Uncertain value of high-sensitive troponin T for selecting patients with acute pulmonary embolism for outpatient treatment by hestia criteria

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Thrombosis Research 187 (2020) 125–130

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Full Length Article

Short-term prognosis of breakthrough venous thromboembolism in anticoagulated patients

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ARTICLE INFO

Keywords:
Venous thrombo-embolism
Anticoagulation
Malignancy
Breakthrough thrombotic events

ABSTRACT

Background: Evidence for guideline recommendations for the treatment of venous thromboembolism (VTE) during anticoagulant therapy is scarce. We aimed to observe and to describe the management of VTE occurring during anticoagulant therapy.

Methods: This prospective multi-center, observational study included patients with objectively confirmed VTE during anticoagulant therapy (breakthrough event), with a follow-up of 3 months, after the breakthrough event.

Results: We registered 121 patients with a breakthrough event, with a mean age of 56 years (range, 19 to 90); 61 were male (50%). Fifty-eight patients (48%) had an active malignancy. At the time of the breakthrough event, 57 patients (47%) were treated with a vitamin K antagonist (VKA), 53 patients (44%) with low-molecular-weight heparin (LMWH) and 11 patients (9%) with direct oral anticoagulants, unfractionated heparin, or VKA plus LMWH. A total of 21 patients (17%) were receiving a subtherapeutic dose of an anticoagulant. The main regimens to treat recurrence in patients on VKA were: switch to LMWH (33%), temporary double treatment with LMWH and VKA (23%), and VKA with a higher target INR (19%). In patients with a breakthrough on LMWH, the most frequently chosen regimen was a permanent dose increase (74%). During 3-month follow-up, 7% of patients had a second breakthrough event and 8% experienced major or clinically relevant non-major bleeding.

Conclusion: There is wide variation in the management of VTE during anticoagulant treatment, reflecting a heterogeneous and complex clinical situation. Despite intensifying anticoagulation, the risk of a second breakthrough event in this population is 7%.

1. Introduction

Ever since the landmark trial by Barritt and Jordan in 1960, it is clear that patients with venous thromboembolism (VTE) benefit from anticoagulant treatment [1]. Currently available long-term treatment options include direct oral anticoagulants (DOACs), vitamin K antagonists (VKAs), and subcutaneous low-molecular-weight heparin (LMWH) [2]. Anticoagulants are very effective and reduce the risk of recurrent VTE by 90–97%. During the first 3–6 months of treatment, the risk of recurrent VTE is about 0,4–2% whereas after treatment the risk of recurrence is 10% in the first year and 36% after 10 years, with a fatal recurrent risk of 4% [3,4]. The risk of recurrent VTE during anticoagulant therapy is particularly high in patients with persistent major provoking factors, such as active cancer or antiphospholipid syndrome [5–7]. During the initial 6 months of treatment, cancer patients have a 7% to 8% risk of developing recurrent VTE despite treatment [8–10]. The management of VTE in cancer patients is further complicated by a 3-fold increased risk of anticoagulant-associated major bleeding [6,7,11]. LMWH is the recommended treatment option for cancer-associated VTE because of superior efficacy to VKA while carrying a

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https://doi.org/10.1016/j.thromres.2020.01.010
Received 19 November 2019; Received in revised form 8 January 2020; Accepted 10 January 2020
Available online 20 January 2020

similar risk of bleeding [8,9,12]. However, recently a randomized controlled trial showed that edoxaban was non-inferior to dalteparin in prevention of cancer related VTE, with a higher risk of major bleeding, mainly gastrointestinal [13]. Likewise, a pilot study comparing rivaroxaban to dalteparin showed similar efficacy and safety [14].

Little is known about the clinical course and optimal therapeutic management of VTE in patients who are already receiving anticoagulant therapy. In contrast to the firm evidence- based treatment of a first VTE, no randomized trials have addressed the management of VTE in already anticoagulated patients. Based on low-quality evidence, the guideline by the American College of Chest Physicians (ACCP) suggests switching treatment to LMWH when VTE occurs during VKA [2,15]. If VTE occurs during LMWH therapy, a dose increase by 25% to 33% is suggested [2,15].

The aim of this prospective cohort study was to evaluate the management of VTE in anticoagulated patients in clinical practice, and to assess the 3-month incidence of recurrent VTE and bleeding.

