Prophylaxis of cancer-associated venous thromboembolism with low-molecular-weight heparin-tinzaparin: Real world evidence

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Abstract. Thromboprophylaxis, as a preventive measure for cancer-associated thrombosis (CAT), may be beneficial for patients with active cancer and high-risk for thrombosis. The present post hoc analysis include a total of 407 patients enrolled in the Greek Management of Thrombosis study, who received thromboprophylaxis with tinzaparin. The objectives of the present analysis were: i) To obtain sufficient evidence for the administration of prophylaxis in patients with active cancer, irrespective of Khorana risk assessment model score; ii) to identify the selection criteria for both dose and duration of tinzaparin; and iii) to evaluate the efficacy and safety of tinzaparin administered for CAT prophylaxis. The main tumor types for the patients included in the present study were as follows: Lung (25.1%), pancreatic (14.3%), breast (9.1%), stomach (8.4%), colorectal (7.9%) and ovarian (7.6%). Furthermore, metastatic disease was observed in 69.5% of the patients. High thrombotic burden agents (HTBAs) were administered to 66.3% of the patients, and 17.4% received erythropoietin. A total of 43.7% of the patients exhibited a Khorana score <2. The results of the present study demonstrated that both the presence of metastatic disease and the use of HTBAs seemed to influence oncologists' decisions for the use of thromboprophylaxis in patients with active cancer, regardless of Khorana score. Tinzaparin, in dose expressed in the standard notation for heparins, i.e., anti-Xa factor international units (Anti-Xa IU), was administered at an intermediate dose (InterD; 8,000-12,000 Anti-Xa IU; once daily) to 52.4% of patients, while the remaining patients received a prophylactic dose (ProD; ≤4,500 Anti-Xa IU; once daily). The average duration of thromoprophylaxis was 5 months. Furthermore, a total of 14 (3.4%) thrombotic events and 6 (1.5%) minor bleeding events were recorded. A total of four thrombotic events were observed following an InterD treatment of tinzaparin, while 10 thrombotic events were observed following ProD treatment. The present study also demonstrated that an InterD of tinzaparin was administered more frequently to patients

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with a body mass index >30 kg/m^2, a history of smoking and a history of metastatic disease, along with administration of erythropoietin. InterD tinzaparin treatment was found to be potentially more efficacious and without safety concerns. The present study is a registered clinical trial (ClinicalTrials.gov code, NCT03292107; registration date, September 25, 2017).

Introduction

Venous thromboembolism (VTE) in patients with cancer (Ca) may exert a notable impact on both mortality and morbidity, as VTE is the second leading cause of death in these patients (1). Assessing the thrombotic burden in patients with active Ca, referring to those who have been diagnosed with a current or recent malignancy, those with metastatic disease, or those who are receiving anticancer treatment, remains a challenge, as patients with active Ca may experience thromboembolic and bleeding complications (2). An individualized assessment of every patient's profile is therefore required (3).

Many predisposing risk factors for VTE are comorbid conditions that require active evaluation and management (4). Advanced age is recognized as a risk factor (5), as the median age at Ca diagnosis is 66 years (6), and patients aged >40 years are at a higher risk of thrombosis, while that risk doubles with each subsequent decade (7). Patients who are obese also experience double the risk of VTE development, compared with normoweight patients, and the results of a previous study demonstrated that the higher the patient's weight, the higher the risk of VTE development (7).

Patients with pancreatic, lung, gastric, uterine corpus and cervical, kidney and brain primary tumors exhibit an increased risk of VTE development (8,9). Moreover, patients with metastatic disease at the time of diagnosis present a 1.4-21.5X greater risk for thromboembolism, compared with patients with non-metastatic disease. Additionally, previous findings demonstrated that mucinous adenocarcinomas, such as those of the pancreas or the lung, and cancers of the gastrointestinal tract, exhibit the highest incidence rate of Ca-related VTE (10-12).

