Chapter 6

Recurrent venous thromboembolism in anticoagulated patients with cancer – management and short-term prognosis

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Abstract

**Background:** Recommendations for management of cancer-related venous thromboembolism (VTE) in patients already receiving anticoagulant therapy are based on low quality evidence. This international registry sought to provide more information on outcomes after a breakthrough VTE in relation to anticoagulation strategies.

**Methods:** Patients with cancer and VTE despite anticoagulant therapy were reported to the registry. Data on treatments, VTE events, major bleeding, residual thrombosis symptoms and death were collected for the following 3 months. Breakthrough VTE and subsequent recurrences were objectively verified. Outcomes with different treatment strategies were compared with Cox proportional hazards regression.

**Results:** We registered 212 patients with breakthrough VTE. Of those, 59% had adenocarcinoma and 73% had known metastases. At the time of the breakthrough event 70% were on low-molecular-weight heparin (LMWH), 27% on a vitamin K antagonist (VKA); 70% had a therapeutic or supratherapeutic dose. After breakthrough the regimen was unchanged therapeutic in 33%, dose increased in 31%, switched to another drug in 24% and other management in 11%. During the 3 following months 11% had another VTE, 8% had major bleeding and 27% died. Of the survivors, 74% had residual thrombosis symptoms. Additional VTE recurrence was less common with LMWH than with VKA (hazard ratio [HR] 0.28; 95% confidence interval [CI], 0.11-0.70) but similar with unchanged or increased anticoagulant intensity (HR 1.09; 95% CI, 0.45-2.63). Bleeding rate did not increase significantly with dose escalation.

**Conclusion:** Morbidity and mortality is high after cancer-related VTE recurrence despite anticoagulation. Further treatment appears more effective with LMWH than with VKA.
Introduction

Treatment of venous thromboembolism (VTE) in patients with active cancer is fraught with difficulties. The risk of recurrent VTE, i.e. treatment failure, is increased about 3-fold compared with patients without cancer\textsuperscript{1-3} and even higher in patients with cancer on chemotherapy\textsuperscript{3}.

In studies on the new oral anticoagulants, with possible selection of patients with less aggressive malignant disease or cancer therapy, the increase was 1.4 fold on the new agents and 2.4-fold on vitamin K antagonists (VKA).\textsuperscript{4} Simultaneously, the risk of bleeding complications is increased 2.5 to 6-fold in patients with malignancies.\textsuperscript{1,2,5} Furthermore, oral anticoagulation might be inadequately absorbed in case of chemotherapy-associated emesis. Drug interactions between antibiotics or antifungals and the oral anticoagulants could contribute to sub- or supratherapeutic levels and tailoring of VKA in thrombocytopenic patients can be challenging. On the other hand, low-molecular-weight heparin (LMWH) requires daily or twice-daily subcutaneous injections, which may result in large, painful subcutaneous haematomas in patients with thrombocytopenia associated with chemotherapy or bone marrow invasion.

Management of recurrent VTE despite adequate anticoagulation poses added challenges. The main options are to intensify the treatment or switch to a different anticoagulant, typically from VKA to therapeutic dose LMWH. The American Society of Clinical Oncology suggests treatment with an alternate anticoagulant, increasing dose of LMWH, or insertion of a vena cava filter.\textsuperscript{6} The Italian Society for Haemostasis and Thrombosis suggests in addition the options of increased intensity of VKA or subcutaneous unfractionated heparin adjusted according to the activated partial thromboplastin time.\textsuperscript{7} A recently published international guideline suggests similar strategies, i.e. a switch from VKA to LMWH, increase of the dose of LMWH or insertion of vena cava filter, recognizing the very low quality of evidence.\textsuperscript{8} In a guidance document on challenging cases with cancer-related thrombosis a switch from VKA to LMWH is “recommended”, whereas for those already on LMWH an increase of the dose is “suggested”.\textsuperscript{9} Physicians may, however, be reluctant to intensify the treatment, fearing an increased risk of bleeding even though the bleeding might be related mainly to cancer invasion and not altered by the anticoagulant regimen. In a retrospective study of 70 patients with cancer and VTE on treatment with VKA or LMWH, intensification of therapy did not seem to increase the risk of bleeding.\textsuperscript{10}

