malfunction
- Instrumental carryover or sample contamination
- Interference
- In-vitro haemolysis
- Hyperbilirubinaemia
- Turbidity
- Heterophile or auto antibodies
- Clotted samples

Adapted from reference 19.

Table 5. Reasons for clinically false negative D-dimer test results.

- Patient started on anticoagulant therapy 24 h before D-dimer tested
- Oral anticoagulant therapy
- Small (often distal) thrombosis and insufficient clot size
- Upper extremity DVT
- Old clots
- Children
- False positive result from radiology
- Deficient fibrinolytic system (tPA deficiency or high PAI level)

DVT: deep venous thrombosis; PAI: plasminogen activator inhibitor; tPA: tissue plasminogen activator.
Adapted from reference 77.

Table 3. Reasons for lack of D-dimer assay standardisation and harmonisation.

- >20 Different monoclonal antibodies used by >30 different assays.
- Antibodies have different analytical sensitivities and specificities.
- D-dimer molecular structure is not homogeneous.
- Antibodies show different cross-reactivity with fibrin degradations products of varying molecular weight.
- There is no internationally certified D-dimer calibrator.

Adapted from reference 10.

Table 2. Age- and sex-specific cutoff levels for the different D-dimer assays adopted in the study

Commercial D-dimer assay (manufacturer) ng/mL	Males ≤70 y	Males >70 y	Females ≤70 y	Females >70 y	Cutoff values currently recommended by manufacturers for VTE exclusion
VIDAS D-dimer Exclusion (bio-Merrieux)	490	1050	600	1300	500
Innovance D-DIMER (Siemens)	500	950	550	1150	500
HemosIL D-dimer HS (Instrumentation Laboratory)	170	345	215	430	230
HemosIL D-dimer (Instrumentation Laboratory)	205	300	225	330	230
STA Liatest D-dimer (Diagnostica Stago)	340	700	450	1050	500

For comparison, the cutoff values recommended by manufacturers for VTE exclusion are also shown.

Table 1 Models to predict recurrent VTE

	Men continue and HER D002 (Pesavento et al. 2014)	Vienna prediction model (Rodger et al. 2008)	DASH-score (Eichinger et al. 2010)
Study design	Prospective cohort	Prospective cohort	Patient level meta-analysis
Patients	646	929	1818
Predictive variables	Men: none		
	Women:		
	age $\geq$ 60 years	Sex	Abnormal D-dimer after anticoagulation
	signs of PTS	Location of first VTE	Age $<$ 50 years
	BMI $\geq$ 30 kg/m^2	D-Dimer after anticoagulation	Male sex
	D-dimer $>$ 250 µg/l during anticoagulation		Hormonal therapy
Increased risk of recurrent VTE	>1 point	>180 points (according to a nomogram)	>1 point
Recurrence rate in patients at low risk	1.6 % (95 % CI, 0.3–4.6)	4.4 % (95 % CI, 2.7–6.2)	3.1 % (95 % CI, 2.3–3.9)

Adv Exp Med Biol - Advances in Internal Medicine (2016)
DOI 10.1007/5584_2016_108

Table 2. Possible underlying conditions for recurrent VTE during anticoagulation

Possible conditions
Insufficient intensity of anticoagulation
Active cancer
Anatomical abnormalities (ie, May-Thurner syndrome)*
Myeloproliferative neoplasms (ie, polycythemia vera, essential thrombocythemia)*
Paroxysmal nocturnal hemoglobinuria*
Phospholipid antibody syndrome*
Heparin-induced thrombocytopenia

*Low level of scientific evidence.

(*Blood*. 2016;127(6):696-702)

Dímero D –elevado tras el cese de los anticoagulantes orales tiene **baja especificidad** para identificar a los pacientes en riesgo de recurrencia de TEV

Palareti G, Cosmi B, Legnani C, et al. D-dimer testing to determine the duration of anticoagulation therapy. N Engl J Med 2006; 355:1780.

Kévorkian JP, Halimi C, Segrestaa JM, et al. Monitoring of patients with deep-vein thrombosis during and after anticoagulation with D-dimer. Lancet 1998; 351:571.

Cosmi B, Legnani C, Tosetto A, et al. Usefulness of repeated D-dimer testing after stopping anticoagulation for a first episode of unprovoked venous thromboembolism: the PROLONG II prospective study. Blood 2010; 115:481.

Dímero D- bajo
no discrimina
el riesgo de recurrencia de TEV

Estudio prospectivo
Tasa de recurrencia de TEV en 319 pacientes (TEV no provocada)
2 determinaciones de dímero-D negativos consecutivos
1ª tras la finalización de tto anticoagulante estándar
2ª un mes después del anticoagulante
Tasa de recurrencia a los 2 años
7 % de pacientes por año
(10 % en hombres, 5 % en las mujeres)

Conclusión

Los niveles bajos de D-dímero en esta población no son útiles y no justifican la retirada de la anticoagulación

Kearon C, Spencer FA, O'Keeffe D, et al. D-dimer testing to select patients with a first unprovoked venous thromboembolism who can stop anticoagulant therapy: a cohort study. Ann Intern Med 2015; 162:27.

Finally, the present subanalysis conducted by PALARETI *et al.* [9] underlines some additional useful information: first, in patients with unprovoked VTE, the presence of negative D-dimer does not exclude a high risk of recurrent VTE, particularly in patients with isolated PE or those older than 70 years; secondly, a positive D-dimer assessment is strongly correlated with a high risk of recurrent VTE, which supports indefinite anticoagulation in most cases; thirdly, patients who had isolated PE are more likely to develop recurrence under the clinical presentation of PE as compared to patients with an initial DVT, and this observation also reinforces the need for indefinite anticoagulation in patients with unprovoked PE rather than in patients with unprovoked DVT.

Eur Respir J 2016; 47: 1313–1314

Table 3 Risk factors associated with recurrent VTE and anticoagulant-related bleeding

Recurrent VTE	Serious or fatal bleeding
Initial unprovoked VTE	Low platelet count
Initial proximal DVT or PE	Previous gastrointestinal bleeding
Residual venous thrombosis	Recent major bleeding
Cancer	Previous stroke
Elevated D-dimer concentrations	Increasing age
when not receiving anticoagulation	Hepatic failure
Male sex	Severe renal impairment
Post-thrombotic syndrome	Diabetes
	Thrombocytopenia
	Poor anticoagulant control

Note: Data from studies.[13,42–47]

Abbreviations: DVT, deep-vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.

THERAPY FOR VTE DISEASE: CHEST GUIDELINE *CHEST* (2016)

No se realizan recomendaciones basadas en el dímero D y el sexo para tomar decisiones sobre la duración del tratamiento en pacientes con un primer TEV no provocado

USE OF UPTODATE

No aconsejan medir los niveles de Dímero-D para decidir (si/no) anticoagulación indefinida

El *momento óptimo* para la determinación del Dímero-D y la eficacia de la anticoagulación indefinida en pacientes con *niveles elevados* de Dímero-D *son inciertos*