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Full Length Article

Tinzaparin in cancer associated thrombosis beyond 6 months: TiCAT study

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ABSTRACT

Introduction: The safety and efficacy of low-molecular-weight heparin (LMWH) treatment in patients with cancer-associated thrombosis (CAT) beyond 6 months are unknown. Our aim was to determine the safety of long-term tinzaparin use in patients with CAT.
Methods: We performed a prospective, open, single arm, multicentre study in patients with CAT receiving treatment with tinzaparin. We evaluated the rate of clinically relevant bleeding events (major and non-major clinically relevant bleeding) and venous thromboembolism (VTE) recurrence.
Results: A total of 247 patients were recruited, with a crude incidence of major bleeding of 4.9% (12/247). The rate of clinically relevant bleeding during months 1–6 and 7–12, was 0.9% [95% confidence interval (95% CI) 0.5 to 1.6%] and 0.6% (95% CI 0.2 to 1.4%) ($p = 0.5$) per patient and month, respectively. Male gender showed greater risk for clinically relevant bleeding with a hazard ratio (HR) of 2.97 (95% CI 1.01 to 8.1; $p = 0.02$). The incidence of VTE recurrence at months 1–6 and 7–12 was 4.5% (95% CI 2.2 to 7.8%) and 1.1% (95% CI 0.1 to 3.9%), respectively. One patient died due to VTE recurrence and two because of severe bleeding.
Conclusions: Treatment with tinzaparin beyond 6 months is safe in patients with CAT.

1. Introduction

The relationship between venous thromboembolism (VTE) and cancer is well established. The absolute incidence of cancer-associated thrombosis (CAT) varies widely depending on the type of tumour, the stage of the cancer and the oncologic treatment received [1–3]. Although the foci were initially localized in symptomatic CAT, it is known that approximately 50% of CAT are incidental [2]. CAT is associated with a higher incidence of recurrence and bleeding [4–6], and these complications are independent risk factors of death [7]. The administration of low-molecular-weight heparin (LMWH) during 3 to 6 months has shown to be effective and safe in patients with CAT [8–10].

The CATCH trial included the largest number of patients with CAT treated with LMWH and showed that the administration of tinzaparin vs. vitamin K antagonists (VKA) during 6 months led to a significant reduction in clinically relevant non-major bleeding (CRNMB) [11]. The main guidelines recommend the administration of LMWH during 3–6 months in patients with cancer-associated VTE [12,13]. In addition, the guidelines of the National Comprehensive Cancer Network (NCCN) recommend anticoagulation treatment to be maintained indefinitely in patients with an active solid tumour or with persistent risk factors [14]. Nonetheless, data related to the use of LMWH beyond 6 months are limited. The only trial carried out with this objective was the Longheva study, which was prematurely closed due to low patient recruitment (NCT01164046). Indeed, the DALTECAN study is the only

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prospective study that has evaluated 185 patients with CAT receiving dalteparin for >6 months [15].

Considering the limited data available on patients with CAT treated beyond 6 months we designed the TiCAT study (Tinzaparin in Cancer-Associated Thrombosis), a prospective, multicentre, open study, to evaluate the safety of long-term tinzaparin treatment in CAT.

2. Methods

2.1. Study design

We performed a multicentre (3 centres), open, single-arm study in adult patients with active cancer diagnosed with symptomatic or asymptomatic VTE: deep vein thrombosis (DVT) or pulmonary embolism (PE) confirmed by objective tests (compression ultrasonography or contrast venography for DVT; helical CT-scan, ventilation-perfusion lung scintigraphy or angiography for PE). The study was approved by the Committees of Ethics and Investigation of the participating hospitals and patients provided written informed consent to participate in the study (authorization of clinical research ethics committee Hospital Universitario Virgen del Rocío).

The inclusion criteria were: patients ≥18 years of age, diagnosed with proximal DVT, PE or both, with active cancer defined as 1) diagnosis of cancer in the 6 months prior to inclusion in the study (excluding basal or squamous cell skin carcinoma) or 2) having received any oncological treatment within the previous 6 months, or 3) presence of metastasis or cancer recurrence. The exclusion criteria included: need for haemodialysis, contraindication or known hypersensitivity to LMWH, pregnancy, non-controlled hypertension or any condition which the investigator considered to impede the patient from completing follow up. Patients with recurrent VTE were allowed to participate into the study.

2.2. Treatment schedule

Patients were recruited at the time of VTE diagnosis. All the patients received tinzaparin (Innohep, LEO Pharma A/S) (175 IU/kg) subcutaneously once a day. The patients or relatives were shown how to inject the drug. The treatment dose remained the same except in the following situations: (I) recurrent VTE; (II) bleeding requiring short-term or indefinite discontinuation of anticoagulant treatment; (III) any other adverse event requiring the discontinuation of tinzaparin; and (IV) patient decision. The dose of tinzaparin was reduced or transitorily discontinued if deemed necessary from a clinical point of view.

In cases presenting a platelet count between 50,000 and 100,000 mm^{-3}, the dose of tinzaparin was reduced by 25% until recovering a count >100,000 mm^{-3}. In cases with a platelet count <50,000 m^3 tinzaparin treatment was discontinued until platelet levels had recovered [16,17]. Patients were allowed to take other drugs if necessary. Anti-Xa determination was requested in patients presenting: (I) recurrent VTE, (II) patients with major bleeding or CRNMB in whom the reintroduction of tinzaparin was considered following the acute bleeding period, and (III) renal insufficiency with creatinine clearance <30 mL/min^{-1}. The target anti-Xa level 4 h after tinzaparin was 0.85 units/mL [18]. We tried to maintain anti-Xa levels close to but <0.85 if the reason was bleeding and close to but >0.85 if the reason was VTE recurrence.