Within the subcommittees on Control of Anticoagulation and on Hemostasis and Malignancy of the International Society on Thrombosis and Haemostasis (ISTH) this international registry was approved and started in 2006. The aims were a) to explore what different antithrombotic regimens were used to manage patients with cancer and VTE despite anticoagulation, and b) to assess the 3-month incidence of recurrent VTE and bleeding on these regimens.
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Methods

Participation in the registry “Recurrent venous thromboembolism in anticoagulated patients with cancer” was open to any investigator. The majority of the investigators were haematologists that were typically consulted by the oncologist caring for the patient with cancer and thrombosis. At two sites cases were captured from a local registry of all patients with cancer and VTE or from a concurrent case-control study on such patients. The registry was announced annually at the meetings of the Standardization and Scientific Committees of the ISTH, posted on the ISTH website, advertised via e-mail to the ISTH members and by distribution of pamphlets at some other congresses. Instructions, case report forms and a sample informed consent form were available to download from the ISTH website. The registry was supported by an unrestricted educational grant from LEO Pharma to ISTH. The company also promoted physician participation in the registry but had otherwise no influence on the design, management, analysis or presentation of results.

Eligible patients were those with 1) active cancer, who 2) developed an objectively verified, new venous thromboembolic event within the previous 12 months, 2) while receiving anticoagulant treatment with unfractionated heparin (activated partial thromboplastin time [aPTT] at least twice the upper limit of normal), LMWH at a daily dose of at least 150 units/kg (1.5 mg/kg) within the first week after a previous VTE or at least 4,000 units/kg (40 mg/kg) thereafter, fondaparinux at a daily dose of 5 mg (weight <50 kg), 7.5 mg (weight 50-100 kg) or 10 mg (weight >100 kg), or a VKA with international normalised ratio (INR) closest to the breakthrough event of 1.8. Patients were excluded if they had basal cell carcinoma, myelodysplastic syndrome, myeloproliferative syndrome, or pre-malignant disease, e.g. carcinoma-in-situ, or if the thromboembolic event was superficial thrombophlebitis. The qualifying event (“breakthrough event”) was, in case of multiple verified thrombotic events on anticoagulation, the first objectively verified event after starting anticoagulant therapy in the setting of active cancer.

The breakthrough event had to be objectively verified. We compared reports of compression ultrasound, venograms, ventilation-perfusion lung scans and computed tomography of the pulmonary arteries, and a recurrence had to be in a different anatomical area from the previous event or reported by the radiologist as a definite extension of the previous thrombus.

We captured information on age, sex, body weight, creatinine, date of cancer diagnosis, type and extent of cancer, current antineoplastic therapy, Eastern Cooperative Oncology Group (ECOG) performance status score at the time of the breakthrough event, date of the breakthrough event and of the closest in time previous VTE event (“previous VTE event”), diagnostic method used for both of these VTE events, antithrombotic treatment (including inferior vena cava filter insertion) given for the previous VTE event initially and at the time of the breakthrough event as well as during the 3 months after the breakthrough event, any levels of INR, aPTT and anti-factor Xa available from the time of
the breakthrough event and thereafter. During the 3-month follow-up after the breakthrough event we captured any additional objectively diagnosed breakthrough VTE events with date, location, and diagnostic method, any major bleeding event – according to ISTH criteria11– with date and location, death or, if alive, whether residual thrombosis symptoms were present.

We calculated the creatinine clearance based on the information available according to the Cockroft-Gault formula.12 The investigators were requested to enclose de-identified diagnostic reports for the different VTE events with the case report forms. These were used for verification that the breakthrough event and further VTE events were new. We classified “therapeutic” doses of LMWH as any daily dose within ±20% of the recommended dose; for bemiparin 92-138 IU/kg, for dalteparin 160-240 IU/kg, for enoxaparin on deep venous thrombosis (DVT) indication 1.2-1.8 mg/kg; for enoxaparin on the pulmonary embolism (PE) indication 1.6-2.4 mg/kg, for nadroparin 152-228 IU/kg, and for tinzaparin 140-210 IU/kg. Doses below or above those ranges were classified as “subtherapeutic” and “supratherapeutic”, respectively. For patients on VKA, “therapeutic” was INR 2.0-3.0 at the time of the breakthrough event.