2. Methods

This was a multicenter, prospective, observational study, conducted between September 2010 and December 2015 in 10 Dutch academic and non-academic hospitals. All patients with objectively confirmed VTE and current anticoagulant treatment for any indication (e.g. atrial fibrillation, prior VTE, or mechanical heart valve) were eligible. Qualifying index events, i.e. breakthrough events, for inclusion in this study were distal or proximal deep vein thrombosis (DVT) of the leg, acute pulmonary embolism (PE), upper extremity DVT, or splanchnic vein thrombosis. DVT was defined as non-compressibility of a previous compressible venous segment or an increase of at least 4 mm of the diameter of the residual thrombus. PE was defined as a new thrombus on computerized tomography pulmonary angiography, new mismatched defect on a ventilation/perfusion lung scan, or new defect on a pulmonary angiogram. Splanchnic vein thrombosis was defined as venous obstruction or absence of flow objectified by ultrasonography, duplex Doppler ultrasound, computerized tomography, or magnetic resonance imaging. Patient with a life expectancy of < 3 months, pregnant women, and patients requiring thrombolytic therapy for their breakthrough VTE were excluded.

Because of the absence of solid data on the risk of a breakthrough VTE during anticoagulant treatment when the study was planned, we did not perform a formal sample size calculation and targeted a sample size of 100 participants.

At baseline, information was collected on provoking factors, location of VTE, anticoagulant treatment at the time of the breakthrough event, and management of the breakthrough event. Anti-factor Xa levels in LMWH recipients and INR in patients treated with VKA were not routinely collected. Active cancer was defined as a cancer diagnosis or treatment within the past 6 months, or recurrent, locally advanced, or metastatic disease. For patients with active cancer, additional information was collected about the type of cancer, presence of distant metastases, and cancer treatment in the last 3 months. All patients were contacted after 3 months after the breakthrough event through telephone or visit. Standardized questions were used, in order to capture data on a second breakthrough event during treatment, anticoagulant-related bleeding, and death.

Anticoagulant regimens at time of the breakthrough event were classified as subtherapeutic, therapeutic, or supratherapeutic. Therapeutic LMWH was defined as within ± 20% of the recommended weight-based dose in patients without renal impairment, i.e. for dalteparin 160–240 IU/kg/24 h, for tinzaparin 140–210 IU/kg/24 h, for nadroparin 69–103 IU/kg/12 h (twice daily dosing), nadroparin 137–205 IU/kg/24 h (once daily dosing), for enoxaparin 0.8–1.2 mg/kg/12 h (twice daily dosing), enoxaparin 1.2–1.8 mg/kg/24 h (once daily dosing). Therapeutic VKA was defined as an INR between 2.0 and 3.5. For patients using a DOAC, rivaroxaban 20 mg once daily, apixaban 5 mg twice daily, edoxaban 60 mg once daily or 30 mg once daily in those qualifying for dose reduction, and dabigatran 150 mg twice daily or 110 mg twice daily in those qualifying for dose reduction were classified as 'therapeutic'. Doses below or above these ranges were classified as 'subtherapeutic' and 'supratherapeutic', respectively. Any case of a combination of two different types of anticoagulants was considered as 'supratherapeutic'.

As this was an observational study, patients were treated at the discretion of treating physicians and not by a standardized treatment protocol. Data and motivation on the (change of) management of the breakthrough thrombotic event were collected on a predefined form, including type and dose of anticoagulant, type of inferior caval vein filter or other mechanical/medical treatment options. Given the observational design, the Medical Ethical Committee of the Amsterdam UMC waived the need for informed consent.

2.1. Primary efficacy and safety outcomes

The primary efficacy outcome was an objectively confirmed, (second) recurrent VTE during three-month follow-up. Patients were contacted at the end of the three-month follow-up period and also in case of an event (either recurrent VTE or bleeding) during this follow-up period. During the follow-up visit or telephone contact, detailed information was collected about an eventually recurrent VTE, such as date and location of the thrombosis and whether this VTE was objectively confirmed, and if so, by which imaging modality. Also, detailed information on any bleeding was collected, such as date, location and severity. Furthermore, if applicable, information on a newly diagnosed malignancy was gathered, including tumor (histological) type, location, (TNM) stage. Lastly, in case of death, the cause was collected, particularly whether the death was related to pulmonary embolism, to other cardiovascular causes such as myocardial infarction or stroke, or to major bleeding.

