Journal of Thrombosis and Haemostasis, **8**: 2436–2442 DOI: 10.1111/j.1538-7836.2010.04022.x

ORIGINAL ARTICLE

Does the clinical presentation and extent of venous thrombosis predict likelihood and type of recurrence? A patient-level meta-analysis

T. BAGLIN,* J. DOUKETIS,† A. TOSETTO,‡ M. MARCUCCI,§ M. CUSHMAN,¶ P. KYRLE,** G. PALARETI,†† D. POLI,‡‡ R. C. TAIT§§ and A. IORIO§

**Department of Haematology, Addenbrooke's Hospital, Cambridge, UK; †Department of Medicine, McMaster University, Hamilton, ON, Canada; ‡Department of Hematology, S. Bortolo Hospital, Vicenza, Italy; §Department of Medicine, University of Perugia, Perugia, Italy; ¶Department of Medicine, University of Vermont, Colchester, VT, USA; **Department of Medicine I, Medical University of Vienna, Vienna, Austria; ††Angiology and Blood Coagulation, University Hospital S. Orsola-Malpighi, Bologna, Italy; ‡‡Centro di Riferimento Regionale per la Trombosi, Azienda Ospedaliero-Universitaria Careggi, Firenze, Italy; and §§Department of Haematology, Royal Infirmary, Glasgow, UK*

To cite this article: Baglin T, Douketis J, Tosetto A, Marcucci M, Cushman M, Kyrle P, Palareti G, Poli D, Tait RC, Iorio A. Does the clinical presentation and extent of venous thrombosis predict likelihood and type of recurrence? A patient-level meta-analysis. *J Thromb Haemost* 2010; **8**: 2436–42.

Summary. *Aim:* To determine if the mode of presentation of venous thromboembolism (VTE), as deep vein thrombosis (DVT) or pulmonary embolism (PE), predicts the likelihood and type of recurrence. *Methods:* We carried out a patient-level meta-analysis of seven prospective studies in patients with a first VTE who were followed after anticoagulation was stopped. We used Kaplan-Meier analysis to determine the cumulative incidence of recurrent VTE according to mode of presentation, and multivariable Cox regression to calculate adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for mode of and extent of DVT as potential risk factors for recurrence. *Results:* The 5-year cumulative rate of recurrent VTE in 2554 patients was 22.6%. In 869 (36.1%) patients with PE, the 5-year rate of any recurrence (DVT or PE) was 22.0%, and recurrence as PE was 10.6%. In 1365 patients with proximal DVT, the 5-year recurrence rate was 26.4%, and recurrence with PE was 3.6%. The risk of recurrence as PE was 3.1-fold greater in patients presenting with symptomatic PE than in patients with proximal DVT (HR, 3.1; 95% CI, 1.9–5.1). Patients with proximal DVT had a 4.8-fold higher cumulative recurrence rate than those with distal DVT (HR, 4.8; 95% CI, 2.1–11.0). *Conclusion:* Whilst DVT and PE are manifestations of the same disease, the phenotypic expression is predetermined. Patients presenting with PE are three times more likely to suffer recurrence as PE than patients presenting with DVT. Patients presenting with calf DVT are at low risk of recurrence and at low risk of recurrence as PE.

Correspondence: Trevor Baglin, Department of Haematology, Addenbrooke's Hospital, Cambridge, UK.
Tel.: + 44 1223 217128; fax: + 44 1223 274871.
E-mail: trevor.baglin@addenbrookes.nhs.uk

Received 2 May 2010, accepted 4 August 2010

Keywords: disease recurrence, epidemiology, prognosis, risk factors, venous thrombosis.

Introduction

In patients with a first episode of venous thromboembolism (VTE), there is controversy as to whether the mode of clinical presentation, as pulmonary embolism (PE) or deep vein thrombosis (DVT), and extent of thrombosis, as proximal or distal DVT, predict the risk of disease recurrence. If this is true, then these factors should be considered when deciding the duration of anticoagulation after a first episode of VTE.