Analysis of the effect of changed anticoagulation intensity was based on transition from “subtherapeutic” to “therapeutic” or from “therapeutic” to “supratherapeutic” versus no such transition. As a sensitivity analysis, we also analyzed for the patients on any kind of heparin before as well as after the breakthrough event the actual increase of the daily dose.

After closure of the registry we asked each center to provide information on the number of patients with cancer and VTE diagnosed annually and on the number of recurrences on anticoagulation – if possible from local hospital diagnosis statistics or as an estimate.

**Statistical analyses**

We did not perform any formal sample size calculation since the event rate for VTE recurrence after a breakthrough event was not known, especially if the treatment was intensified or changed. Likewise, there was at the time of registry start no reliable information on rates of major bleeding after intensified anticoagulation. We assumed that the majority of patients would have the breakthrough event on VKA or LMWH and we wanted at least 100 patients on one of those drugs. Thus, we aimed at a total of 200 patients.

Results are presented with mean and standard deviation (SD) for normal distributions and median and interquartile range (IQR) for skewed distributions. Comparisons of binomial distributions between groups were done with Chi square test or, in case of less than 10 in any subset, with Fisher’s exact test. Hazard ratios (HR) and 95% confidence intervals (CI) were estimated using Cox proportional hazards regression. Survival during 3 months after the breakthrough event without recurrent VTE or without major bleeding is shown with Kaplan-Meier plots.
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The registry was approved by the local Research Ethics Board or Institutional Review Board as a retrospective chart review in those jurisdictions where this was required.

Results

Study population characteristics

The index breakthrough events that we captured occurred over a 10-year period, from June 30, 2004 to June 4, 2014. Seventeen sites in 10 countries contributed a total of 212 cases. They were followed until death or for a maximum of 3 months and events after that time point have been censored. The patient and thrombosis characteristics at the time of breakthrough are shown in Table 6.1. The 4 cases with atrial fibrillation and the case with superficial thrombophlebitis as original indication for anticoagulation did not constitute protocol violations.

The cancer-related characteristics are shown in Table 6.2. The case report form contained a limited number of options for cancer site and type and included “other”, which was not always specified by the investigator. Prostate cancer was specified in 2 cases but there might also be such cases in the “genito-urinary” group. Adenocarcinoma was by far the most common cancer type (59%). The majority of cases (73%) were known to have metastatic disease. Sixteen patients had ECOG score 0 (asymptomatic) and 5 had ECOG score 4 (bedridden). Most patients had current chemotherapy, either alone (44%) or in combination with other cancer therapy (10%) but 27% had no ongoing treatment for malignancy.

The breakthrough event

The characteristics of the breakthrough event and the anticoagulant treatment at the time of this diagnosis are reviewed in Table 6.3. Current treatment was with LMWH in the majority (70%) and with VKA in 27%. The most common LMWH was dalteparin (57%), followed by enoxaparin (24%). Seventy percent of the patients had a therapeutic or supratherapeutic dose of anticoagulant at the time of the breakthrough event. For 3 of 4 patients on unfractionated heparin the aPTT was available from the event and 2 were therapeutic (57 s and 92 s). Anti-factor Xa was only available for 21 patients on LMWH and it was >0.3 U/mL and >0.7 U/mL in 20 and 11 of those cases, respectively, with a mean of 0.79 ±0.34 U/mL, but the timing in relation to the last dose is unknown.

Anticoagulation management after the breakthrough event is shown in Table 6.4. In 17 cases (8%) the initial treatment after the breakthrough VTE was merely with continuation of the same subtherapeutic dose or change to another anticoagulant but still at subtherapeutic dose, or even with a decrease of intensity. In another 70 patients (33%) the regimen was unchanged therapeutic intensity with the same drug. For 51 patients (24%) the anticoagulant drug was changed; another 66 (31%) had the same drug continued but at
an increased dose; 7 (3%) had been on and continued with supratherapeutic intensity. For long-term therapy a switch from VKA at breakthrough to a heparin (mostly LMWH) was much more common (33 cases) than in the opposite direction (6 cases). The initial dose regimen after the breakthrough was reduced in intensity for long-term anticoagulation for 13 patients (6%).