Recurrent DVT was defined as non-compressibility of a previous compressible venous segment or an increase of at least 4 mm of the diameter of the residual thrombus. Recurrent PE was defined as a new thrombus on computerized tomography pulmonary angiography, new mismatched defect on a ventilation/perfusion lung scan or new defect on a pulmonary angiogram. Splanchnic vein thrombosis was defined as venous obstruction or absence of flow objectified by ultrasonography, duplex Doppler ultrasound, computerized tomography or magnetic resonance imaging.

The primary safety outcome was the composite of major or clinically relevant non-major bleeding according to the ISTH criteria [15]. Major bleeding was defined as clinically overt bleeding that either (1) was associated with a drop in hemoglobin level of 1.24 mmol/L (2 g/dL) or more, (2) led to transfusion of 2 or more units of whole blood or red cells, (3) was located in a critical area or organ, such as intraspinal, intracranial, intraocular, intra-articular, retroperitoneal, or pericardial, or intramuscular with compartment syndrome, or (4) fatal bleeding [15]. Clinically relevant non-major bleeding was defined as any sign or symptom of hemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that did not meet the criteria for the definition of major bleeding but did meet at least one of the following criteria: (1) requiring medical intervention by a healthcare professional, (2) leading to hospitalization or increased level of care, or (3) prompting a face to face (i.e., not just a telephone or electronic communication) evaluation [16,17]. All outcome events were adjudicated by two experienced clinicians (M.C. and S.M.), who were blinded to the management of the breakthrough event.

Death was considered to be due to PE if this diagnosis was documented at autopsy, if the patient died shortly after objectively confirmed symptomatic PE in the absence of any alternative diagnosis, or patient died suddenly and PE could not be ruled out.

2.2. Statistical analyses

Descriptive statistics were used for demographics and clinical characteristics of patients with different treatments. Kaplan-Meier survival analysis was performed to graphically illustrate the cumulative incidence of a second breakthrough event and the composite of major and clinically relevant non-major bleeding. The cumulative incidence of recurrent VTE and bleeding were compared between cancer patients and patients without cancer using the log-rank test with the significance level at 0.05. All statistical analyses were performed in R, version 3.2.2 (R Foundation for Statistical Computing, Vienna, Austria, www.R-project.org).

3. Results

A total of 121 patients were diagnosed with a (symptomatic) breakthrough event during anticoagulant treatment, in one of the participating centers and therefore included in this observational study. The median age of the study group was 56 years (range, 19 to 90) and 50% were male. The indication for anticoagulation prior to the breakthrough event was previous VTE in 103 patients (85%), atrial fibrillation (AF) in 9 patients (7%), and both in 3 patients (3%). Other baseline characteristics are presented in Table 1. Thirteen patients included in the present study were also included in an international registry on recurrent VTE in cancer patients [16]. Five patients were lost to follow-up during the 3-month follow-up.

3.1. Breakthrough event characteristics

The breakthrough event was a lower extremity DVT in 60 patients (50%) and PE with or without DVT in 41 patients (34%); the remaining 16% of patients had other types of VTE (Table 1).

A major provoking factor was present at the time of breakthrough event in 86 patients (71%): 58 patients had active cancer and 8 patients had antiphospholipid syndrome. Thirty-five patients had an unprovoked breakthrough VTE (Table 1). Sixty-nine percent of malignancies were solid cancers, with the most prevalent tumor types being breast (10%), pancreatic (10%), lung (9%), and gynaecological (9%) cancer (Table 2). Distant metastases were present in 22 patients (38%); 39 patients (67%) were receiving cancer therapy (Table 2).

Anticoagulant treatment at the time of the breakthrough event was VKA therapy in 57 patients (47%), LMWH in 53 patients (44%), VKA plus LMWH in 4 patients (3%), and rivaroxaban, dabigatran, edoxaban, or unfractionated heparin in 7 patients (7%, Table 1). In patients with cancer, the majority (N = 40, 69%) was receiving LMWH, whereas patients without cancer were predominantly receiving VKA (N = 42, 67%, Table 3). In cancer patients, 49 patients (84%) were receiving therapeutic or supratherapeutic treatment, which was the case in 46 patients (73%) without cancer (Table 3). Twenty-two patients had an unprovoked breakthrough event while receiving therapeutic or supratherapeutic anticoagulant therapy.

