The location of deep-vein thrombosis as a predictive factor for recurrence and cancer discovery after proximal deep-vein thrombosis

Few studies have investigated the possible influence of the anatomic location of deep-vein thrombosis (DVT) on the evolution of the disease. Using a database of a randomized trial involving 400 patients with proximal DVT, we performed multivariate analyses to identify independent predictors of DVT recurrence and cancer discovery within two years. Besides known cancer at inclusion, the upper limit of DVT and its lateralization were independent risk factors for DVT recurrence with a hazard ratio (HR) of 1.75 [95% CI=1.00-3.07] for iliocaval DVT compared to femoro-popliteal DVT, and a HR of 1.88 [1.07-3.30] for right DVT compared to the left one. Among patients without known cancer at baseline (344 patients), bilateral DVT was an independent predictive factor of cancer discovery with a HR of 6.28 [2.06-19.15] compared with unilateral one. This study demonstrates that the location of DVT is an independent risk factor of DVT recurrence and cancer discovery.

Haematologica 2007; 88:(3)e40-e41

Few studies have investigated the possible influence of the anatomic location of DVT on the evolution of the disease and its significance.[1-3] They showed that proximal DVT compared to distal DVT[2] was an independent predictor of recurrence, and that patients with iliofemoral DVT had significantly greater risk of developing recurrent venous thromboembolism than did patients with femoral or popliteal DVT.[3] The association between DVT and cancer is well established.[4-6] In addition, several studies have suggested a relationship between the location of DVT (left or right, unilateral or bilateral) and cancer.[7-8] The issue of the location of DVT as a possible independent risk factor for DVT recurrence and cancer discovery therefore needs to be clarified.

In a recent large, randomized, clinical trial studying the efficacy and safety of vena caval filters in the prevention of pulmonary embolism in patients with proximal DVT, 400 patients with proximal DVT with or without pulmonary embolism were followed up for two years.[9] We used this database to determine whether the location of DVT is an independent predictor of DVT recurrence and cancer discovery.

The design of the PREPIC study was previously published.[9] Recurrent DVT was diagnosed by the appearance of a new intraluminal filling defect on venography, or a lack of compressibility at a new site or an extension to a new venous segment of the thrombus on duplex ultrasonography. In the absence of consensus on systematic screening, specific tests for cancer (such as mammography or prostate-specific antigen) in patients without any known cancer at inclusion were left to the discretion of the physician. The following characteristics were prospectively tested as potential independent risk factors for DVT recurrence and for cancer discovery in patients without any known cancer at inclusion: age, sex, body mass index, history of venous thromboembolism, surgery within the past 60 days, recent immobilization, known cancer, associated pulmonary embolism (confirmed by a high-probability lung scan or pulmonary angiography), the location of proximal DVT and the etiology: transient risk factors, permanent risk factor or idiopathic DVT.Evaluation of predictors of long-term events was performed using Cox proportional hazards models. The hazard ratio (HR) and associated 95% confidence interval (CI) were calculated with adjustment on treatment groups. Data on patients who died or were lost to follow-up were censored. Stepwise modeling was performed to screen potential variables (univariate models) for inclusion in the final model (multivariate model).

At two years, recurrent DVT occurred in 58 patients (cumulative rate, 16.8%). By univariate analyses, the presence of a filter, known cancer, surgery within the past 60 days, immobilization, iliac or caval proximal DVT, and right-sided proximal DVT were potential predictors of DVT recurrence. Multivariate analysis confirmed that known cancer (HR=2.23), insertion of filter (HR=1.95), right-sided proximal DVT (HR=1.88) and iliac or caval proximal DVT (HR=1.75; p=0.05) were independent risk factors for DVT recurrence (Table 1). There was no significant difference in recurrence rate related to age, sex, recent immobilization or surgery.

Among the 344 patients without known cancer at inclusion, 16 cancers (seven of the lung, three of the prostate, two of the pancreas, two of the colorectum, one of the stomach and one of the bladder) were discovered within two years after proximal DVT. By univariate analysis, male sex, idiopathic proximal DVT and bilateral proximal DVT at inclusion were potential predictors of cancer discovery. Multivariate analysis confirmed that these three parameters were independent predictors of cancer discovery : men gender (HR=7.18), bilateral DVT (HR=6.28) and idiopathic DVT (HR=4.14) (Table 2).

Besides insertion of filter[9] and known cancer at inclusion,[1,2,5] this study shows that the upper limit of DVT and its lateralization were independent risk factors for DVT recurrence. Besides male gender (to be confirmed by further studies) and idiopathic DVT [6,8,10] this study confirms that bilateral DVT[8] was a predictive factor of cancer discovery within the following two years.

