Recurrent venous thromboembolism under anticoagulant therapy:
A high risk in adenocarcinoma?

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Dear Sir,

Venous thromboembolism (VTE) is a major complication in patients suffering from active cancer. In both population-based case-control studies and clinical trials, active cancer is present in one out of five patients suffering from an acute symptomatic VTE event (1, 2). Although specific risk estimates of VTE by cancer type, stage and treatment options are poorly estimated, studies have suggested an especially high risk of VTE in the case of the following cancer types: haematological malignancies, lung or gastrointestinal cancers (3, 4). Within a given primary location, the risk of VTE differs according to histology, e.g. lung cancer patients with adenocarcinoma appear to have a higher risk of VTE than lung cancer patients with a squamous cell carcinoma (5). The event of VTE compromises survival of cancer patients, and the worse prognosis is partly linked to a high risk of VTE recurrence. In that instance, recent studies aimed to evaluate different therapeutic options, such as prolonged anticoagulation and/or the use of low molecular weight heparins (6, 7).

Since May 2000, a prospective observational register of VTE is maintained in our University Hospital. We herein analyzed this database, with the aim of assessing the VTE recurrence rate in cancer patients, with special attention to tumor histology.

All patients, aged over 18 years, living in one of the four Brest districts in Western France, and hospitalized with a well-documented symptomatic VTE were eligible for enrolment in the register. The diagnostic criteria applied in case of a clinical suspicion of VTE have been described previously (8). Among the major acquired risk factors, attention was paid to the presence of active cancer, defined as either i) a diagnosis of cancer, other than basal-cell or squamous cell carcinoma of the skin, within 12 months before the VTE event, ii) any treatment for cancer within the previous 12 months, iii) recurrent or metastatic cancer or iv) the diagnosis of cancer after the VTE event, following an usual screening (clinical examination, chest x-ray and routine blood sampling). Follow up of cancer patients took place throughout the study period at 6-month intervals via scheduled outpatient appointments, review of patients files, and/or phone calls to both general practitioners and patients. Data on follow-up included death, recurrence of VTE and management of anticoagulant therapy. The diagnosis of recurrent DVT by CUS was based on either a previously compressible venous segment that could no longer be compressed or an extension of 90 mm or more of the thrombus in the case of a previously abnormal venous segment (9). The diagnosis of recurrent PE was based on i) a high probability lung scan, with the presence of new or enlarged segmental perfusion defects, ii) a central filling defect outlined by contrast material or a complete occlusion in a segmental or more proximal pulmonary artery previously visualized on an helical computed tomography, or iii) an intra-luminal filling defect or a sharp cut-off in a previously normal vessel on pulmonary angiography. Collection of data ended in August 2004. In the absence of recent data – within two months of endpoint – deaths certificate registers held in the place of birth of the patients were checked to ensure completeness.

From May 2000 to August 2004, data from 1,068 patients suffering from acute VTE were gathered in the register (median of age 64.4 years, 476 men). Active cancer was diagnosed in 147 patients (13.8%, median of age 71.5 years, 88 men, 78 adenocarcinoma). Median (range) of follow-up after diagnosis was 303 days (3 – 1,469). Cancer was already known before the VTE event in 99 patients, while diagnosis of cancer took place at the time of VTE diagnosis in 30 patients; in the remaining 18 patients, cancer was diagnosed during follow-up. At the endpoint, 96 out of these 147 cancer patients had died. Recurrence of VTE was diagnosed in 28/147 patients (19%) and the median of time between the two VTE events was 43 days. Among the 28 recurrent events, 17 occurred while on anticoagulant therapy [14 patients receiving either a low molecular weight heparin adapted to body weight (n=3) or an oral anticoagulant with an INR ratio of 2 or more (n=11) vs. three patients receiving an oral anticoagulant therapy at a sub therapeutic level]. Among the remaining 11 patients with recurrent venous thromboembolism and active cancer that had previously stopped antithrombotic treatment, anticoagulation was stopped at least six months after its initiation in eight cases and, due to major bleeding, within the first month in three cases.

VTE recurrence occurred in 17 out of the 78 patients suffering from an adenocarcinoma and in 11 out of 69 patients suffering from another type of malignancy (22% vs. 17% ns) (Fig. 1). Mean age (± SD) of patients with adenocarcinoma was 73.7 years (± 7.8) and mean age of patients with other type of malig-
nancy was 66.1 years (± 10.8). The presence of metastases was mentioned in 10 out of 17 patients with adenocarcinoma and in six out of 11 patients with other type of malignancy.

Recurrence while on anticoagulant therapy at therapeutic levels was observed in 12/17 patients with an adenocarcinoma (70.6%; 95% CI: 44.0 – 89.7%) and in 2/11 patients with another type of malignancy (18.2%; 95% CI: 2.3 – 51.8%) (p= 0.018, Fisher’s exact test). All patients suffering from a recurrent event while on anticoagulant at therapeutic levels died before the endpoint time of the follow-up.

Consistent with previous findings, our study shows a high VTE recurrence rate in patients suffering from active cancer. In addition, recurrences while on anticoagulant at therapeutic levels were associated with a poor prognosis and were observed mostly in patients suffering from adenocarcinoma.

Since the description by Trousseau of patients suffering from a DVT episode as the first manifestation of a gastric carcinoma, patients with adenocarcinoma are believed to have a high risk of developing a DVT during the course of their malignancy (10). In further descriptive studies aimed at identifying active cancer as a risk factor in view of a VTE episode, pancreas, prostate, colorectal, stomach and lung were frequent primary locations pointed out (3, 11). Finally, the cohort study of 678 lung cancer patients performed by Blom et al. showed that the risk of VTE is higher for patients with adenocarcinoma than for those with squamous cell carcinoma, with a hazard ratio of 3.1 (95% CI: 1.4 – 6.9). Data from our study suggest in addition a high risk of recurrence for adenocarcinoma while on anticoagulation at therapeutic levels. The fact that most of those patients were on oral anticoagulant is consistent with recent research. Wahrenbrock et al. have shown that carcinoma mucins can activate platelets and generate thrombi in an in vitro model, an effect markedly diminished in P- or L-selectin deficient mice or in the presence of heparin (12). This beneficial effect of heparin was not observed in P- or L-selectin deficient mice, suggesting that heparin acts through blockade of P- and L-recognition of ligands, and not through thrombin depression. Inhibition of thrombin by adding hirudin to the model instead of heparin did not block platelet aggregation. It was thus suggested that circulating mucins can interact with leukocyte L-selectin and platelet P-selectin without requiring accompanying thrombin generation. Consistently, dalteparin, a low-molecular-weight heparin, has recently been shown to have a superior efficacy to warfarin in a large trial of patients with active cancer and a VTE episode (7).

Although such an observational study was not designed to test the hypothesis of a superiority of low-molecular-weight heparin over oral anticoagulant therapy and can thus not avoid potential biases, our data suggest that special attention might be paid to the type of malignancy in future interventional trials.

**References**