Breakthrough VTE, when the previous event (= the indication for anticoagulation) had been DVT, was further DVT in 64%, PE in 24%, both DVT and PE in 11% and mesenteric vein thrombosis in 1%. When the previous event was PE, breakthrough VTE was further PE in 35%, DVT in 58% and both DVT and PE in 7%. For those with both DVT and PE originally, breakthrough was the combination in 10%, only DVT in 57% and only PE in 33%. Each original event of portal and cerebral sinus vein thrombosis reoccurred as progression in the same respective location.

**Recurrent VTE during follow-up**

During the 3-month follow-up 24 patients (11%) had additional recurrent VTEs, none of which occurred during the first week. Recurrence was observed among 8% of patients who continued subtherapeutic anticoagulation, 13% of those with unchanged therapeutic regimen, 7% of those with altered drug but same intensity, 9% of those with increased intensity, and 15% of those on supratherapeutic intensity. The risk of recurrence did not seem to differ between those who had their anticoagulant intensity unchanged versus those with intensity increased after breakthrough (HR 1.09; 95% CI, 0.45-2.63; Figure 6.1a). This was also true when we compared the daily dose of unfractionated heparin/LMWH/fondaparinux before and after the breakthrough event, using a cut off of 20% increase in dose (6% recurrence with less increase, 11% with more increase) or 25% increase (7% vs. 11%, respectively). Recurrence occurred in 29% of those on VKA versus 9% of those on LMWH (HR 0.28; 95% CI, 0.11-0.70; Figure 6.1b). The beneficial effect of LMWH was seen both among those with treatment switched from VKA to LMWH (8% recurrence) and among those remaining on LMWH, all variants of dose changes included (10% recurrence). Recurrent VTE was seen in 13% of patients with adenocarcinoma, in 18% with squamous cell carcinoma, but in none of the patients with hematopoietic malignancies. The cancer sites with the highest incidence of recurrence were lung (20%) and pancreas (19%). The stage of the cancer did not seem to make a difference with respect to recurrence with 12%, 9% and 9% in patients with metastases, local cancer or in remission, respectively. Recurrence was recorded in 10% of those receiving chemotherapy and 21% of those who were not receiving any antineoplastic therapy (P=0.045). The ECOG score did neither differ between those with or without further recurrence, nor between those on chemotherapy or on no anti-cancer therapy. Seven patients had an additional, objectively verified recurrence of VTE during the 3 months.
Bleeding, death and residual thrombosis symptoms during follow-up

Major bleeding during the 3 months occurred once in 12 patients and twice in 5 patients; overall in 8% of the patients. The bleeding events appeared to be front-loaded, with 4 of the events occurring during the first week (Figure 6.2). The first bleeding event occurred in 2 of 20 patients (10%) while on supratherapeutic anticoagulant intensity, in 15 of 165 (9%) on therapeutic doses and in none of 21 on subtherapeutic anticoagulation. All 17 first bleeding events were in patients treated with LMWH (9%) (odds ratio vs. VKA, 4.63; 95% CI, 0.27-79.8; calculated by adding 0.5 to each treatment and outcome).

There were 57 deaths (27%), occurring at a steady rate during the 3-month follow-up. There was no difference in mortality between patients with DVT alone or with PE ±DVT as the breakthrough event (27% for both). Mortality was similar among patients treated after the breakthrough event with LMWH or VKA (29% and 26%, respectively). The attributed cause of death was in 49 cases (86%) progression of cancer, respiratory failure in 2, stroke, peripheral arterial ischemia, and cardiac arrest due to suspected PE in 1 each, and unknown in 3. Thus, there were no objectively verified VTE or bleeding events that were fatal. For 145 patients, still alive at 3 months, there was information available on residual thrombosis symptoms, which were present in 108 (74%).