The risk of fatal PE is two to four times greater in patients with symptomatic PE as compared with patients with symptomatic DVT alone [1–5]. Therefore if recurrence is more likely to be PE than DVT then the consequences of recurrence are potentially greater in patients with a first event manifesting as symptomatic PE. Previous studies suggest that 75% of recurrences are PE in patients initially presenting with PE, compared with 20% in patients presenting with DVT [1,3,5].

Similarly, thrombus mass seems to affect the risk of VTE recurrence. Quantitation of thrombus mass has not been validated clinically other than to dichotomise patients into those with thrombus confined to the calf and those with more extensive thrombosis (i.e. proximal extension including PE). Initial studies suggest that the risk of recurrent VTE is lower in patients with DVT confined to the calf [6,7].

However, previous studies have been subject to unavoidable methodological limitations in relation to both type and rate of recurrence. With these considerations in mind we have performed a patient-level meta-analysis of prospective studies that included patients who received standardized anticoagulant therapy and were followed for up to 5 years after treatment was stopped.

The aim was to assess the effect of the mode of clinical presentation and the extent of thrombosis on the risk and mode of disease recurrence in patients after a first episode of VTE.

Methods

The process for obtaining patient-level data and undertaking a pooled analysis was defined by a core group of investigators (J. Douketis, A. Tosetto and A. Iorio) who prespecified the study selection criteria and analysis plan.

The primary objective of the patient-level meta-analysis was to develop a clinical prediction guide anchored on post-anticoagulation D-dimer status (positive or negative) to identify patients at low and high risk of recurrent VTE in whom anticoagulation might be stopped or continued. As a secondary objective, which is the focus of the present study, we aimed to assess the effect of initial clinical presentation on risk of recurrence using the same database but not utilizing post-anticoagulation D-dimer data.

Study selection

The selection of studies for this patient-level meta-analysis adopted the search strategy used for a prior study-level meta-analysis assessing the predictive value of post-anticoagulation D-dimer that involved one of the authors (J. Douketis) [8]. Using the same search strategy, major electronic databases (i.e. MEDLINE, EMBASE, CINAHL and the Cochrane Central Register of Controlled Trials) were searched from their inception to July 2010 (Appendix 1). We supplemented this search by reviewing conference abstracts and contacted content experts but no additional studies were identified.

Source study characteristics

Included studies (Table 1) had the following characteristics: (i) randomized trial or prospective cohort study of patients with a first symptomatic VTE (proximal or distal deep vein thrombosis, pulmonary embolism or both); (ii) all patients received standard anticoagulant therapy consisting of 5–10 days of heparin and ≥ 3 months of a vitamin K antagonist; (iii) all patients had clinical follow-up for recurrent symptomatic VTE after anticoagulant therapy was stopped, with outcomes objectively confirmed and independently adjudicated; and (iv) D-dimer was measured after stopping anticoagulant therapy. As mentioned, this last characteristic relating to post-anticoagulation D-dimer status was not needed for the present analysis but was used for a companion study [9].

Source study quality assessment

We planned to evaluate the internal validity of included studies and its effect on the reliability of our meta-analysis. However, for meta-analyses of prognostic studies, there are no standardized quality criteria or checklists available. We aimed to investigate the risk of bias based on theoretical considerations and adapting available quality assessment schemes to our included studies [10,11].

Development of patient database

The principal authors of eligible studies were contacted to explain the meta-analysis objectives and analysis plan. After all authors agreed to share their databases, these were transferred to a central depository under the auspices of two investigators (A. Iorio and M. Marcucci). Data were checked, explanations for coding and uncertain or missing data were clarified, and a single pooled database was developed. For two studies (randomized trials) that allocated some patients with a positive D-dimer to resume anticoagulation [12,13], such patients were excluded from the analyses.

Statistical analyses

We modelled the outcomes 'overall VTE recurrence' (i.e. cumulated DVT and/or PE) and 'recurrence as PE or DVT', separately considered, on the following populations: (i) the whole population; (ii) patients presenting as PE; (iii) patients presenting as proximal DVT; (iv) patients presenting as distal DVT; and (v) patients who had a recurrence (outcome number two only).

Time-to-event analysis was performed by Kaplan-Meier estimates with cumulative recurrence rates reported at different years of follow-up (and 95% confidence intervals, CI). Averaged (annualized) recurrence rates are also presented as events per 100 patient-years estimated from the 3 and 5 years follow-up with calculation of 95% CI.