3.2. Management of breakthrough event

In VKA treated patients, management consisted of a switch to LMWH in 33%, temporary addition of LMWH in 23%, and increase of target INR to 3.0 to 4.0 in 19% (Table 4). Among the patients receiving LMWH at the time of the breakthrough event, treating physicians most frequently increased the LMWH dose (74%, Table 4).

The management regimen resulted in intensified treatment for 79 patients (65%) (Table 5a). In 25 patients (21%), the treatment was not intensified and kept at a subtherapeutic, therapeutic, or supratherapeutic dose (Table 5a). In 4 patients (3%) the treatment intensity was decreased from supratherapeutic to therapeutic with a switch from VKA to LMWH in 2 patients, switch from DOAC to VKA in one patient, and switch from LMWH to argatroban due to heparin-induced

Table 1
Baseline characteristics.

Characteristic	N = 121
Age, years, median (range)	56 (19–90)
Male, n (%)	60 (50)
Body mass index, kg/m^2, mean (SD)	27 (6)
Creatinine clearance, mL/min, median (IQR)	96 (73–121)
Indication for anticoagulation, n (%)	
- Venous thromboembolism	103 (85)
- Atrial fibrillation	9 (7)
- Venous thromboembolism and atrial fibrillation	3 (3)
- Other	2 (2)
- Unknown	4 (3)
Type of VTE, n (%)	
- Lower extremity deep vein thrombosis	60 (50)
Distal	6 (5)
Proximal	54 (45)
- Pulmonary embolism ± deep vein thrombosis	41 (34)
- Upper extremity deep vein thrombosis	11 (9)
- Inferior caval vein thrombosis	3 (2)
- Splanchnic vein thrombosis	3 (2)
- Other	3 (2)
Provoking factors, n (%)	
- None	35 (29)
- Active cancer[a]	58 (48)
- Antiphospholipid syndrome	8 (7)
- Immobilization	9 (7)
- Oral contraceptives	4 (3)
- Central venous catheter	8 (7)
- Long-haul flight ≥8 h	1 (1)
- Other[b]	9 (7)
- Unknown	4 (3)
Anticoagulant treatment at time of breakthrough, n (%)	
- Vitamin K antagonists	57 (47)
- Low-molecular-weight heparin	53 (44)
- Vitamin K antagonist and low-molecular-weight heparin	4 (3)
- Rivaroxaban	3 (3)
- Dabigatran	2 (2)
- Unfractionated heparin	1 (1)
- Concomitant antiplatelet agents, n (%)	8 (7)

IQR: interquartile range; PICC: peripherally inserted central catheter; SD: standard deviation; VTE: Venous thromboembolism.

[a] Cancer diagnosis or any anticancer treatment in the past 6 months, or recurrent or metastatic cancer.

[b] Other risk factors as reported by the treating physician: one case of VTE due to extensive retroperitoneal fibrosis with compression of the veins, one post-kidney transplantation, one after PICC catheter removal, one during pregnancy, one during chemotherapy, one case of thrombus in the right atrium due to implantable cardioverter defibrillator wire in situ, one patient had focal liver cirrhosis as risk factor and in 3 patients a risk factor was reported present, without further specification.

Table 2
Baseline characteristics of 58 cancer patients.

Characteristic	n, (%)
Solid cancer	40 (69)
- Breast	6 (10)
- Pancreas	6 (10)
- Lung	5 (9)
- Gynaecological	5 (9)
- Colorectal	4 (7)
- Esophagus	3 (5)
- Kidney	2 (3)
- Prostate	2 (3)
- Other	7 (12)
Distant metastasis	22 (38)
Hematological	16 (28)
- Polycythemia vera or essential thrombocytosis	5 (9)
- Leukemia	4 (7)
- Lymphoma	4 (7)
- Multiple myeloma	3 (5)
Unknown	2 (3)
Cancer therapy in the past 3 months	39 (67)

Table 3
Treatment intensity at time of breakthrough event.