Table 6.1 | General characteristics of the included cases at breakthrough event

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n = 212</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, mean (±SD)</td>
<td>62.5 (12.5)</td>
</tr>
<tr>
<td>Female sex, N (%)</td>
<td>97 (46)</td>
</tr>
<tr>
<td>Body weight, kg, mean (±SD)</td>
<td>76.9 (19.1)</td>
</tr>
<tr>
<td>Creatinine clearance, mL/min, mean (±SD)</td>
<td>95.5 (45.7)</td>
</tr>
<tr>
<td>Indication for anticoagulation, N (%)</td>
<td></td>
</tr>
<tr>
<td>Deep venous thrombosis lower extremity</td>
<td>136 (64)</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>43 (20)</td>
</tr>
<tr>
<td>Both</td>
<td>21 (10)</td>
</tr>
<tr>
<td>Deep venous thrombosis other site*</td>
<td>7 (3)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>4 (2)</td>
</tr>
<tr>
<td>Duration of anticoagulation, days, median (IQR)</td>
<td>80 (32-232)</td>
</tr>
</tbody>
</table>

Abbreviations: SD, standard deviation; IQR, interquartile range
*Other sites were internal jugular vein (2), inferior vena cava and hepatic vein (1), portal vein (1), cerebral sinus (1), superficial phlebitis (1), unknown site (1).
Table 6.2 | Cancer-related characteristic of the included cases

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n = 212</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cancer site</strong></td>
<td></td>
</tr>
<tr>
<td>Genito-urinary</td>
<td>51 (24)</td>
</tr>
<tr>
<td>Lung</td>
<td>44 (21)</td>
</tr>
<tr>
<td>Colorectal</td>
<td>35 (17)</td>
</tr>
<tr>
<td>Breast</td>
<td>17 (8)</td>
</tr>
<tr>
<td>Pancreas</td>
<td>16 (8)</td>
</tr>
<tr>
<td>Hematopoietic system</td>
<td>13 (6)</td>
</tr>
<tr>
<td>Stomach/esophagus</td>
<td>7 (3)</td>
</tr>
<tr>
<td>Brain</td>
<td>5 (2)</td>
</tr>
<tr>
<td>Other sites with &lt;5 each †</td>
<td>24 (11)</td>
</tr>
<tr>
<td><strong>Cancer type</strong></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>126 (59)</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>17 (8)</td>
</tr>
<tr>
<td>Leukemia, lymphoma, myeloma</td>
<td>17 (8)</td>
</tr>
<tr>
<td>Non-small cell lung cancer</td>
<td>9 (4)</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>4 (2)</td>
</tr>
<tr>
<td>Other†</td>
<td>18 (8)</td>
</tr>
<tr>
<td>Unknown</td>
<td>21 (10)</td>
</tr>
<tr>
<td><strong>Stage</strong></td>
<td></td>
</tr>
<tr>
<td>In remission</td>
<td>11 (5)</td>
</tr>
<tr>
<td>Local</td>
<td>44 (21)</td>
</tr>
<tr>
<td>Metastatic</td>
<td>154 (73)</td>
</tr>
<tr>
<td>Unknown</td>
<td>3 (1)</td>
</tr>
<tr>
<td><strong>ECOG performance status score, median (IQR)</strong></td>
<td>1 (1-2)</td>
</tr>
<tr>
<td><strong>Current cancer therapy</strong></td>
<td></td>
</tr>
<tr>
<td>Chemotherapy alone</td>
<td>93 (44)</td>
</tr>
<tr>
<td>Chemotherapy in combination‡</td>
<td>21 (10)</td>
</tr>
<tr>
<td>Surgery</td>
<td>12 (6)</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>10 (5)</td>
</tr>
<tr>
<td>Hormonal therapy</td>
<td>9 (4)</td>
</tr>
<tr>
<td>Growth factors</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Immune therapy</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>No current treatment</td>
<td>58 (27)</td>
</tr>
<tr>
<td>Unknown</td>
<td>7 (3)</td>
</tr>
</tbody>
</table>

Abbreviations: ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range. Data are provided as N (%) unless otherwise stated. †Includes adrenal, bone, liver, mouth, larynx, prostate, unknown site and “other” ‡Chemotherapy was combined with radiotherapy (11), anti-angiogenetics (3), growth factors (2), hormones (2), or 1 each of immune therapy, surgery or “other”. §In 1 case each combined with growth factors or radiotherapy.
Table 6.3 | Characteristics of the breakthrough event