2.3. Follow up

After the diagnosis of VTE and the administration of tinzaparin, the patients were initially followed by visits at one month and then every 3 months until death or end of study to evaluate clinical criteria of safety and efficacy. Patients undergoing an anti-Xa determination were seen weekly until the optimum dose was established. The patients and relatives were told to call the consulting office on the presentation of any event, and if this event could not be resolved by telephone it was evaluated in the consulting office.

2.4. Outcome measures

The primary variable of safety was the rate of clinically relevant bleeding (major bleeding or CRNMB) comparing the two initial periods of follow-up: 1 to 6 months and 7 to 12 months. CRNMB, minor and major bleedings were defined according to the guidelines of the International Society on Thrombosis and Haemostasis (ISTH) [19]. The secondary variables of safety were the time to the first CRNMB or any haemorrhagic event, and tolerance to extended tinzaparin treatment was measured by adherence to treatment. The primary variable of efficacy was the rate of recurrent symptomatic VTE objectively demonstrated

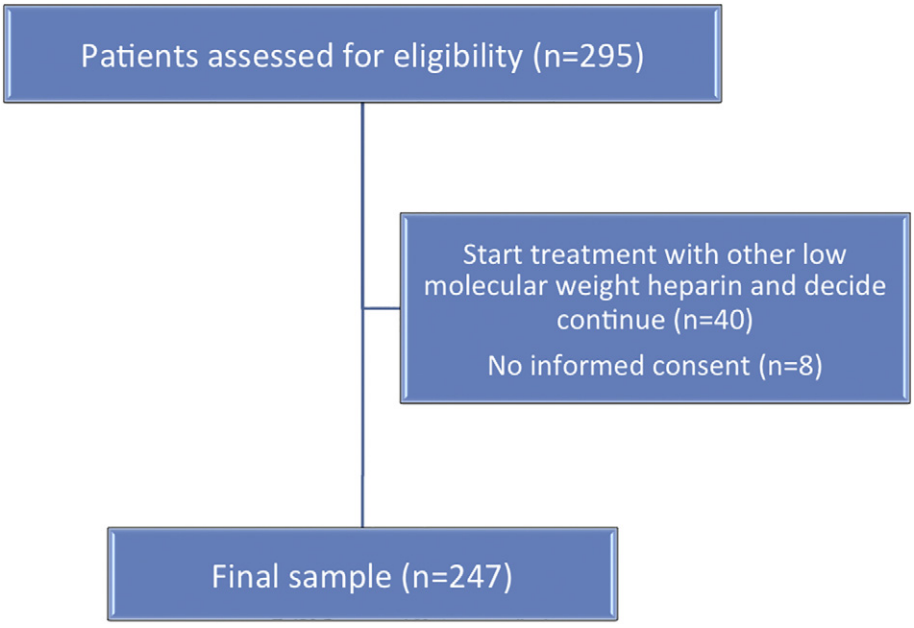

Fig. 1. Flow diagram.

by imaging tests (proximal DVT and/or PE) and the time until recurrent VTE. Clinical suspicion of recurrent VTE was diagnosed with the same methods as those used for the initial diagnosis of VTE.

2.5. Statistical analysis

Approximately 287 patients were considered necessary to have 135 evaluable patients completing at least 12 months of tinzaparin treatment, assuming 47% deaths at 12 months, as was observed in the LITE study [9]. The sample size calculation was based on the desired precision (width of the two-sided 95% confidence interval [95% CI]) for the estimation of the major bleeding rate during 12 months of treatment. We utilized the LITE study data to assign an expected crude rate of major bleeding events of 7% at 12 months; 135 evaluable patients completing 6 months of tinzaparin treatment were required with the precision level of 5% (half width of the two-sided 95% CI for the incidence rate) using normal approximation. Enrollment was to be stopped when 135 patients had completed 12 months of treatment.

Quantitative variables are expressed as (mean ± standard deviation) and the qualitative variables are expressed as percentages. The primary analysis of safety was performed by comparing the patient bleeding rates–month at 1–6 months and at 7–12 months and their 95% CI using the Clopper-Pearson exact method. The rate was defined as the number of patients with bleeding divided by the total number of patients and month at risk of bleeding. We used the Student's *t*-test (or Mann-Whitney *U* test when appropriate) and the χ^2 test (or Fisher's exact test when appropriate) to compare continuous or categorical variables. We analysed the time to the first clinically relevant bleeding using the Kaplan-Meier method (Mantel-Cox Log Rank test). The proportion of patients with symptomatic recurrent VTE during the 12 months study period was summarized with a 95% confidence interval (95% CI). A p value <0.05 was considered statistically significant. The statistical analyses were carried out using the IBM SPSS Statistics v19 software.

