

Blood Coagulation, Fibrinolysis and Cellular Haemostasis

Predicting recurrences or major bleeding in cancer patients with venous thromboembolism

Findings from the RIETE Registry

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Summary

Cancer patients with acute venous thromboembolism (VTE) have an increased incidence of recurrences and bleeding complications while on anticoagulant therapy. Methods RIETE is an ongoing registry of consecutive patients with acute VTE. We tried to identify which cancer patients are at a higher risk for recurrent pulmonary embolism (PE), deep vein thrombosis (DVT) or major bleeding. Up to May 2007, 3,805 cancer patients had been enrolled in RIETE. During the first three months of follow-up after the acute, index VTE event, 90 (2.4%) patients developed recurrent PE, 100 (2.6%) recurrent DVT, 156 (4.1%) had major bleeding. Forty patients (44%) died of the recurrent PE, 46 (29%) of bleeding. On multivariate analysis, patients aged <65 years (odds ratio [OR]: 3.0; 95% confidence interval [CI]: 1.9–4.9),

with PE at entry (OR: 1.9; 95% CI: 1.2–3.1), or with <3 months from cancer diagnosis to VTE (OR: 2.0; 95% CI: 1.2–3.2) had an increased incidence of recurrent PE. Those aged <65 years (OR: 1.6; 95% CI: 1.0–2.4) or with <3 months from cancer diagnosis (OR: 2.4; 95% CI: 1.5–3.6) had an increased incidence of recurrent DVT. Finally, patients with immobility (OR: 1.8; 95% CI: 1.2–2.7), metastases (OR: 1.6; 95% CI: 1.1–2.3), recent bleeding (OR: 2.4; 95% CI: 1.1–5.1), or with creatinine clearance <30 ml/min (OR: 2.2; 95% CI: 1.5–3.4), had an increased incidence of major bleeding. With some variables available at entry we may identify those cancer patients with VTE at a higher risk for recurrences or major bleeding.

Keywords

Cancer, venous thromboembolism, bleeding, recurrences

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Introduction

Cancer patients with venous thromboembolism (VTE) have an increased incidence of VTE recurrences and anticoagulant-related bleeding complications compared with those without cancer (1–5). Reliable information on the factors determining the risk for VTE recurrences or major bleeding complications may facilitate better use of therapy by improving selection of patients in whom its benefit will likely outweigh the risk, and by identifying those who may benefit from careful management. In

addition, early detection and prompt therapy of complications with supportive measures might reduce mortality.

A number of variables (including age, cancer, renal insufficiency, recent bleeding or the clinical presentation of VTE) have been associated with a worse outcome in patients with VTE. However, those with cancer are an heterogeneous group due to differences in tumor site, therapy, extent or time interval between diagnosis of cancer and diagnosis of VTE. Some of these variables might also influence the outcome in cancer patients with VTE.

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The RIETE Registry is an ongoing, international (Spain, France, Italy, Israel, Argentina), multicenter, prospective registry of consecutive patients presenting with symptomatic acute VTE confirmed by objective tests (5–9). In this analysis we assessed the three-month outcome in all VTE patients with active cancer, trying to identify which clinical variables at baseline may predict recurrent pulmonary embolism (PE), recurrent deep-vein thrombosis (DVT), or major bleeding.

Patients and methods

Inclusion criteria

Consecutive patients with symptomatic, acute DVT or PE, confirmed by objective tests (contrast venography or ultrasonography for suspected DVT; pulmonary angiography, lung scintigraphy, or helical computed tomography [CT] scan for suspected PE), are enrolled in RIETE. Patients are excluded if they are currently participating in a therapeutic clinical trial, or if they will not be available for a three-month follow-up. All patients provide oral consent to their participation in the registry, according to the requirements of the ethics committee within each hospital.

Follow-up

Patients are managed according to the clinical practice of each participating hospital and were not subject to any predetermined intervention. After VTE diagnosis, all patients are followed-up for at least three months. During each visit, any signs or symptoms suggesting VTE recurrences or bleeding complications were noted. Each episode of clinically suspected recurrent DVT or PE was documented by repeat compression ultrasonography, venography, lung scanning, helical CT scan or pulmonary angiography.

Study endpoints

The major outcomes for this study were the development of symptomatic, objectively confirmed, recurrent PE (with or without DVT signs), recurrent DVT alone, or major bleeding during the first 90 days of anticoagulant therapy. Bleeding complications were classified as ‘major’ if they were overt and required a transfusion of two units of blood or more, or were retroperitoneal, spinal or intracranial, or when they were fatal. Fatal bleeding was defined as any death occurring shortly after a major bleeding episode. Fatal PE, in the absence of autopsy, was defined as any death appearing shortly after PE diagnosis, in the absence of any alternative cause of death. Study endpoints are adjudicated by the attending physicians. In case of doubt (i.e. in the absence of objective confirmation of the cause of death) the final decision was taken by the RIETE Adjudication Committee.