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n = 212</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deep venous thrombosis</td>
<td>130 (61)</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>58 (27)</td>
</tr>
<tr>
<td>Both</td>
<td>21 (10)</td>
</tr>
<tr>
<td>Other*</td>
<td>3 (1)</td>
</tr>
</tbody>
</table>

Diagnostic method†
For deep venous thrombosis, n=151
- Ultrasound | 138 (91) |
- Computed tomography | 12 (8) |

For pulmonary embolism, n=79
- Computed tomography (chest ±abdomen) | 50 (63) |
- Computed tomography pulmonary arteries | 16 (20) |
- Ventilation-perfusion scan | 15 (19) |

For thrombosis other sites, n=3
- Computed tomography | 3 (100) |

Anticoagulant treatment at time of breakthrough‡
- UFH, subtherapeutic dose | 4 (2) |
- LMWH, subtherapeutic | 49 (23) |
- LMWH, therapeutic | 94 (44) |
- LMWH, supratherapeutic | 6 (3) |
- Fondaparinux, subtherapeutic | 2 (1) |
- Fondaparinux, therapeutic | 4 (2) |
- VKA, INR <2.0 | 6 (3) |
- VKA, INR 2.0-3.0 | 29 (14) |
- VKA, INR >3.0 | 17 (8) |
- VKA, INR unknown | 5 (2) |

Anticoagulant intensity at time of breakthrough§
- Subtherapeutic | 59 (28) |
- Therapeutic | 125 (59) |
- Supratherapeutic | 23 (11) |
- Unknown | 5 (2) |

Abbreviations: UFH, unfractionated heparin; LMWH, low-molecular-weight heparin; VKA, vitamin K antagonist; INR, international normalised ratio. Data are provided as n (%).

*One each was mesenteric, portal, and cerebral sinus vein thrombosis
†For some patients several methods were used for diagnosis. For 1 patient reported to have both deep venous thrombosis and pulmonary embolism only ventilation-perfusion scan was done.
‡Some patients had more than one anticoagulant treatment. Five patients also had inferior vena cava filter.
§According to the most effective drug if more than one concomitantly. Inferior vena cava filter was not accounted.
### Table 6.4 | Changes in anticoagulant therapy after breakthrough event

<table>
<thead>
<tr>
<th>Change performed</th>
<th>First week*</th>
<th>Long-term*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continued or changed to subtherapeutic</td>
<td>17 (8)</td>
<td>21 (10)</td>
</tr>
<tr>
<td>Continued same drug, subtherapeutic intensity</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Switched to other drug, still subtherapeutic</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Decreased the intensity</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Continued therapeutic intensity and same drug†</td>
<td>70 (33)</td>
<td>85 (40)</td>
</tr>
<tr>
<td>Changed to another type of drug</td>
<td>51 (24)</td>
<td>41 (19)</td>
</tr>
<tr>
<td>From VKA to LMWH/UFH/fondaparinux</td>
<td>44</td>
<td>33</td>
</tr>
<tr>
<td>From UFH to LMWH</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>From UFH to VKA</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>From LMWH to UFH</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>From LMWH to VKA</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>From fondaparinux to LMWH</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>From fondaparinux to VKA</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Increased from subtherapeutic to therapeutic‡</td>
<td>44 (21)</td>
<td>39 (18)</td>
</tr>
<tr>
<td>Increased from therapeutic to supratherapeutic</td>
<td>22 (10)</td>
<td>14 (7)</td>
</tr>
<tr>
<td>Continued same drug, supratherapeutic intensity</td>
<td>7 (3)</td>
<td>6 (3)</td>
</tr>
<tr>
<td>Information on dose not available</td>
<td>1 (0.5)</td>
<td>6 (3)</td>
</tr>
</tbody>
</table>

Abbreviations: UFH, unfractionated heparin; LMWH, low-molecular-weight heparin; VKA, vitamin K antagonist