3. Results

3.1. Study population

From January 2009 to September 2015, 295 patients were evaluated, with a final sample of 247 patients, 198 (80.2%) and 136 (55.1%) of whom completed the 6 and 12 month follow up, respectively (Flow chart. Fig. 1). The mean age of the patients was 62.4 ± 13.4 years, and 55% were men. The most frequent histology was adenocarcinoma (38.1%). Of the patients included, 91.9% (227/247) had solid tumours with the most frequent being of the lung (16.6%) and breast (14.2%). One third of the patients (31%) were diagnosed with VTE more than one year after the diagnosis of the neoplasm, with the remaining patients being diagnosed at less than one month (15.5%), at 1 to 3 months (10.5%), 3 to 6 months (21%) and at 6 to 12 months (22%). At the time of VTE diagnosis, 66% (161/247) presented metastasis, and 62% (154/247) of the patients were receiving active oncological treatment. The most frequent oncological treatment was with classical cytostatic drugs (52.2%). One third of the patients were under 2 or 3 simultaneous oncological treatments. Seven per cent had moderate (creatinine clearance <50 mL/min/1.73 m^2) or severe renal insufficiency (creatinine clearance <30 mL/min/1.73 m^2) at the initiation of the study. The mean duration of tinzaparin treatment was 15.6 ± 13.2 months. Adherence during the study was 97% (7 patients decided to discontinue tinzaparin treatment). Table 1 shows the basal characteristics of the patients with CAT included in the study.

Table 1
Baseline characteristics of the patients included in the study.

Characteristic	Total cohort ($n = 247$) *n* (%)
Age, mean ± SD (years)	62.4 ± 13.4
Male, *n* (%)	135 (54.7)
Weight, mean ± SD (kg)	75.8 ± 14.1
Hematologic cancer *n* (%)	20 (8.1)
Solid tumour, *n* (%)	
Lung	41 (16.6)
Breast	35 (14.2)
Colorectal	27 (10.9)
Kidney	25 (10.1)
Bladder	14 (5.7)
Ovarian	12 (4.9)
Prostate	10 (4)
Pancreas	7 (2.8)
Brain	6 (2.4)
Histology, *n* (%)	
Adenocarcinoma	94 (38.1)
Ductal	22 (8.9)
Epidermoid	21 (8.5)
Lymphoma	14 (5.7)
Urothelial	13 (5.3)
Sarcoma	6 (2.4)
Clear cells	6 (2.4)
Glioblastoma	4 (1.6)
Leukemia	3 (1.2)
Myeloma	3 (1.2)
Others	61 (24.7)
ECOG performance status score, *n* (%)	
0	57 (23.6)
1	149 (61.6)
2	28 (11.6)
3	6 (2.5)
4	2 (0.8)
VTE presentation, *n* (%)	
DVT	128 (51.8)
PE	75 (30.4)
DVT + PE	44 (17.8)
Incidental VTE, *n* (%)	81 (32.8%)
Renal dysfunction, *n* (%)	
• (CrCL 30–50 mL/min)	16 (6.5%)
• (CrCl < 30 mL/min)	1 (0.4%)
Oncological treatment	
Classic cytostatic	129 (52.2%)
• Platinum compounds	49 (19.8%)
Monoclonal antibody	26 (10.6%)
• Angiogenesis inhibitor	14 (5.7%)
• Non angiogenesis inhibitor	12 (4.9%)
Anti-tyrosine kinase inhibitors	9 (3.6%)
mTORi	3 (1.2%)
Hormone treatment	13 (5.3%)
Growth stimulating factors	7 (2.8%)
Corticosteroids	6 (2.4%)
Radiotherapy	11 (4.5%)
Without oncological treatment	79 (32%)
Unknown	14 (5.7%)
Number of simultaneous oncological treatments	
1	53 (21.5%)
2	59 (23.9%)
3	31 (12.6%)
4	11 (4.5%)

VTE: venous thromboembolism; SD: standard deviation; DVT, deep vein thrombosis; PE, pulmonary embolism. mTORi: mammalian target of rapamycin inhibitors; CrCl, creatinine clearance.

3.2. Outcomes

Twenty-one (8.5%) bleeding episodes were reported during the follow up. At 12 months, the number of clinically relevant bleeding events expressed as the sum of the major bleeding events and CRNMB were 18 (7.3%), 12 (4.9%) of which were major bleeding and 6 (2.4%) CRNMB. Seven major bleeding events occurred during the first 6 months, with 12 within 12 months, and two leading to death. The percentage of major and clinically relevant bleeding at 6 and 12 months was 3.1% and 5.4%, and 6.3% and 9.1%, respectively (Fig. 2). The rate of clinically relevant bleeding events in the first 6 months compared to the 7–12 month period was 0.9% patient-month (95% CI 0.5 to 1.6%) vs. 0.6% patient-month (95% CI 0.2 to