Hazard ratios (HRs) were calculated by study-stratified Cox proportional hazards modeling, including two- and three-level variables for clinical presentation and extent of disease. The hazard ratios were also adjusted for other putative confounders (age, sex, provoked or unprovoked VTE, hormone therapy).

The STATA (version 9.2, Statacorp, College Station, TX, USA) software package was used for statistical analysis.

Results

Seven studies were included in the meta-analysis, comprising 2554 patients after a first episode of VTE [12–18]. The mean duration of follow-up was 27.1 ± 19.6 months (median 22.3 months, inter-quartile range 0.2–117.3). The patients were classified according to the clinical presentation and the extent of the thrombus in patients with symptomatic DVT alone (Table 2). The initial mode of presentation was unspecified in 38 patients. For 111 patients presenting with DVT we did not know if a PE was associated or not; 2405 (94.2%) patients had a specified presentation and 869 had symptomatic PE (36.1%).

Source study quality assessment

After assessing factors that might affect the quality of a prognostic study, such as defining the inception cohort,

Table 1 Source study characteristics

Author, year (reference)	Study design	Inclusion (exclusion) criteria	Index VTE	Assay (Type)	Normal D-dimer value (μg/L)	Quantitative D-dimer	Monitoring for recurrent VTE	Study quality assessment according to modified NOS criteria (selection/outcome)*
Palareti, 2003 [12]	Prospective cohort, single center	First VTE (excluded: lupus anticoagulant)	Leg DVT and/or PE	VIDAS (ELISA)	≤ 500	Available	Clinical visits 3 months after stopping VKA then every 6 months. Instructions to contact if symptomatic.	4/3
Eichinger, 2003 [15]	Prospective cohort, single center	First unprovoked VTE (excluded: surgery, trauma or pregnancy within past 3 months; cancer; APS; natural coagulation inhibitor deficiency; long-term anticoagulation)	Leg DVT and/or PE	Asserachrom (ELISA)	< 250	Available	Clinical visits every 3 months for 1 year then every 6 months	3/3
Palareti, 2006 [16]	RCT, multicenter	First unprovoked VTE (excluded: recent pregnancy or puerperium, fracture or plaster casting of leg, immobilization for ≥ 3 consecutive days, surgery with general anesthesia; active cancer; APS; antithrombin deficiency; serious liver or renal disease; other indication/ contraindication for anticoagulation; limited life expectancy; geographic inaccessibility)	Proximal leg DVT and/or PE	Simply red (qualitative)	Qualitative (abnormal vs. normal)	Available (VIDAS, ELISA)*	Clinical visits every 3–6 months. Instructions to contact if symptomatic	4/3
Shrivastava, 2006 [18]	RCT, multicenter	Unprovoked VTE (excluded: surgery or trauma within 90 days of index event; APS; prior or active cancer; life expectancy < 3 years)	Leg DVT and/or PE	Liatest (Stago)	< 500	Available	Clinical visits every 2 months	3/3
Tait, 2007 [13]	Prospective cohort, multicenter	Acute VTE within past 5 weeks (excluded: life expectancy < 3 months; anticipated duration of anticoagulation > 1 year; unavailable for follow-up)	DVT and/or PE	VIDAS (ELISA)	< 500	Available	Nurse visit at 3 months, 1 year, 2 years after stopping VKA. Instructions to contact if symptomatic	Not applicable
Baglin, 2008 [14]	Prospective cohort, single center	First VTE (excluded: postoperative- or pregnancy -associated VTE; APS; cancer; thrombosis within 6 weeks of surgery; other indication for prolonged anticoagulation)	Proximal leg DVT and/or PE	MDA (LIA)	< 500	Available	Yearly follow-up	3/3
Poli, 2008 [17]	Prospective cohort, single centre	First unprovoked VTE or VTE due to reversible risk factors (excluded: APS or active cancer)	Proximal leg DVT and/or PE	IL-Test (LIA)	< 250	Not available	Follow-up twice in the first year and once thereafter. Instructions to contact if symptomatic	4/3

APS, antiphospholipid antibody; INR, international normalized ratio; VKA, vitamin K antagonist; VTE, venous thromboembolism; DVT, deep vein thrombosis; PE, pulmonary embolism. *If published results refer to a qualitative D-dimer assay, quantitative results were available and used in the sensitivity analysis.

prognostic variable and outcomes and length of follow-up, we considered the studies included in our meta-analysis to be at low risk of bias. In some studies there was a lack of blinding to prognostic information in the outcome assessment and in all studies patients were not blinded to their D-dimer results [15,17,18].