*Comparisons are versus the regimen at the breakthrough event. Data are provided as n (%).
†For the first week the drugs were VKA (2), LMWH (66) and fondaparinux (2); for the long-term they were VKA (11), LMWH (72) and fondaparinux (2)
‡For the first week these changes were within LMWH (39) or one each within UFH, from UFH to LMWH, from LMWH to UFH and from fondaparinux to LMWH; for the long-term they were within LMWH (36) or one each from LMWH to VKA and from fondaparinux to VKA.
Figure 6.1 | Probability of survival without recurrent venous thromboembolism (VTE) according to whether the intensity of anticoagulation was changed (A) or to the anticoagulant used (LMWH, n=179; VKA, n=21) (B) after the breakthrough event. Short vertical lines indicate deaths.
Figure 6.2 | Probability of survival without major bleeding event (MBE). Short vertical lines indicate deaths.
Discussion

We have here presented the results of an international registry on patients with cancer who had recurrent VTE despite receiving anticoagulant therapy. All anticoagulant regimens were eligible, representing different strategies in 10 countries. Of the 212 patients registered with breakthrough VTE, 11% had additional recurrence of VTE and 8% had major bleeding during the 3-month follow-up. The main findings were that LMWH, after a breakthrough event, seemed more effective than VKA to prevent further recurrences (HR 0.28; 95% CI, 0.11-0.70), whereas increased anticoagulant intensity did not appear to provide better protection than maintaining the same intensity as before. The risk of bleeding on the post-breakthrough regimen was numerically higher with LMWH than with VKA but the difference was not statistically significant, keeping in mind that the number of patients that were still receiving VKA was small. The mortality rate during the 3 months after a breakthrough VTE was high (27%) and the prevalence of residual thrombosis symptoms among the 3-month survivors was remarkably high (74%).

Very limited original data have been published on the management of recurrent cancer-associated thrombosis on anticoagulant therapy. Carrier et al published an analysis of a retrospective cohort covering period April 2003 – June 2008 with 70 patients on LMWH (n=47) or on VKA (n=23), who after the recurrence had the dose of LMWH increased by 20-25% or were switched from VKA to therapeutic dose LMWH, respectively.\textsuperscript{10} In a sequential cohort from the same group, covering the period July 2008 – December 2012 another 55 patients with recurrence on LMWH (n=49) or on VKA (n=6) had the same change in management.\textsuperscript{13} Together in these cohorts 11 patients (8%) had additional recurrent VTE during 3 months of follow-up, which compares well with the 9% recurrence rate on LMWH in our registry. Furthermore, in a study on patients with recurrent VTE on warfarin, 20 had cancer and were switched to therapeutic dose LMWH; one of those had another recurrence.\textsuperscript{14} The authors of these previously published cohorts concluded that escalation of the dose of LMWH seems effective to prevent further recurrences. However, there was no comparison with patients without dose escalation. In our analysis it appeared that increased intensity of anticoagulation was not the decisive factor to improve efficacy but rather the treatment with LMWH instead of VKA.

It has previously been reported that recurrent VTE on anticoagulation (n=17) was more common in patients with adenocarcinoma than with other types of malignancy.\textsuperscript{15} In our population we actually observed a numerically higher rate of recurrence during the 3-month follow-up in patients with squamous cell carcinoma (18%) than in those with adenocarcinoma (13%), but we do not have sufficient data to adjust for possible confounders.

The event rate of major bleeding in the previous cohorts combined was 4.8% (6 patients) during 3 months\textsuperscript{10,13} – close to the 8% reported by us. Sim-
ilarly to previous results, we could not identify an increased risk of bleeding with supratherapeutic anticoagulation compared to therapeutic intensity. In agreement are also the ominous data on overall survival with a 3-month mortality 25%\textsuperscript{13} and 27% in our material and a median survival of 11.4 months.\textsuperscript{10} Causes of death and prevalence of post-thrombotic syndrome have, to our knowledge, not been reported in this specific group of patients.

The “inadequate” anticoagulant management after the breakthrough event (in 8-10%) with a maintained subtherapeutic or even reduced dose could have been due to concerns about a high risk of bleeding, e.g. thrombocytopenia or recent history of bleeding. We did not collect information on the reason for the therapeutic choices.