In conclusion, by multivariate analyses, this prospective study shows that the location of the DVT was an independent predictor of recurrence of DVT and cancer discovery within two years. If these findings are confirmed by further large prospective epidemiologic studies, the location of thrombosis should be taken into consideration in order to optimally adapt the intensity and duration of anticoagulant therapy after an initial episode of DVT. In addition, these results lend support to the plea for an extensive search for occult cancer in patients with bilateral proximal DVT.

Table 1. Multivariate proportional hazard analyses of potential predictors of recurrence of DVT within two years after index proximal DVT

Characteristic	Hazard Ratio	95% CI	P value
Sex			
Filter insertion			
No filter	1.00	...	
Filter	1.95	1.08-3.56	.026
Heparin allocation			
Unfractionated heparin	1.00	...	
Low-molecular-weight heparin	1.19	0.68-2.08	.55
Significant predictors			
Cancer	2.23	1.09-4.56	.027
Side of proximal DVT at inclusion			
Left	1.00	...	
Right	1.88	1.07-3.30	.029
Upper limit of proximal DVT			
Femoral or popliteal	1.00	...	
Iliac or caval	1.75	1.00-3.07	.050
Non-significant predictors			
Recent immobilization	0.89	0.41-1.94	0.80
Surgery within the past 60 days	0.53	0.15-1.76	0.26

Table 2. Multivariate proportional hazard analyses of potential predictors of cancer discovery within two years after proximal DVT in patients without known cancer at inclusion

Characteristic	Hazard Ratio	95% CI	P value
Sex			
Filter utilization			
No filter	1.00		
Filter	1.32	0.44-3.92	.59
Heparin administration			
Unfractionated heparin	1.00	. .	
Low-molecular-weight heparin	1.55	0.55-4.42	.40
Symptom gravity			
Moderate	3.18	1.00-10.14	.0496
Proximal DVT location			
Unilateral	1.00	. .	
Bilateral	6.78	2.06-19.15	.0013
Etiology of proximal DVT			
Secondary DVT (transient or permanent risk factor)	1.00	. .	
Idiopathic DVT	4.14	1.26-13.57	.019

Acknowledgments: This study was funded in part by a grant from the Ministère de la Santé and the Fondation de l'Avenir. The authors gratefully acknowledge the contributions of all members of the PREPIC Study Group listed in reference no. 13. They are also indebted to Jean-Yves Darmon and Yves Cadroy (MediBridge Clinical Research, Velizy, France) for providing editorial assistance.x.

Silvy Laporte, Bernard Tardy, Sara Quenet, Andréa Buchmüller-Cordier, Sylvie Chabaud, Magali Epinat, Hervé Decousus, Patrick Mismetti, for the PREPIC Study Group.

Correspondence: Silvy Laporte

Thrombosis Research Group, Clinical Pharmacology Dept., University Hospital Bellevue

F-42055 Saint-Etienne France

Phone: +33 4 77 12 77 88 Fax: +33 4 77 12 78 20

Key words: Proximal DVT; recurrent DVT ; cancer; risk factor; epidemiology

References

1 Prandoni P, Lensing AW, Cogo A, et al. The long-term clinical course of acute deep venous thrombosis. Ann Intern Med 1996;125:1-7.
2 Hansson PO, Sorbo J, Eriksson H. Recurrent venous thromboembolism after deep vein thrombosis: incidence and risk factors. Arch Intern Med 2000;160:769-74.
3 Douketis JD, Crowther MA, Foster GA, Ginsberg JS. Does the location of thrombosis determine the risk of disease recurrence in patients with proximal deep vein thrombosis? Am J Med 2001;110:515-9.
4 Goldberg RJ, Seneff M, Gore JM, et al. Occult malignant neoplasm in patients with deep venous thrombosis. Arch Intern Med 1987;147:251-3.
5 Nordstrom M, Lindblad B, Anderson H, Bergqvist D, Kjellstrom T. Deep venous thrombosis and occult malignancy: an epidemiological study. Br Med J 1994;308:891-4.
6 Schulman S, Lindmarker P. Incidence of cancer after prophylaxis with warfarin against recurrent venous thromboembolism. Duration of Anticoagulation Trial. N Engl J Med 2000;342:1953-8.
7 Ouriel K, Green RM, Greenberg RK, Clair DG. The anatomy of deep venous thrombosis of the lower extremity. J Vasc Surg 2000;31:895-900.
8 Rance A, Emmerich J, Guedj C, Fiessinger JN. Occult cancer in patients with bilateral deep-vein thrombosis. Lancet 1997;350:1448-9.
9 Decousus H, Leizorovicz A, Parent F, et al. for the PREPIC Study Group. A clinical trial of vena caval filters in the prevention of pulmonary embolism in patients with proximal deep-vein thrombosis. N Engl J Med 1998;338:409-15.
10 Prandoni P, Lensing AWA, Buller HR, et al. Deep-vein thrombosis and the incidence of subsequent symptomatic cancer. N Engl J Med 1992;327:1128-33.