Outcome 1: recurrence as any VTE (DVT and/or PE)

The cumulative recurrence rate at 5 years for all VTE was 22.6% (95% CI, 18.9–27.1) and was the same in patients presenting with symptomatic PE (with or without DVT) and in patients presenting with symptomatic DVT alone: 22.0% (16.3–29.8) vs. 23.2% (18.5–29.2); HR, 0.96 (0.75–1.24). This lack of difference in recurrence rates persisted when the comparison was between PE and proximal DVT alone: HR, 0.85 (0.66–1.10).

Amongst patients presenting with DVT (independent of its association with PE), those with proximal DVT had a more than 4-fold higher cumulative rate of all recurrent VTE compared with patients with distal DVT confined to the calf: HR, 4.76 (95% CI, 2.06–10.98).

Outcome 2: recurrence as PE or DVT separately considered

There were 869 patients presenting initially with PE, in whom the 5-year cumulative rate of recurrence as PE was 10.6% and as DVT 11.4%. There were 1365 patients presenting initially with proximal DVT alone, in whom the cumulative rate of recurrence as PE was 3.8% and as DVT 22.8%. There were 171 patients presenting initially with distal DVT alone, in whom the cumulative rate of recurrence as PE was 1.2% and as DVT 6.4%.

The risk of recurrence as PE was 3-fold higher in patients presenting with PE than in patients presenting with proximal DVT: HR, 3.10 (1.87–5.13). The risk of recurrence as PE was 4-fold higher in patients presenting with proximal DVT alone compared with distal DVT, although this difference was not statistically significant: HR, 4.46 (0.59–33.88).

When we performed the analysis only on patients who had recurrence, the risk of recurrence as PE was more than 4-fold greater in patients presenting with symptomatic PE compared with proximal DVT: HR, 4.66 (2.70–8.06). This finding, where the initial mode of presentation as PE predicted recurrence as PE, persisted when the analysis was limited to patients with initial unprovoked VTE who developed recurrence: HR, 4.41 (2.47–7.90).

Cumulative and annualized recurrence rates in each category at 1, 3 and 5 years are summarized in Table 3 and the risk of recurrent thrombosis and recurrence as PE according to initial clinical presentation and extent of thrombosis is presented in Table 4.

Discussion

The results of this patient-level meta-analysis have important implications for clinical care. The study shows that patients presenting with a first episode of PE are at the same risk of recurrent VTE as patients presenting with a first episode of DVT alone. However, they are 3-fold more likely to suffer PE than DVT as a recurrence. Given that the risk of fatal PE is two to four times greater in patients with symptomatic PE, the mode of initial presentation is an important factor in determining the duration of anticoagulant therapy in individual patients after a first episode of VTE. The latest recommendation from the American College of Chest Physicians states that after an episode of DVT or PE patients should receive anticoagulant treatment, currently with an oral vitamin K antagonist for at least 3 months. After this period, all patients with unprovoked thrombosis should be evaluated for the risk-benefit ratio of long-term anticoagulation (i.e. continuing treatment). For patients with a first thrombosis that is a proximal DVT or PE, and in whom risk factors for bleeding are absent and for whom good anticoagulant monitoring is achievable, long-term treatment is recommended [19]. In addition to this recommendation, other factors to consider in individual patients are the burden of long-term (lifelong) anticoagulation, the patient's preference and most importantly the potential consequences of recurrence. This meta-analysis confirms that a recurrence is more likely to be PE after a first episode of PE and therefore a recurrence is more likely to be fatal than if the first episode is DVT. Furthermore, the risk of