VKA treatment, *N* = 57	No cancer, N = 42 (%)	Cancer, *N* = 15 (%)	Total *N* = 57 (%)
VKA, INR < 2.0	11 (26)	4 (27)	15 (26)
VKA, INR 2.0–3.5	25 (60)	9 (60)	34 (60)
VKA, INR > 3.5	4 (9)	2 (13)	6 (11)
VKA, INR unknown	2 (5)	0 (0)	2 (4)
LMWH, *N* = 53	**No cancer, *N* = 13 (%)**	**Cancer, N = 40 (%)**	**Total N = 53 (%)**
LMWH, sub-therapeutic	2 (15)	3 (8)	5 (9)
LMWH, therapeutic	8 (62)	30 (75)	38 (72)
LMWH, supra-therapeutic	2 (15)	5 (12)	7 (13)
LMWH, unknown	1 (8)	2 (5)	3 (6)
Other, *N* = 11	**No cancer, N = 8 (%)**	**Cancer, N = 3 (%)**	**Total N = 11 (%)**
VKA and LMWH	2 (25)	2 (67)	4 (36)
Rivaroxaban 20 mg od	1 (13)	1 (33)	2 (18)
Rivaroxaban 15 mg bid	1 (13)	0 (0)	1 (9)
Dabigatran 150 mg bid	2 (25)	0 (0)	2 (18)
Edoxaban 60 mg od	1 (13)	0 (0)	1 (9)
UFH, sub-therapeutic dose	1 (13)	0 (0)	1 (9)

INR: international normalised ratio; LMWH: low-molecular-weight heparin; UFH: unfractionated heparin; VKA: vitamin K antagonists;

Table 4
Changes in anticoagulant therapy to treat breakthrough event.

VKA at breakthrough N = 57	No cancer, N = 40 (%)	Cancer, *N* = 14 (%)	Total *N* = 57 (%)
VKA switched to LMWH	11 (27)	8 (57)	19 (33)
VKA switched to DOAC	3 (8)	0 (0)	3 (5)
VKA at therapeutic INR	1 (3)	1 (7)	2 (4)
VKA increased to supra-therapeutic INR	10 (25)	1 (7)	11 (19)
LMWH added to VKA temporarily	10 (25)	3 (22)	13 (23)
LMWH added to VKA permanently	5 (12)	1 (7)	6 (11)
Unknown, N = 3			3 (5)
LMWH at breakthrough N = 53	**No cancer, N = 12 (%)**	**Cancer, N = 40 (%)**	**Total N = 53 (%)**
LMWH permanent dose increase	6 (50)	33 (83)	39 (74)
LMWH same dose continued	2 (17)	5 (12)	7 (13)
LMWH switch to VKA at supra-therapeutic INR	1 (8)	0 (0)	1 (2)
VKA added to LMWH	3 (25)	2 (5)	5 (9)
Unknown, N = 1			1 (2)
DOAC at breakthrough N = 3	**No cancer, N = 2 (%)**	**Cancer, N = 1 (%)**	**Total N = 3 (%)**
DOAC switched to VKA	1 (50)	0 (0)	1 (33)
DOAC switched to LMWH	1 (50)	1 (100)	2 (67)
Other N = 12	No cancer, *N* = 9	Cancer, N = 3	

DOAC: direct oral anticoagulants; INR: international normalised ratio; LMWH: low-molecular-weight heparin; UFH: unfractionated heparin; VKA: vitamin K antagonists.

thrombocytopenia in one patient.

Data on the anticoagulant intensity at time of the breakthrough event were missing for 6 patients and on the management at time of the breakthrough event for 7 patients, (Tables 5a and 5b).

3.3. Recurrent VTE, bleeding and death during 3 months follow-up

During 3-month follow-up, 6 patients (5%) developed recurrent VTE, of whom 4 had active cancer (Fig. 1). Five of the 6 events occurred in patients in whom anticoagulant treatment was intensified from subtherapeutic to therapeutic ($N = 2$) or from therapeutic to supratherapeutic ($N = 3$). In the remaining patient, the supratherapeutic treatment regimen was not changed after the breakthrough event. During follow-up, 12 patients out of 121 (10%) died, often due to cancer progression (10/12). Fatal PE, including sudden death in which PE could not be ruled out, occurred in 2 out of 12 patients. In a worst-case scenario assuming these two patients had fatal PE, the case fatality risk would be 17% (95% CI 5–45%). Including the latter patients in whom PE could not be ruled out ($n = 2$), the 3-month risk of a second breakthrough event ($n = 8$) was 6.6% (95% CI 3.4–13%).