In non-cancer populations with VTE, the localisation of a recurrence typically concurs with that of the initial event.\textsuperscript{16,17} In this registry we had the unexpected finding that of 43 patients with previous PE the breakthrough event was for only 35% another PE, for 58% DVT, and for 7% both. It is unclear whether the natural course is different in patients with cancer or possibly in patients with incidental PE. We did not capture information on symptoms but if we surmise that those with PE diagnosed by computed tomography or ventilation-perfusion scan had symptoms (and those by computed tomography of chest and abdomen were incidental), the recurrences among those 20 patients were as PE in 30% and as DVT in 70%. In a recent study on predictors of recurrence of VTE in patients with cancer the mortality was higher among those with recurrent PE ±DVT than with DVT alone.\textsuperscript{18} In our material the mortality did not differ between these two subsets, possibly due to a very poor prognosis in any patient with cancer and recurrent VTE despite anticoagulation or due to a different selection of patients.

The strengths of this study are 1) the size of the population – larger than the previously published cohorts combined, 2) the inclusion of different management strategies, 3) the collection of data on causes of death and on residual thrombosis symptoms, and 4) the objective verification of recurrent VTE by comparing diagnostic imaging reports from the first VTE, the breakthrough VTE and – for the 24 cases – the subsequent VTE(s). This is also the first multicenter, international study on this population.

The main limitation is the registry design, in which non-consecutive patients are recruited. Prospective cohort studies and even more so – randomised controlled trials – would be very challenging to perform due to the sporadic occurrence of these cancer-related breakthrough events. Our recruitment rate for the registry was an average of 21 cases/year and in the two previously published cohorts it was 15/year. Another limitation is the partly retrospective collection of data. However, based on the timing of reporting of baseline data and 3-month follow-up data, for approximately 2/3 of the cases follow-up information was collected prospectively. We were not able to collect systematic data on factor Xa levels for patients on heparins or reliable data to
calculate time in therapeutic range for patients on warfarin. Finally, we do not 
know which events were incidental. Patient selection for the different regi-
mens is a strong determinant of outcomes, and one that we are unable to 
estimate or measure. This results in uncertainty regarding relative efficacy or 
safety of the different regimens reported.

We anticipated an accrual rate of 2 patients per center and year and aimed 
for 50 participating sites and a completion time of 3 years. Despite multiple 
efforts of advertising the registry, we only had 17 recruiting sites, with some of 
these activated late. Thus, although keeping up with the per-site accrual rate, 
it took 10 years to complete the registry. This illustrates the difficulties one can 
anticipate in a randomised, controlled trial with this patient population.

A justified question is whether 2 patients per year represents the real inci-
dence and how representative our population is. In an epidemiologic study 
from the Olmsted county, there were during a 17-year period 1543 cases of 
incident VTE. Of those, 371 patients had active cancer known before the VTE, 
corresponding to 22 cases per year. We may assume that almost all of those 
patients were treated with anticoagulation. Prandoni et al reported that in a 
prospective cohort of patients with VTE the 12-month cumulative recurrence 
rate among the 181 patients with cancer was 20.7%, but approximately half of 
them had received less than 6 months of anticoagulation. The real number of 
cases per year may vary widely between hospitals, depending on their profile 
and geography. According to the estimates we received at the end of the 
registry, the sites diagnosed an average of 8 (range 2-20) recurrences on anti-
coagulation annually. The proportion of those that became recruited to this 
registry at the different sites was mean 42% (±28; range 5%-95%), with those 
participating for a very short time having the lowest proportions. The overall 
mean annual recruitment is estimated at 48% of actually diagnosed cases.

We conclude that patients with cancer-related recurrent VTE on antico-
agulation have high rates of recurrent VTE, major bleeding and death during 
the 3-month period after a breakthrough event. The recommendation to 
use LMWH rather than VKA for patients with cancer and VTE, as based on 
meta-analytic data and a recent trial, also pertains to patients with break-
through events. Surprisingly, we did not find evidence that increasing anti-
coagulant intensity in patients already receiving LMWH reduced the risk of 
recurrent breakthrough events. Dose escalation could be individualised and 
tailored for the patients with pronounced VTE-related symptoms and might 
not be required longer than until the symptoms abate, although this has not 
been adequately studied.
Recurrent venous thromboembolism in cancer patients

Reference list