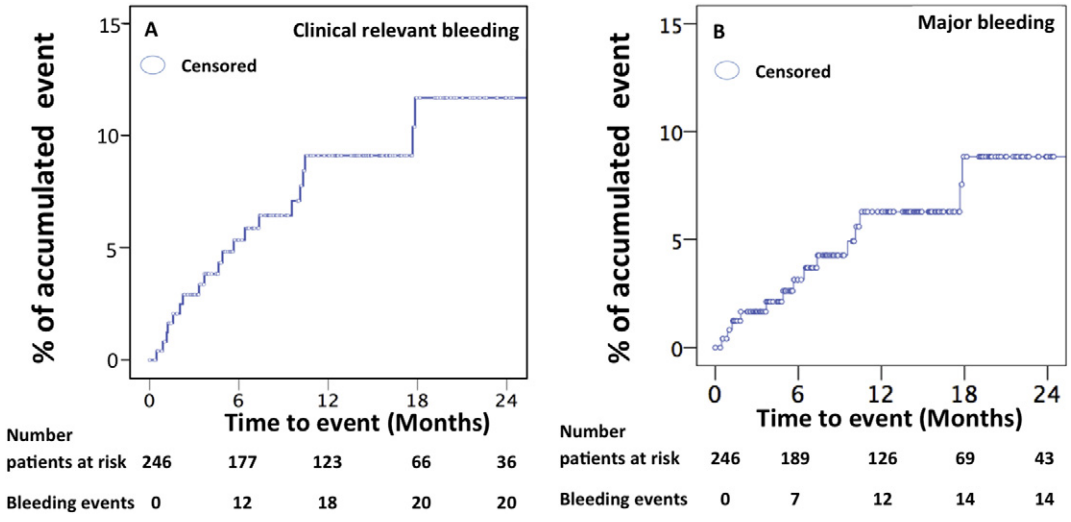

Fig. 2. Kaplan–Meier estimate of the time to the first occurrence of clinically relevant bleeding (A) and major bleeding (B).

1.4%) ($p = 0.5$) (Table 2). In Table 3 we show bleeding sites and outcome of the bleeding.

At 12 months, there were 13 recurrences of VTE (5.3%; 95% CI 2.8 to 8.8%). From months 7–12, 2 patients presented VTE recurrence, with an incidence of 1.1% (95% CI 0.1 to 3.9%) compared to months 1–6 during which 11 patients presented recurrence with an incidence of 4.5% (95% CI 2.2 to 7.8%) ($p = 0.08$) (Table 4). The percentage of VTE recurrence at 6 and 12 months was 4.7% and 6%, respectively (Fig. 3). Five patients had thrombocytopenia; one case presented upper gastrointestinal bleeding and in another case anticoagulant treatment needed to be discontinued due to severe thrombocytopenia. This patient presented recurrence of symptomatic DVT 3 months later.

Thirty-nine patients (15.8%, 95% CI 11.5% to 21%) died during the first 6 months and 62 (25.1%, 95% CI 19.8% to 31%) during the first 12 months, respectively. The underlying cancer was the main cause of death (90%), while one patient died as a result of recurrent PE and 2 patients died due to bleeding. We compared and did not find statistically significant differences in all-cause mortality, major bleeding and VTE recurrences between symptomatic and incidental VTE.

4. Discussion

As previous studies with LMWH up 6 months after CAT, the TiCAT study demonstrated that treatment with tinzaparin from months 7–12 after the diagnosis of VTE is safe with a low incidence of clinically relevant bleedings and recurrences. The global incidence of major bleeding during the first 6 months was 2.8% (95% CI 1.1 to 5.5%), being similar to the value obtained in the CATCH study (2.7%) [11]. One strength of our study was that we studied clinically relevant bleeding from a more clinical and practical point of view. The efficacy of the treatment was measured in terms of recurrent VTE, the secondary objective of our study, showed a trend for a lower recurrence with a global incidence of 4.5% (95% CI 2.2 to 7.8%) in the first 6 months and a lower incidence during months 7–12 (1.1%; 95% CI 0.1 to 3.9%; $p = 0.08$). The incidence of recurrent VTE during the first 6 months was similar to that described in

Table 2
Rates of major bleeding and clinically relevant bleeding.

Total ($N = 247$)	Rate of major bleeding			Rate of clinically relevant bleeding		
Time period	Rate (n/subject months at risk[b])	%	95% CI[a]	Rate (n/subject months at risk[b])	%	95% CI[a]
1–6 months	7/1320	0.5	0.2, 1.1	12/1320	0.9	0.5, 1.6
7–12 months	5/933	0.5	0.2, 1.2	6/933	0.6	0.2, 1.4
1–12 months	12/2253	0.5	0.3, 0.9	18/2253	0.8	0.5, 1.3
2–6 months	5/1073	0.5	0.2, 1.1	10/1073	0.9	0.4, 1.7
2–12 months	10/2006	0.5	0.2, 0.9	16/2006	0.8	0.5, 1.3
By month[c]						
1st month	2/247	0.8	0.1, 2.9	2/247	0.8	0.1, 2.9
2nd month	2/241	0.8	0.1, 3	3/241	1.2	0.3, 3.6
3rd month	0/232	0	0, 1.6	2/232	0.8	0.1, 3.1
4th month	1/222	0.5	0, 2.5	2/222	0.9	0.1, 3.2
5th month	1/206	0.5	0, 2.7	2/206	1	0.1, 3.5
6th month	1/198	0.5	0, 2.8	1/198	0.5	0, 2.8
7th month	1/183	0.5	0, 2.7	1/183	0.5	0, 2.7
8th month	1/174	0.6	0, 3.2	1/174	0.6	0, 3.2
9th month	0/164	0	0, 2.2	0/164	0	0, 2.2
10th month	1/152	0.7	0, 3.6	1/152	0.7	0, 3.6
11th month	2/147	1.4	0.2, 4.8	3/147	2	0.4, 5.8
12th month	0/136	0	0, 2.7	0/136	0	0, 2.7

Clinically relevant bleeding: major bleeding or clinically relevant non-major bleeding.
[a] 95% CI, 95% confidence interval, two-tailed exact Clopper-Pearson.
[b] Denominator was the total subject-months at risk during the time period.
[c] Adjudicated events were those that had been reviewed and confirmed by the Central Adjudication Committee. Events recorded during the study but after 365 days of treatment are included in the 12th month counts.