The composite of major or clinically relevant non-major bleeding occurred in 10 patients (8%), of whom 7 had cancer (Fig. 2). Five of these 10 bleeding events were adjudicated as major bleeding. Bleeding occurred during supratherapeutic and therapeutic anticoagulant treatment in 8 and 2 patients, respectively. Seven of the bleeding events occurred in patients with intensified anticoagulant treatment, 2 bleeding events occurred in patients who had remained on the same treatment intensity and 1 bleeding occurred in a patient who was on therapeutic anticoagulant (the treatment intensity at time of breakthrough was unknown; Tables 5a and 5b).

4. Discussion

This observational study provides clinical information on the management and outcome of breakthrough VTE events during anticoagulant treatment in a broad spectrum of patients. Many different treatment approaches in a heterogeneous population were observed, which illustrates the complexity of this clinical problem and consequently the challenge for one straightforward guideline. Also, large studies or guidelines on the diagnostic-work-up of recurrent VTE, especially during anticoagulant therapy, are lacking.

Breakthrough events are uncommon; and if VTE develops despite anticoagulation, it can often be ascribed to underlying patient-related or treatment-related factors [4,18]. Most of the breakthrough events occurred in patients with an intrinsic persistent thrombotic tendency, such as those with active cancer or antiphospholipid syndrome. Treatment-related causes for a breakthrough event could include subtherapeutic anticoagulation due to drug-drug or drug-food interactions, prescription errors, and non-compliance.

Whereas the majority of patients without cancer received VKA treatment at baseline, most of the cancer patients were treated with LMWH, which was in accordance with international guidelines, at the time of inclusion [2]. Cancer patients with a breakthrough event during LMWH were managed with a dose increase in > 80% of cases, which is the suggested treatment in this population [2,18]. Despite increasing the treatment intensity, the risk of a second breakthrough event was higher in cancer patients (9%), while bleeding rates were also higher (12%). This illustrates the challenges in the management of VTE in a population that has an intrinsic thrombotic as well as bleeding tendency. The risks of a second breakthrough event and major bleeding in cancer patients observed in the present study were lower as compared to previous studies [4,18–20]. For example Schulman and colleagues found a second breakthrough in 11% of the 212 observed patients with cancer, with a major bleeding risk of 8% and 27% died in 3 months follow-up. This might be due to differences in study population, such as lower percentage of cancer patients and within our cancer population were fewer with metastatic disease (38% versus 55–73%) and a relatively high proportion of patients with hematological cancer (28%) [8,9,11,18].

Although most breakthrough events were managed by intensified anticoagulant treatment, still 24% of patients were continued on the

Table 5a
Management at time of breakthrough event and events during 3-month follow-up.

Management breakthrough event	Anticoagulant intensity at time of breakthrough event				3 months follow-up	
	Subtherapeutic $N = 21$	Therapeutic $N = 76$	Supratherapeutic $N = 18$	Unknown $N = 6$*	Second breakthrough	Bleeding, major/CRNM
Increase intensity	18	61	0	–	5	7
Same intensity	1	12	12	–	1	2
Decreased intensity	0	0	4	–	0	0
Unknown	2	3	2	–	0	0

CRNM: clinically relevant non-major.

same or a decreased dose, whereas Schulman et al. found a percentage of 33% with an unchanged therapeutic dose of anticoagulation (73% had LMWH) [18]. The specific considerations for these clinical decisions may include perceived non-compliance or a very high risk of bleeding as judged by the treating physician.

This study in both cancer and non-cancer patients providing data on the treatment strategies and outcomes after breakthrough VTE can help in the design of future management studies on breakthrough events. Strengths include the prospective data collection, multicenter design, and adjudication of outcome events by two experts who were blinded for treatment information. Some aspects of this study merit consideration. The observational aspect of the study gave the treating physician only some treating suggestions, without randomisation between the various treatment options. Since the choice for a specific approach is strongly correlated with patient- and physician-related factors, we were not able to draw conclusions about the risk of a breakthrough during follow-up or bleeding associated with these approaches in this population. In addition, anti-factor Xa levels in LMWH recipients and INR in patients treated with VKA were not routinely available, hampering the interpretation of management decisions. Furthermore, a therapeutic INR at the moment of a breakthrough does not reflect a consistent, stable therapeutic range in the weeks before presentation. Most patients used LMWH or VKA, however nowadays an increasing number of patients, also those with cancer, receive direct oral anticoagulants.