Table 2 Clinical presentation of initial venous thromboembolism

		Clinical presentation of initial venous thromboembolism								
Study (reference)	Patients assessed	Proximal DVT	Proximal DVT + PE	Proximal DVT ± PE	Distal DVT	Distal DVT + PE	Distal DVT ± PE	Isolated PE	Unspecified VTE	Unspecified PE
Palareti, 2003	529	387	82	–	38	2	–	20	–	–
Eichinger, 2003	567	203	–	–	133	–	–	–	–	231
Palareti, 2006	501	310	95	–	–	–	–	96	–	–
Shrivastava, 2006	149	–	–	93	–	–	18	–	38	–
Tait, 2007	250	133	–	–	–	–	–	–	–	117
Baglin, 2008	271	–	–	156	–	–	–	–	115	–
Poli, 2008	287	176	75	–	–	–	–	36	–	–
Pooled	2554	1209	252	249	171	2	18	152	153	348

DVT, deep vein thrombosis; PE, pulmonary embolism.

Table 3 Recurrent venous thromboembolism: mode of recurrence

Initial diagnosis		Pulmonary embolism (± DVT)	Proximal DVT (without PE)	Calf DVT (without PE)
Any recurrence (DVT or PE)				
1 year	Cumulative recurrence (95% CI)	7.4% (5.7–9.5)	8.4% (6.9–10.2)	None
3 years	Cumulative recurrence (95% CI)	14.7% (11.7–18.4)	15.6% (13.0–18.7)	0.9% (0.1–6.3)
	Annual recurrence (95% CI)	5.4 per 100 pt-years (4.4–6.6)	6.1 per 100 pt-years (5.2–7.2)	0.5 per 100 pt-years (0.1–2.2)
5 years	Cumulative recurrence (95% CI)	22.0% (16.3–29.8)	26.4% (20.5–34.1)	7.6% (3.0–18.9)
	Annual recurrence (95% CI)	5.1 per 100 pt-years (4.2–6.2)	6.0 per 100 pt-years (5.2–7.0)	1.0 per 100 pt-years (0.4–2.5)
Recurrence as pulmonary embolism				
1 year	Cumulative recurrence (95% CI)	3.7% (2.6–5.4)	1.3% (0.8–2.1)	None
3 years	Cumulative recurrence (95% CI)	7.2% (5.2–10.0)	2.5% (1.6–4.0)	1.2% (0.2–8.2)
	Annual recurrence (95% CI)	2.6 per 100 pt-years (2.0–3.5)	0.9 per 100 pt-years (0.6–1.4)	0.3 per 100 pt-years (0.0–1.9)
5 years	Cumulative recurrence (95% CI)	10.6% (7.2–15.7)	3.6% (1.8–7.3)	1.2% (0.2–8.2)
	Annual recurrence (95% CI)	2.5 per 100 pt-years (1.9–3.3)	0.9 per 100 pt-years (0.6–1.3)	0.2 per 100 pt-years (0.0–1.5)

DVT, deep vein thrombosis; PE, pulmonary embolism.

Table 4 Risk factors for recurrent venous thromboembolism

Initial diagnosis	Risk of any recurrence (DVT or PE)	
PE vs. any DVT alone	HR 0.96 (95% CI, 0.75–1.24; $P = 0.758$) LR = 76.29 ($P < 0.001$)	
PE vs. proximal DVT alone	HR 0.85 (95% CI, 0.66–1.10; $P = 0.211$) LR = 96.84 ($P < 0.001$)	
Proximal DVT vs. distal DVT (± PE)	HR 4.20 (95% CI, 1.78–9.92; $P = 0.001$) LR = 68.20 ($P < 0.001$)	
Proximal DVT vs. distal DVT alone	HR 4.76 (95% CI, 2.06–10.98; $P < 0.001$) LR = 96.84 ($P < 0.001$)	
	Risk of recurrence as PE	
PE vs. any DVT alone	HR 3.55 (95% CI, 2.17–5.81; $P < 0.001$) LR = 41.88 ($P < 0.001$)	
PE vs. proximal DVT alone	HR 3.10 (95% CI, 1.87–5.13; $P < 0.001$) LR = 45.14 ($P < 0.001$)	
Proximal DVT vs. distal DVT alone	HR 4.46 (95% CI, 0.59–33.88; $P = 0.149$) LR = 45.14 ($P < 0.001$)	
	Risk of recurrent PE*	
	All patients	Unprovoked VTE
PE vs. proximal DVT alone	HR 4.66 (95% CI, 2.70–8.06; $P < 0.001$)	HR 4.41 (95% CI, 2.47–7.90; $P < 0.001$)