Study variables and definitions

The following parameters are recorded in RIETE: patient's baseline characteristics; clinical status including any coexisting or underlying conditions; clinical characteristics of the malignancy (site, extent, time interval between diagnosis of cancer and diagnosis of VTE); additional risk factors for VTE; the treatment received upon VTE diagnosis; and the outcome during the first three months of therapy. Active cancer was defined as newly

diagnosed cancer or when receiving anti-neoplastic treatment of any type (i.e. surgery, chemotherapy, radiotherapy, hormonal, support therapy, or combined treatments). Immobilized patients are defined as non-surgical patients who had been immobilized (i.e. total bed rest with bathroom privileges) for ≥ 4 days in the two-month period prior to VTE diagnosis. Surgical patients are defined as those who underwent an operation in the two months prior to VTE. Recent bleeding was considered in those patients suffering major bleeding < 30 days prior to VTE. The first creatinine measured after VTE diagnosis was the one used to calculate creatinine clearance, according to the Cockcroft and Gault formula (10).

Data collection and monitoring

The attending physicians ensure that eligible patients were consecutively enrolled. Data are recorded on to a computer-based case report form at each participating hospital and submitted to a centralized coordinating center through a secure website. Encryption of data is used to enhance confidentiality and security. Data quality is regularly monitored and documented electronically to detect inconsistencies or errors, which are resolved by the local coordinators. Data quality is also monitored by periodic visits to participating hospitals, by contract research organizations, who compare the medical records with the data in the web. A data audit is performed at periodic intervals. Patient identities remain confidential because they are identified by a unique number assigned by the study coordinating center, which is responsible for all data management.

Statistical analysis

Odds ratios and corresponding 95% confidence intervals were calculated using the Epidat 3.1 program, and a p -value < 0.05 was considered to be statistically significant. The significance of a number of variables available at baseline on the incidence of recurrent PE, recurrent DVT, or major bleeding within the first three months of therapy was tested by univariate analysis (using Chi-Square test for categorical variables and t -test for numerical variables). Those variables identified by the univariate analysis as potential risk factors and achieving a significance level of $p < 0.1$ were considered for inclusion in a multivariate logistic regression analysis to identify independent risk factors for each of the study outcomes.

Results

Up to May 2007, a total of 18,883 patients with symptomatic, objectively confirmed, acute VTE had been enrolled in RIETE and followed-up for three months. Of them, 3,805 (20%) had active cancer. Their clinical characteristics, treatment details, and three-month outcome are depicted in Table 1. Of these, 889 (23%) patients died during the three-month study period: 403 died of disseminated malignancy, 49 of recurrent PE, 40 of major bleeding, 24 of sudden dyspnea (with no objective tests to confirm or rule out fatal PE), 51 other reasons, 322 unknown.

Recurrent PE

Ninety (2.4%) patients developed recurrent PE (either recurrent PE alone or recurrent DVT and PE) during the study period: 54

Table 1: Clinical characteristics and three-month outcome of the 3,805 cancer patients with acute VTE.