Also, patients did not undergo standardized imaging, including ultrasound of the legs and a chest CT-scan, at baseline and follow-up; in some cases it is therefore hard to conclude that patients have an actual "breakthrough" event. Two out of the ten participating centers, were academic hospitals, specializing in hematologic cancers, resulting in a relatively high proportion of hematologic patients, and possibly also in a higher proportion of patients with VTE at other sites, such as upper extremity-, splanchnic- and inferior caval vein thrombosis. Since breakthrough events are uncommon, complex cases may be overrepresented in the present study, which could limit the generalizability. Centers did not routinely collect lists of excluded patients, which make it difficult to assess the risk of selection bias. Finally, no data on long-term follow-up were available and 5 of the 121 patients were lost to follow up (4%).

This study showed that in clinical practice many different approaches in the management of breakthrough events are followed, demonstrating the challenges physicians encounter when facing this clinical problem. Therefore, large management studies are urgently needed to evaluate the clinical practice and clinical outcome of different strategies in patients with breakthrough events.

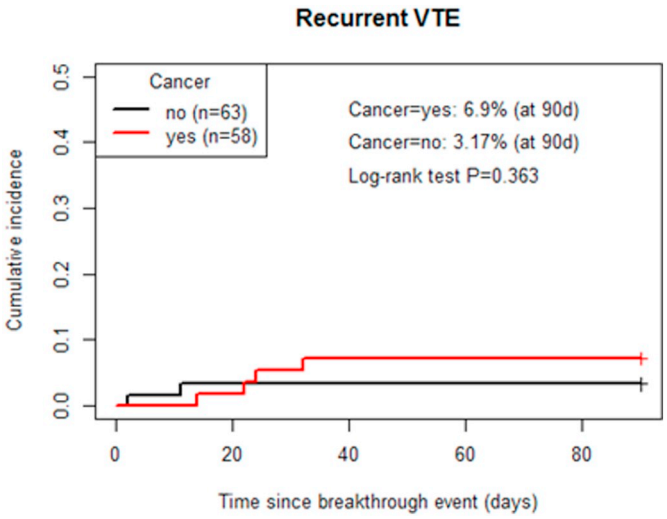

Fig. 1. Cumulative incidence of recurrent VTE during 3-month follow-up. VTE: venous thromboembolism.

Addendum

J. van Es, Y.W. Cheung, N. Van Es, V.E.A. Gerdes and S. Middeldorp planned and designed this study. J. van Es, Y.W. Cheung, N. Van Es, F.A. Klok, C.E.A. Dronkers, M. ten Wolde, M. Kruip, M.V. Huisman, K. Meijer, P.W. Kamphuisen, V.E.A. Gerdes, and S. Middeldorp recruited cases and revised the manuscript.

Funding

The research was conducted as an investigator-initiated observation study and was carried out with no external funding. None of the authors have interests to disclose.

Table 5b
Management at time of breakthrough event and events during 3-month follow-up in 6 patients of which the anticoagulant intensity at time of the breakthrough event was unknown.

Management breakthrough event	Anticoagulant intensity at time of breakthrough event	3 months follow-up	
	Unknown N = 6	Second breakthrough	Bleeding, major/CRNM
Therapeutic	2	0	1
Supratherapeutic	3	0	0
Unknown	1	0	0

CRNM: clinically relevant non-major.

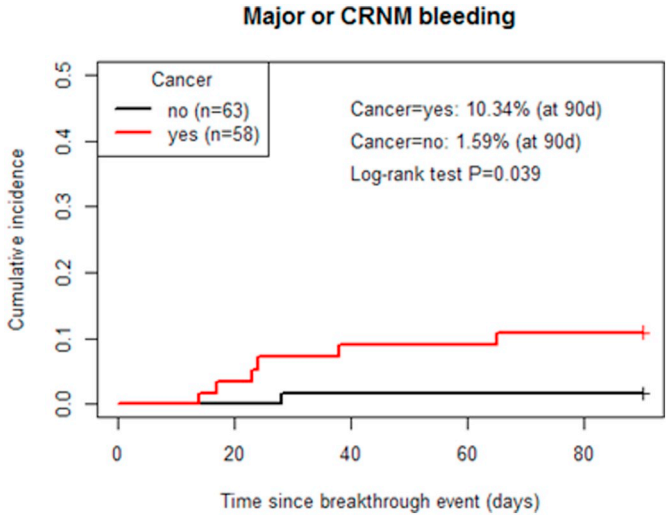

Fig. 2. Cumulative incidence of major and clinical relevant non-major bleeding during 3-month follow-up.

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