Table 3
Bleeding sites and outcome of the bleeding in cancer associated thrombosis.

Bleeding type	Site	Outcome
NMCRB	Decrease in platelets (50,000) and petechial	Alive
NMCRB	Haematoma in the thigh	Alive
NMCRB	Intermittent haematuria ($n = 2$)	Alive
NMCRB	Haematuria	Alive
NMCRB	Bleeding secondary to trauma and thrombocytopenia (70,000)	Alive
Major bleeding	Decrease of more than two points in haemoglobin values ($n = 5$)	Alive
Major bleeding	Intermittent bleeding with transfusion requirement	Alive
Major bleeding	Intra-abdominal haematoma secondary to intervention requiring surgical intervention.	Alive
Major bleeding	Severe vaginal bleeding due to suture dehiscence	Alive
Major bleeding	Upper gastrointestinal bleeding plus decrease of more than two points in haemoglobin values	Alive
Major bleeding	Upper gastrointestinal bleeding	Alive
Major bleeding	Upper gastrointestinal bleeding	Death
Major bleeding	Massive haemoptysis	Death

NMCRB: non-major clinically relevant bleeding.

the CATCH study (6.9%) [11]. Table 5 summarizes comparative results of the different studies regarding extension of LMWH.

The CLOT study was the first to use LMWH in CAT patients during the first 6 months after the diagnosis of VTE and demonstrated the efficacy of dalteparin with patients presenting a low number of major bleeding events [8]. The use of tinzaparin in the CATCH study showed a similar efficacy to that of VKA but the safety profile was higher in the group receiving LMWH, with a significant reduction in CRNMB [11]. On comparing LMWH and VKA, one meta-analysis reported a significant reduction in the relative risk of recurrent VTE of 53%, although no differences were found in major bleeding events or in survival [20]. Based on the studies available, all the international guidelines currently recommend the administration of LMWH for at least 6 [21,22] or 3–6 months in patients with CAT [23].

Although most clinical studies have compared LMWH during the first 6 months of anticoagulant treatment, oncological patients with VTE most likely need indefinite treatment or treatment until the cancer is cured [24]. Direct acting oral anticoagulants (DAOCs) such as the thrombin inhibitor dabigatran and factor Xa inhibitors (apixaban, edoxaban and rivaroxaban) are effective treatments to prevent and treat VTE in the general population [25]. However, the efficacy and safety of these drugs in CAT patients is unknown and thus, they are not recommended in these patients [26].

The mortality at 6 and 12 months in our series was 15.8% (95% CI 11.5 to 21) and 25.1% (95% CI 19.8 to 31), respectively. The percentage of patients with metastasis in our study (66%) was higher than in the CATCH study (55%) [11] but similar to that of the CLOT (67%) [8] and DALTECAN studies (62.6%) [15]. Despite the high percentage of patients with metastasis with similar histology and localizations, in our series the mortality at 6 months was lower than the 32% and 47% described in previous studies [8,26] and with a mortality at 12 months of 39% [15]. This may be due to the rapid advances in oncological treatments

Table 4
Incidence of adjudicated new or recurrent venous thromboembolism (deep vein thrombosis/pulmonary embolism).

Total ($N = 334$)			
Time period	Incidence n/N[a]	(%)	95% CI[b]
1–6 months	11/247	4.5	2.2, 7.8
7–12 months	2/184	1.1	0.1, 3.9
1–12 months	13/247	5.3	2.8, 8.8
2–6 months	7/240	2.9	1.2, 5.9
2–12 months	9/240	3.8	1.7, 7

[a] Denominator is the number of patients at risk for that period.
[b] 95% CI: 95% confidence interval, two-tailed exact Clopper-Pearson.

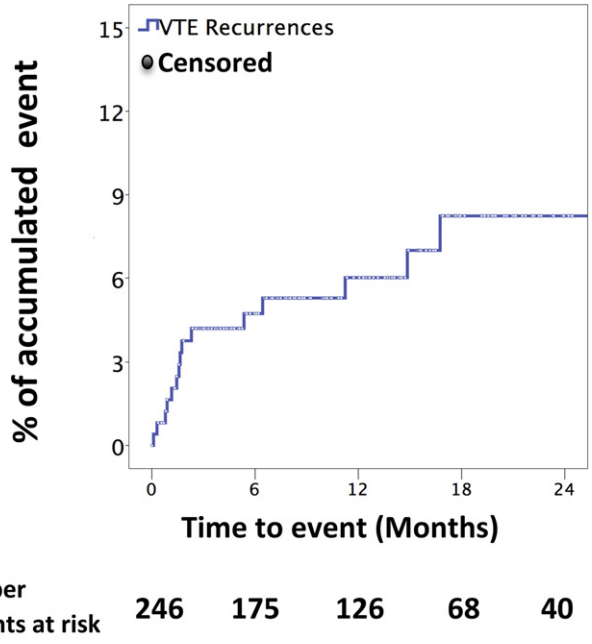

Fig. 3. Time to venous thromboembolism (VTE) recurrence. The Kaplan–Meier estimate of the time to first occurrence of new VTE.

achieved in the last years. Results related to the efficacy and safety of dalteparin and tinzaparin obtained in the DALTECAN and the TiCAT studies reinforce the need for long-term treatment in cancer-associated thrombosis. Although this evidence could be extrapolated to other LMWHs, it should be taken into account that despite having a similar mechanism of action the molecular weights of the different LMWHs vary, resulting in differences in their activity against factor Xa and thrombin as well as their affinity for plasma proteins and their plasma half-lives [27].