	Patients, N	Recurrent PE	Recurrent DVT	Major bleeding	Remaining patients
	3805	90	100	156	3473
Clinical characteristics					
Gender (males)	2086 (55%)	51 (57%)	60 (60%)	89 (57%)	1896 (55%)
Age <65 years	1230 (32%)	49 (54%) [‡]	44 (44%) [†]	48 (31%)	1097 (32%)
Body weight <65 kg	1263 (33%)	31 (34%)	28 (28%)	64 (41%)*	1147 (33%)
Underlying conditions					
Recent major bleeding	131 (3.4%)	3 (3.3%)	4 (4.0%)	18 (12%) [‡]	108 (3.1%)
CrCl <30 ml/min	613 (16%)	15 (17%)	9 (9.0%)	48 (31%) [‡]	547 (16%)
Anemia	2127 (56%)	50 (56%)	54 (54%)	113 (72%) [‡]	1920 (55%)
Risk factors for VTE					
Surgery	617 (16%)	14 (16%)	12 (12%)	16 (10%)*	575 (17%)
Immobility ≥4 days	805 (21%)	17 (19%)	23 (23%)	55 (35%) [‡]	715 (21%)
Prior VTE	548 (14%)	14 (16%)	16 (16%)	16 (10%)	504 (15%)
VTE characteristics					
Clinically overt PE	1830 (48%)	61 (68%) [‡]	43 (43%)	71 (46%)	1669 (48%)
Cancer characteristics					
Metastatic	1684 (44%)	48 (54%)	49 (51%)	90 (61%) [‡]	1507 (43%)
Diagnosis <3 months earlier	1464 (38%)	46 (51%) [†]	54 (54%) [‡]	67 (43%)	1303 (37%)
Site of cancer					
Lung	461 (12%)	18 (20%)*	25 (25%) [‡]	16 (10%)	405 (12%)
Breast	483 (13%)	10 (11%)	3 (3.0%) [†]	7 (4.5%) [†]	463 (13%)
Gastrointestinal	813 (21%)	22 (24%)	17 (17%)	41 (26%)	735 (21%)
Pancreas	134 (3.5%)	0	7 (7.0%)	4 (2.6%)	123 (3.5%)
Genitourinary	1096 (29%)	19 (21%)	26 (26%)	53 (34%)	1005 (29%)
Haematologic	285 (7.5%)	3 (3.3%)	6 (6.0%)	12 (7.7%)	266 (7.7%)
Cerebral	199 (5.2%)	11 (12%) [†]	7 (7.0%)	8 (5.1%)	173 (5.0%)
Other	334 (8.8%)	7 (7.7%)	9 (9.0%)	15 (9.6%)	303 (8.7%)
Treatment					
Initial therapy, LMWH	3491 (92%)	78 (87%)	89 (89%)	134 (86%) [†]	3201 (92%)
Long-term, AVK drugs	1643 (43%)	29 (32%)*	39 (39%)	45 (29%) [‡]	1534 (48%)
Long-term, LMWH	1855 (49%)	42 (47%)	57 (57%)	73 (47%)	1689 (52%)
Inferior vena cava filter	146 (3.8%)	13 (14%) [‡]	16 (16%) [‡]	12 (7.7%) [‡]	106 (3.1%)
3-month outcome[#]					
Fatal bleeding	46 (1.2%)	0	1 (1.0%) [‡]	46 (30%) [‡]	0
Fatal recurrent PE	49 (1.3%)	40 (44%) [‡]	0	9 (5.8%) [‡]	0
Overall death	889 (23%)	52 (58%) [‡]	28 (28%)	93 (60%) [‡]	728 (21%)

Comparisons between patients with recurrent PE, recurrent DVT, or major bleeding, and those with no such complications: *p<0.05, †p<0.01, ‡p<0.001. #Some patients developed more than one event. VTE, venous thromboembolism; DVT, deep-vein thrombosis; PE, pulmonary embolism; UFH, unfractionated heparin; LMWH, low-molecular-weight heparin; AVK, anti-vitamin K; CI, confidence intervals.

during the first month, 23 in the second, 13 in the the third month. Of these, six patients first had major bleeding, then developed the PE after discontinuing anticoagulant therapy. Forty patients (44%) died of the recurrent PE. Patients with recurrent PE were significantly younger, presented with clinically overt PE at entry

more often, had a more recent diagnosis of cancer, and more frequently lung or brain cancer, than those who did not recur (Table 1). On multivariate analysis, only patients aged <65 years, with clinically overt PE at entry, or with cancer detected <3 months earlier had an increased risk for recurrent PE (Table 2).

Table 2: Multivariate analysis on the risk to develop recurrent PE, recurrent DVT, or major bleeding.

	Odds ratio (95% CI)	P-value
Recurrent PE		
Age <65 years	3.0 (1.9–4.9)	<0.001
Diagnosis <3 months earlier	2.0 (1.2–3.2)	0.005
Clinically overt PE	1.9 (1.2–3.1)	0.01
Recurrent DVT		
Diagnosis <3 months earlier	2.4 (1.5–3.6)	<0.001
Age <65 years	1.6 (1.0–2.4)	0.04
Major bleeding		
Recent major bleeding	2.4 (1.1–5.1)	0.03
CrCl <30 ml/min	2.2 (1.5–3.4)	<0.001
Immobilization ≥4 days	1.8 (1.2–2.7)	0.005
Metastatic cancer	1.6 (1.1–2.3)	0.03

PE, pulmonary embolism; DVT, deep-vein thrombosis; CrCl, creatinine clearance; CI, confidence intervals.

Recurrent DVT

One-hundred patients (2.6%) had recurrent DVT (48 in the first month, 35 second, 17 third). Five of them presented the DVT shortly after withdrawing therapy due to major bleeding, two had simultaneously major bleeding and recurrent DVT. Their 28% death rate at three months was not significantly higher to the 21% rate in patients with no recurrences or bleeding (Table 1). Those subsequently developing recurrent DVT were younger, more often diagnosed of cancer <3 months before the VTE event, had more frequently lung or pancreatic cancer, but less often brain or breast malignancies (Table 1). On multivariate analysis, only patients <65 years, or with <3 months since cancer diagnosis were independently associated with an increased risk for recurrent DVT (Table 2).