*Including only patients with a recurrent venous thromboembolism. DVT, deep vein thrombosis; PE, pulmonary embolism.

chronic thromboembolic pulmonary hypertension is 15–20 times greater after recurrent PE [20]. Therefore, the balance of benefit and risk of long-term anticoagulation is different in patients with PE and DVT. A higher value should be applied to prevention of recurrent VTE and a lower value to the burden of long-term anticoagulant therapy in patients presenting with PE.

A further finding of the study is confirmation that patients with DVT confined to the calf are at lower risk of overall recurrence and at low risk of recurrence as PE. The risk of any recurrence of VTE was 4-fold lower compared with patients with symptomatic proximal DVT or PE and the absolute risk of recurrence as PE was only 0.2% per year, with a cumulative recurrence of 1.2% after 5 years of follow-up. We acknowledge that due to the low number of events the recalculated power of this assessment was 23.1%. This finding also has implications for clinical management decisions. The balance of benefit and risk of long-term anticoagulation is different in patients with distal DVT alone and a lower value should be applied to prevention of recurrent VT and a higher value to the burden of long-term anticoagulant therapy.

DVT and PE are manifestations of the same disease, venous thromboembolism. It remains to be determined why some patients have a tendency to present with symptomatic PE as opposed to symptomatic DVT alone, and vice versa. Nevertheless, this study confirms that there is indeed a consistent tendency, with the mode of recurrence strongly reflecting the initial presentation. This is interesting as most, if not all, patients who present with symptomatic DVT have asymptomatic PE and, conversely, the majority presenting with symptomatic PE have asymptomatic DVT [21]. This study shows that whilst DVT and PE are manifestations of the same pathology the phenotypic expression of the disease is predetermined. So far the only factor known to influence this predetermined tendency is the *F5*G1691A mutation producing the mutant factor V Leiden coagulant protein (F5R06Q). Patients with this mutation are 2-fold less likely to present with PE as an initial episode of VT compared with patients without

the mutation (i.e. the mutation is protective with regard to a first PE) [22]. This result was confirmed in a *post-hoc* analysis of our patient database, where we found that patients with the factor V Leiden mutation had a 2.6-fold lower likelihood of presenting initially with PE than DVT ($\chi^2 = 10.6$, $P = 0.001$). The molecular basis of this finding remains unknown. In addition, we also found that patients with the prothrombin gene mutation had a 2.1-fold lower likelihood of presenting initially as PE than DVT, although this difference did not attain statistical significance ($\chi^2 = 1.3$, $P = 0.260$).

The tendency for DVT to embolize seems to be constant over time. In a study employing repeat perfusion lung scanning 7 days after diagnosis of DVT or PE new perfusion defects were present in 18% of patients with initial PE compared with only 6% in patients presenting with symptomatic DVT [23]. In a random 5% sample of Medicare claims in the United States from 1986 to 1989, Kniffin *et al.* [3] identified 7174 cases of PE and 8923 cases of DVT. A subsequent diagnosis of PE within 1 year of hospital discharge after initial treatment was made in 8.0% of patients with initial PE compared with only 1.7% in patients with initial DVT. In-hospital mortality associated with PE and DVT was 21% and 3%, respectively, and 1-year mortality was 2-fold higher in patients with initial PE (39% vs. 21%) [3]. Murrin *et al.* [5] used linked hospital discharge records to examine the influence of mode of presentation on recurrence and found that patients presenting with PE were four times more likely to be rehospitalized with a diagnosis of PE within 6 months of diagnosis of VT compared with patients with initial DVT. Douketis *et al.* [1] reported a meta-analysis of clinical trials and found that symptomatic PE accounted for recurrence after completion of anticoagulant treatment in 81% of patients with initial PE compared with only 22% of patients with initial DVT. Each of these studies had associated unavoidable methodological limitations, including sampling bias, retrospective recruitment and study-level data. This patient-level meta-analysis of more than 2500 unselected patients recruited into prospective cohort studies is not subject to such weaknesses and it confirms that thrombus burden and mode of initial presentation are simple and easily recognized risk factors that predict likelihood and type of recurrence. These simple clinical factors therefore predict the consequential mortality and morbidity of recurrence should it occur and they should be taken into consideration when determining an individual patient's risk profile with regard to duration of anticoagulant therapy.