Evidence regarding the duration of anticoagulant treatment in cancer associated thrombosis is low, and the current guidelines suggest that treatment should be administered for 6 months or even longer if the cancer is still active, although these recommendations are not based on randomized trials. The use of residual vein thrombosis (RVT) to optimize the duration of LMWH treatment in patients with cancer-associated thrombosis was evaluated in the DACUS study (Cancer- Duration of Anticoagulation based on Compression Ultrasonography) [28]. In this study, patients with a first proximal DVT or PE and active cancer with residual DVT on ultrasonography (US) imaging after completing 6 months of LMWH therapy were randomized to receive another 6 months of LMWH or to stop therapy and be thereafter followed for 12 months. The additional 6 months of LMWH reduced recurrent VTE, but in patients whose anticoagulation was stopped the risk of recurrent VTE was the same as in those who had been treated for 6 or 12 months. In the same study, LMWH was stopped after 6 months in all the patients without residual DVT, and these patients showed a low risk of recurrence during the next year (three episodes in 91 patients). These findings have not changed the guideline recommendations for the treatment of VTE in patients with cancer." [29].

Our study has several limitations. First, it was an open single-arm study. Although we know that randomized clinical studies provide greater evidence, in some situations these are very difficult or practically impossible to undertake. Indeed, the only clinical study (Longheva study) had to be closed due to low recruitment (NCT01164046). The lack of a control group might limit the interpretation of the results and this may have induced a bias on including less severe patients. However, in our series, the percentage of patients with metastasis was elevated (66%), and we included tumours with a bad prognosis such as those of the lung (16.6%), kidney (10%) or pancreas (2.8%). Second, we included

Table 5
Table comparing the major results of the different studies regarding the extension of LMWH.

	TiCAT (tinzaparin)	DALTECAN (dalteparin)	LITE (arm tinzaparin)	CATCH (arm tinzaparin)	CLOT (arm dalteparin)
n	247	334	100	449	338
	M12*: 136 (55.1%)	M12*: 109 (32.6%)	M12*: 53 (53%)	M6*: 268 (60%)	M6*: 208 (61.5%)
Age	62	64	–	60	62
DVT[c]	70%	61%	92%	85.1%	70%[a]
PE[d]	48%	51%	21%	42.1%	30%[b]
Renal disease (CrCl[e] <50 mL/min)	17/247 (7%)	11/334 (3.3%)	–	15%[c]	–
Lung	16.6%	16.8%	–	10.7%	12%
Pancreas	2.8%	9.3%	–	–	4%
Metastases	66%	63%	47%	55%	67%
Dead	Overall 62/247 (25.1%) M1-6: 39 (15.8%) M7-12: 23 (9.3%)	116/334 (33.8%)	Overall 47/100 M1-3: 20 (20%) M4-12: 27 (27%)	M1-6: 150 (33.4%)	M1-6: 130 (38%)
Major bleeding	Overall 12/247 (4.9%) M1-6: 7 (2.8%; 0.5%/pt/month) M7-12: 5 (2.1%; 0.5%/pt-month)	Overall 34/334 (10.2%) M1-6: 26 (7.8%; 1.7%/pt/month) M7-12: 8 (2.4; 0.7%/pt-month)	M1-12: 7 (7%)	M1-6: 12 (2.7%)	M1-6: 19 (5.6%)
VTE[f] recurrences	Overall 13/247 (5.6%) M1-6: 11 (4.5%) M7-12: 2 (1.1%)	Overall 37/334 (11.1%) M1-6: 29 (8.7%) M7-12: 8 (2.4%)	Overall: 7 (7%) M1-3: 6 (6%) M4-12: 1 (1%)	M1-6: 31 (6.9%)	M1-6: 27 (8%)

* Data obtained at 12 months;
[a] Defined as CrCl < 60 mL/min;
[b] PE, with or without DVT;
[c] Deep vein thrombosis;
[d] Pulmonary embolism;
[e] Creatinine clearance;
[f] Venous thromboembolism; pt/months: data obtained per patient/month; M1-6: During months 1 to 6; M7-12: During months 7 to 12; M1-3: During months 1 to 3; M4-12: During months 4 to 12.

patients with incidental VTE, and this could potentially imply a bias by including patients with a better prognosis and fewer complications. At present, the international guidelines recommend the same treatment for symptomatic and incidental CAT [19,29]. Evidence related to the prognosis of incidental CAT is very scarce since it is usually described in retrospective or small series. Van der Hulle et al. recently analysed 11 cohorts with incidental PE (926 patients) and found that recurrence, major bleeding events and mortality at 6 months were 5.8% (95% CI 3.7–8.3%), 4.7% (95% CI 3.0–6.8%), and 37% (95% CI 28–47%), respectively [30]. We analysed patient survival, major bleeding events and recurrent VTE and did not find any differences between patients with symptomatic versus incidental VTE.