Major bleeding

One-hundred fifty-six patients (4.1%) developed major bleeding (109 in the first month, 32 second, 15 in the third month), the most common sites being the gastrointestinal tract (47%), genitourinary (19%), or the brain (8.3%). Forty-six (29%) of these patients died of bleeding. Patients who subsequently bled weighed less, and had recent bleeding, immobility, creatinine clearance <30 ml/min, anemia, or metastatic cancer more frequently than those who did not bleed. Those receiving initial therapy with low-molecular-weight heparin (LMWH) bled less often than those receiving unfractionated heparin, while those on long-term therapy with vitamin K antagonists (VKA) bled less frequently than those on LMWH (Table 1). On multivariate analysis, only patients with recent bleeding, creatinine clearance <30 ml/min, immobility, or metastases had an increased risk for major bleeding (Table 2).

Discussion

Our data, obtained from a large prospective series of consecutive patients with cancer and VTE, reveal that with some variables

available at entry it is possible to identify those at an increased risk for VTE recurrences or major bleeding during the first three months of anticoagulant therapy. In our series, recurrent PE appeared in 2.4% of patients, and 44% of them died. Major bleeding occurred in 4.1%, and 29% also died. Thus, its clinical impact is considerable.

Accumulating evidence suggests that both the intensity and duration of treatment should be tailored to the risk of recurrences or bleeding in an individual patient, particularly in those with cancer, renal insufficiency, or very elderly (11–16). In the overall population of patients with VTE we recently reported that some variables at entry (age, recent bleeding, cancer, renal insufficiency, PE at baseline and anemia) may be useful to identify those at an increased risk for major bleeding (17). However, in VTE patients with cancer the presence of anemia seems to have little influence on outcome. Alternatively, the presence of metastases and the time interval between diagnosis of cancer and diagnosis of VTE proved to have more influence on outcome. Thus, our findings may be of added value in comparison with a model applicable to all patients with VTE. Interestingly, we failed to find any influence of the tumor site on outcome. On univariate analysis patients with breast cancer bled less often, and those with lung cancer recurred more often, but these differences disappeared on multivariate analysis.

Unexpectedly, we found patients receiving long-term therapy with LMWH to have an increased incidence of major bleeding and VTE recurrences compared to those on VKA. Four randomized trials, conducted in large cancer populations, have demonstrated that LMWH can be used for the long-term therapy of VTE, resulting in significantly reduced rates of recurrent VTE compared with VKA, without any increase in bleeding (18–21). Accordingly, the Seventh American College of Chest Physicians Consensus Guidelines recommend for cancer patients with VTE the use of LMWH at fixed doses for the first 3–6 months (22). However, the RIETE Registry was set up in 2001, and many patients had been recruited before the publication of the guidelines. In addition, the use of VKA is often problematic in patients with advanced cancer, due to a high risk of drug interactions, malnutrition, dehydration, or difficulties with periodic monitoring of the prothrombin time. Thus, it is likely that many doctors had prescribed VKA mainly to those patients with less advanced malignancies.

In this study, selection bias was avoided by including consecutive patients with objectively confirmed VTE, but it has potential limitations that should be addressed. First, the small percentage of events may imply overfitting, and hence over-optimistic results. Thus, the predictive model needs to be validated with a separate data set. Second, while the frequency of major bleeding in our study was similar to that reported in several randomized clinical trials (and this is important because, unlike the careful patient selection that characterizes clinical trials, our patient population reflects routine, unmonitored medical practice involving a broad spectrum of patients with VTE), the incidence of recurrences is slightly lower. Actually, in clinical practice many doctors may be reluctant to perform diagnostic tests to VTE patients with terminal cancers with dyspnea or swollen limbs. Third, the risk of recurrent PE or bleeding is probably modified by characteristics that change during the course of

therapy, such as differences in the intensity of anticoagulation when receiving VKA, the use of concomitant drugs, or the presence of intercurrent illnesses. Fourth, in RIETE we do not gather information on other potential risk factors, such as tumor histology and cancer treatment, that would likely influence the results.

In summary, we identified some variables easily available at entry that may identify those cancer patients with VTE at a higher risk for recurrences or major bleeding. This information has to be validated in further studies in order to help clinicians to weigh the risks and benefits of prescribing anticoagulant therapy in an individual patient.

APPENDIX

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