In summary, whilst DVT and PE are manifestations of the same disease, the phenotypic expression is predetermined. Patients presenting with PE are three times more likely to suffer recurrence as PE than patients presenting with DVT. Patients presenting with calf DVT are at low risk of recurrence and at low risk of recurrence as PE.

Disclosure of Conflict of Interests

The authors state that they have no conflict of interest.

Appendix 1. Literature search strategy

Database: Ovid MEDLINE(R) <1950 to July Week 2 2010>
1 exp anticoagulants/(158855)
2 anticoagulant$.mp. (61033)
3 anticoagulant$.mp. (61033)
4 1 or 2 or 3 (170616)
5 Adult/(3354712)
6 exp fibrin degradation products/(5840)
7 D-dimer.mp. (4370)
8 6 or 7 (7724)
9 exp recurrence/or recurrence.mp. (277845)
10 recurrent$.mp. (152573)
11 9 or 10 (365286)
12 exp predictive value of tests/or predictive value.mp. (128598)
13 11 or 12 (486309)
14 Thromboembolism.mp. or exp thromboembolism/(45309)
15 Venous thrombosis.mp. or exp venous thrombosis/(45293)
16 Pulmonary embolism.mp. or exp pulmonary embolism/(32211)
17 14 or 15 or 16 (102347)
18 4 and 5 and 8 and 13 and 17 (264)

References

1 Douketis JD, Kearon C, Bates S, Duku EK, Ginsberg JS. Risk of fatal pulmonary embolism in patients with treated venous thromboembolism. *JAMA* 1998; **279**: 458–62.
2 Heit JA, Silverstein MD, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ 3rd. Predictors of survival after deep vein thrombosis and pulmonary embolism: a population-based, cohort study. *Arch Intern Med* 1999; **159**: 445–53.
3 Kniffin WD Jr, Baron JA, Barrett J, Birkmeyer JD, Anderson FA Jr. The epidemiology of diagnosed pulmonary embolism and deep venous thrombosis in the elderly. *Arch Intern Med* 1994; **154**: 861–6.
4 Laporte S, Mismetti P, Decousus H, Uresandi F, Otero R, Lobo JL, Monreal M. Clinical predictors for fatal pulmonary embolism in 15,520 patients with venous thromboembolism: findings from the Registro Informatizado de la Enfermedad TromboEmbolica venosa (RIETE) Registry. *Circulation* 2008; **117**: 1711–6.
5 Murin S, Romano PS, White RH. Comparison of outcomes after hospitalization for deep venous thrombosis or pulmonary embolism. *Thromb Haemost* 2002; **88**: 407–14.
6 Pinede L, Ninet J, Duhaut P, Chabaud S, Demolombe-Rague S, Durieu I, Nony P, Sanson C, Boissel JP. Comparison of 3 and 6 months of oral anticoagulant therapy after a first episode of proximal deep vein thrombosis or pulmonary embolism and comparison of 6 and 12 weeks of therapy after isolated calf deep vein thrombosis. *Circulation* 2001; **103**: 2453–60.
7 Schulman S, Rhedin AS, Lindmarker P, Carlsson A, Larfars G, Nicol P, Loogna E, Svensson E, Ljungberg B, Walter H. A comparison of 6 weeks with 6 months of oral anticoagulant therapy after a first episode of venous thromboembolism. Duration of Anticoagulation Trial Study Group. *N Engl J Med* 1995; **332**: 1661–5.
8 Verhovsek M, Douketis JD, Yi Q, Shrivastava S, Tait RC, Baglin T, Poli D, Lim W. Systematic review: D-dimer to predict recurrent disease after stopping anticoagulant therapy for unprovoked venous thromboembolism. *Ann Intern Med* 2008; **149**: 481–90. W94.
9 Iorio A, Douketis JD, Marcucci M, Baglin T, Cushman M, Eichinger S, Palareti G, Poli D, Tait RC, Tosetto A. D-dimer to predict thrombosis recurrence after unprovoked venous thromboembolism: effect of patient- and D-dimer-related factors on recurrence prediction. *J Thromb Haemost* 2009; **7**: OC-TH-002.
10 Altman DG. Systematic reviews of evaluations of prognostic variables. *Br Med J* 2001; **323**: 224–8.