In summary, our findings support the use of tinzaparin beyond 6 months in patients with CAT because of its good safety profile. Considering the clinically relevant bleeding events, we believe that our study provides a more clinical and practical view.

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Author contributions

Study concept and design: LJP, ASL, RO; acquisition, analysis, or interpretation of data: all authors; drafting of the manuscript: all authors; critical revision of the manuscript for important intellectual content: all authors; statistical analysis: JMPF, LJP; study supervision: LJP, ASL, RO.

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Conflicts of interest

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References

[1] A.J. Walker, T.R. Card, J. West, C. Crooks, M.J. Grainge, Incidence of venous thromboembolism in patients with cancer - a cohort study using linked United Kingdom databases, Eur. J. Cancer 49 (6) (2013) 1404–1413, http://dx.doi.org/10.1016/j.ejca.2012.10.021.
[2] N. van Es, S.M. Bleker, M. Di Nisio, Cancer-associated unsuspected pulmonary embolism, Thromb. Res. 133 (Suppl. 2) (2014) S172–S178, http://dx.doi.org/10.1016/S0049-3848(14)50028-X.
[3] N. van Es, S.M. Bleker, I.T. Wilts, E. Porreca, M. Di Nisio, Prevention and treatment of venous thromboembolism in patients with cancer: focus on drug therapy, Drugs 76 (3) (2016) 331–341, http://dx.doi.org/10.1007/s40265-015-0526-3.
[4] A.Y. Lee, M.N. Levine, Venous thromboembolism and cancer: risks and outcomes, Circulation 107 (23 Suppl. 1) (2003) I17–I21, http://dx.doi.org/10.1161/01.CIR.0000078466.72504.AC.

[5] A.Y. Lee, E.A. Peterson, Treatment of cancer-associated thrombosis, Blood 122 (14) (2013) 2310–2317, http://dx.doi.org/10.1182/blood-2013-04-460162.
[6] J.F. Timp, S.K. Braekkan, H.H. Versteeg, S.C. Cannegieter, Epidemiology of cancer-associated venous thrombosis, Blood 122 (10) (2013) 1712–1723, http://dx.doi.org/10.1182/blood-2013-04-460121.
[7] G. Gussoni, S. Frasson, M. La Regina, P. Di Micco, M. Monreal, RIETE Investigators, Three-month mortality rate and clinical predictors in patients with venous thromboembolism and cancer. Findings from the RIETE registry, Thromb. Res. 131 (1) (2013) 24–30, http://dx.doi.org/10.1016/j.thromres.2012.10.007.
[8] A.Y. Lee, M.N. Levine, R.I. Baker, C. Bowden, A.K. Kakkar, M. Prins, et al., Randomized comparison of low-molecular-weight heparin versus oral anticoagulant therapy for the prevention of recurrent venous thromboembolism in patients with cancer (CLOT) investigators. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer, N. Engl. J. Med. 349 (2) (2003 Jul 10) 146–153, http://dx.doi.org/10.1056/NEJMoa025313.
[9] R.D. Hull, G.F. Pineo, R.F. Brant, A.F. Mah, N. Burke, R. Dear, et al., LITE Trial Investigators, Long-term low-molecular-weight heparin versus usual care in proximal-vein thrombosis patients with cancer, Am. J. Med. 119 (12) (2006) 1062–1072, http://dx.doi.org/10.1016/j.amjmed.2006.02.022.
[10] G. Meyer, Z. Marjanovic, J. Valcke, B. Lorcerie, Y. Gruel, P. Solal-Celigny, et al., Comparison of low-molecular-weight heparin and warfarin for the secondary prevention of venous thromboembolism in patients with cancer: a randomized controlled study, Arch. Intern. Med. 162 (15) (2002) 1729–1735.
[11] A.Y. Lee, P.W. Kamphuisen, G. Meyer, R. Bauersachs, M.S. Janas, M.F. Jarner, et al., CATCH Investigators, Tinzaparin vs warfarin for treatment of acute venous thromboembolism in patients with active cancer: a randomized clinical trial, JAMA 314 (7) (2015) 677–686, http://dx.doi.org/10.1001/jama.2015.9243.
[12] M.B. Streiff, B. Holmstrom, A. Ashrani, P.L. Bockenstedt, C. Chesney, C. Eby, et al., Cancer-associated venous thromboembolic disease, version 1.2015, J. Natl. Compr. Cancer Netw. 13 (9) (2015) 1079–1095.
[13] G.H. Lyman, K. Bohlke, A.A. Khorana, N.M. Kuderer, A.Y. Lee, J.I. Arcelus, et al., American Society of Clinical Oncology. Venous thromboembolism prophylaxis and treatment in patients with cancer: American society of clinical oncology clinical practice guideline update, J. Clin. Oncol. 2015; 33 (6) (2014) 654–656, http://dx.doi.org/10.1200/JCO.2014.59.7351.
[14] NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®), Venous Thromboembolic Disease, http://williams.medicine.wisc.edu/vtecancer.pdf, Version 1.2014, Accessed date: 23 June 2014.
[15] C.W. Francis, C.M. Kessler, S.Z. Goldhaber, M.J. Kovacs, M. Monreal, M.V. Huisman, et al., Treatment of venous thromboembolism in cancer patients with dalteparin for up to 12 months: the DALTECAN study, J. Thromb. Haemost. 13 (6) (2015) 1028–1035, http://dx.doi.org/10.1111/jth.12923.
[16] M. Carrier, P. Prandoni, Controversies in the management of cancer-associated thrombosis, Expert. Rev. Hematol. 10 (1) (2017) 15–22, http://dx.doi.org/10.1080/17474086.2017.1257935.
[17] R.B. Ibrahim, M.D. Skewes, P. Kuriakose, 'Sailing in troubled waters': a review of the use of anticoagulation in adult cancer patients with thrombocytopenia, Blood Coagul. Fibrinolysis 27 (6) (2016) 615–630, http://dx.doi.org/10.1097/MBC.0000000000000539.
[18] D.A. Garcia, T.P. Baglin, J.I. Weitz, M.M. Samama, American College of Chest Physicians, Parenteral anticoagulants: antithrombotic therapy and prevention of thrombosis, American College of Chest Physicians Evidence-based Clinical Practice Guidelines, 9th ed., Chest, 141 (2 Suppl), 2012, pp. e24S–e43S, http://dx.doi.org/10.1378/chest.11-2291.
[19] S. Kaatz, D. Ahmad, A.C. Spyropoulos, S. Schulman, Subcommittee on Control of Anticoagulation, Definition of clinically relevant non-major bleeding in studies of anticoagulants in atrial fibrillation and venous thromboembolic disease in non-surgical patients: communication from the SSC of the ISTH, J. Thromb. Haemost. 13 (11) (2015) 2119–2126.
[20] E.A. Akl, L. Kahale, M. Barba, I. Neumann, N. Labedi, I. Terrenato, et al., Anticoagulation for the long-term treatment of venous thromboembolism in patients with cancer, Cochrane Database Syst. Rev. 7 (2014), CD006650. http://dx.doi.org/10.1002/14651858.CD006650.pub4.
[21] G.H. Lyman, A.A. Khorana, N.M. Kuderer, A.Y. Lee, J.I. Arcelus, E.P. Balaban, et al., American Society of Clinical Oncology Clinical Practice, Venous thromboembolism prophylaxis and treatment in patients with cancer: American Society of Clinical Oncology clinical practice guideline update, J. Clin. Oncol. 31 (17) (2013) 2189–2204, http://dx.doi.org/10.1200/JCO.2013.49.1118.
[22] J.C. Easaw, M.A. Shea-Budgell, C.M. Wu, P.M. Czaykowski, J. Kassis, B. Kuehl, et al., Canadian consensus recommendations on the management of venous thromboembolism in patients with cancer. Part 2: treatment, Curr. Oncol. 22 (2) (2015) 144–155, http://dx.doi.org/10.3747/co.22.2587.
[23] S.V. Konstantinides, A. Torbicki, G. Agnelli, N. Danchin, D. Fitzmaurice, N. Galiè, et al., Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC), ESC guidelines on the diagnosis and management of acute pulmonary embolism, Eur. Heart J. 2014; 35 (43) (2014) 3033–3069, http://dx.doi.org/10.1093/eurheartj/ehu283.
[24] H.R. Büller, G. Agnelli, R.D. Hull, T.M. Hyers, M.H. Prins, G.E. Raskob, Antithrombotic therapy for venous thromboembolic disease: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy, Chest 126 (3 Suppl) (2004) 401S–428S.
[25] N. van Es, M. Coppens, S. Schulman, S. Middeldorp, H.R. Büller, Direct oral anticoagulants compared with vitamin K antagonists for acute venous thromboembolism: evidence from phase 3 trials, Blood 124 (12) (2014) 1968–1975, http://dx.doi.org/10.1182/blood-2014-04-571232.
[26] A.Y. Lee, M. Carrier, Treatment of cancer-associated thrombosis: perspectives on the use of novel oral anticoagulants, Thromb. Res. 133 (Suppl. 2) (2014) S167–S171, http://dx.doi.org/10.1016/S0049-3848(14)50027-8.
[27] J. Hirsh, T.E. Warkentin, S.G. Shaughnessy, S.S. Anand, J.L. Halperin, R. Raschke, et al., Heparin and low-molecular-weight heparin: mechanisms of action, pharmacokinetics, dosing, monitoring, efficacy, and safety, Chest 119 (1 Suppl) (2001) 64S–94S.
[28] M. Napolitano, G. Saccullo, A. Malato, D. Sprini, W. Ageno, D. Imberti, et al., Optimal duration of low molecular weight heparin for the treatment of cancer-related deep vein thrombosis: the Cancer-DACUS Study, J. Clin. Oncol. 32 (32) (2014) 3607–3612.
[29] C. Kearon, E.A. Akl, J. Ornelas, A. Blaivas, D. Jimenez, H. Bounameaux, et al., CHEST guideline and expert panel report, Chest 149 (2) (2016) 315–352, http://dx.doi.org/10.1016/j.chest.2015.11.026.
[30] T. van der Hulle, P.L. den Exter, B. Planquette, G. Meyer, S. Soler, M. Monreal, et al., Risk of recurrent venous thromboembolism and major hemorrhage in cancer-associated incidental pulmonary embolism among treated and untreated patients: a pooled analysis of 926 patients, J. Thromb. Haemost. 14 (1) (2016) 105–113, http://dx.doi.org/10.1111/jth.13172.