11 Merlin T, Weston A, Tooher R. Extending an evidence hierarchy to include topics other than treatment: revising the Australian 'levels of evidence'. *BMC Med Res Methodol* 2009; **9**: 34.
12 Palareti G, Legnani C, Cosmi B, Valdre L, Lunghi B, Bernardi F, Coccheri S. Predictive value of D-dimer test for recurrent venous thromboembolism after anticoagulation withdrawal in subjects with a previous idiopathic event and in carriers of congenital thrombophilia. *Circulation* 2003; **108**: 313–8.
13 Tait RC, Lowe G, McColl MD, McMahon A, Robertson I, King CR, Clarke S, Conkie J, Roditi GH, Walker ID. Predicting risk of recurrent venous thrombosis using a 5-point scoring sysytem including fibrin D-dimer. *J Thromb Haemost* 2007; **5**(Suppl. 2): 60.
14 Baglin T, Palmer C, Luddington R, Baglin C. Unprovoked recurrent venous thrombosis: prediction by D-dimer and clinical risk factors. *J Thromb Haemost* 2008; **6**: 577–82.
15 Eichinger S, Minar E, Bialonczyk C, Hirschl M, Quehenberger P, Schneider B, Weltermann A, Wagner O, Kyrle PA. D-dimer levels and risk of recurrent venous thromboembolism. *JAMA* 2003; **290**: 1071–4.
16 Palareti G, Cosmi B, Legnani C, Tosetto A, Brusi C, Iorio A, Pengo V, Ghirarduzzi A, Pattacini C, Testa S, Lensing AW, Tripodi A. D-dimer testing to determine the duration of anticoagulation therapy. *N Engl J Med* 2006; **355**: 1780–9.
17 Poli D, Antonucci E, Ciuti G, Abbate R, Prisco D. Combination of D-dimer, F1 + 2 and residual vein obstruction as predictors of VTE recurrence in patients with first VTE episode after OAT withdrawal. *J Thromb Haemost* 2008; **6**: 708–10.
18 Shrivastava S, Ridker PM, Glynn RJ, Goldhaber SZ, Moll S, Bounameaux H, Bauer KA, Kessler CM, Cushman M. D-dimer, factor VIII coagulant activity, low-intensity warfarin and the risk of recurrent venous thromboembolism. *J Thromb Haemost* 2006; **4**: 1208–14.
19 American College of Chest Physicians. Antithrombotic therapy for venous thromboembolic disease. *Chest* 2008; **133**: 454S–545S.
20 Pengo V, Lensing AW, Prins MH, Marchiori A, Davidson BL, Tiozzo F, Albanese P, Biasiolo A, Pegoraro C, Iliceto S, Prandoni P. Incidence of chronic thromboembolic pulmonary hypertension after pulmonary embolism. *N Engl J Med* 2004; **350**: 2257–64.
21 Kearon C. Natural history of venous thromboembolism. *Circulation* 2003; **107**(23 Suppl. 1): I22–30.
22 Turkstra F, Karemaker R, Kuijer PM, Prins MH, Buller HR. Is the prevalence of the factor V Leiden mutation in patients with pulmonary embolism and deep vein thrombosis really different? *Thromb Haemost* 1999; **81**: 345–8.
23 Monreal M, Lafoz E, Ruiz J, Callejas JM, Arias A. Recurrent pulmonary embolism in patients treated because of acute venous thromboembolism: a prospective study. *Eur J Vasc Surg* 1994; **8**: 584–9.