Patients with active Ca who are undergoing systemic treatment are among the highest-risk populations for thromboembolic complications. High thrombotic burden agents (HTBAs) include platinum compounds, 5-fluorouracil, capecitabine, gemcitabine, hormonal therapy, anti-angiogenesis treatment, such as bevacizumab, and supportive treatment, such as corticosteroids or erythropoietin (13). In addition, VTE affects patients who are being treated with immunotherapy, either as monotherapy or in combination with other agents (14). The results of a previous study demonstrated that ~1 in 3 patients may develop thrombosis, which may exert a negative impact on survival (15).

Thrombotic events in patients with active Ca may lead to complications in anticancer treatment, which may cause delays in receiving treatment and affect treatment outcomes, thus contributing to psychological and physical stress. The aforementioned effects may also exacerbate the socioeconomic burden of Ca, and they may exert a negative impact on the patients' quality of life. Both progression-free survival (PFS) and overall survival (OS) in patients who experience thromboembolic events during systemic antineoplastic treatment are markedly affected, compared with patients who do not experience VTE events (1,16,17).

In that context, the Hellenic Society of Medical Oncology (HeSMO) conducted the Greek Management of Thrombosis (GMaT) study (ClinicalTrials.gov identifier, NCT03292107) (18), a prospective multicenter observational study aiming to record clinical practice in Ca-associated thrombosis (CAT) management. The present post hoc analysis aimed to obtain evidence for the justification of prophylaxis administration in patients with active Ca, irrespective of their assessment for VTE as this is evaluated via the Khorana score. The present study also aimed to identify factors influencing the decision making process of oncologists for the selection of dose and duration of thromboprophylaxis, and to evaluate the efficacy and safety of tinzaparin overall, as well as per dose used.

Materials and methods

Study source and patient criteria. The present study is a post hoc analysis of primary prophylaxis of CAT in patients with active Ca. The study source was GMaT (18), a prospective multicenter observational study (ClinicalTrials.gov code, NCT03292107), designed to collect data associated with the management of CAT in routine clinical practice and was conducted in a total of 18 oncology departments across Greece. GMaT was conducted in Greece and a total of 18 oncology departments participated. GMaT was conducted in accordance to Helsinki declaration and was approved by the Bioethics/Scientific Committees as St. Andrew Hospital, Patras, Greece (approval number, 193-9/8/16, 9th August, 2016). Participating patients signed an informed consent form. The inclusion criteria were as follows: Age ≥18 years, histologically confirmed solid tumors, use of anticoagulants for primary prophylaxis or treatment, performance status of Eastern Cooperative Oncology Group (ECOG) 0-2 and life expectancy beyond six months.

The protocol used in the study source did not provide specific guidance on the anticoagulant prophylaxis methods, as oncologists followed their own individual or clinical practices. The primary objective of the CAT prophylaxis was to record the various approaches to thromboprophylaxis. Secondary aims were to assess the incidence of VTE events, to record efficacy and bleeding events and to assess the safety of current clinical practice. VTE events were objectively confirmed by internationally recommended imaging techniques (19,20).

For all patients, bleeding events were classified using those recommended from the International Society on Thrombosis and Haemostasis criteria (21-23). The follow-up period was 12 months following patient enrolment. In total, 546 patients with active Ca who were treated in an ambulatory setting were included in the GMaT study. Out of these, 120 patients were diagnosed with objectively confirmed VTE, for which they received treatment. Moreover, 426 patients were considered to be at risk for VTE and received thromboprophylaxis.

The study source reported the justification for the administration of prophylaxis in patients with active Ca, irrespective of Khorana score. In accordance with recent American Society of Clinical Oncology guidelines, Khorana scores have changed

from ≥3 and <3, to ≥2 and <2 (24); thus, the present study reported results based on the updated Khorana score values.

Moreover, the updated values were used to investigate the low molecular weight heparin (LMWH) dose selection, and to evaluate the safety and efficacy of the two different dose schemes; namely, prophylactic dose (ProD) and intermediate dose (InterD) used for primary prophylaxis of CAT.

As tinzaparin is used in the majority of cases and different anticoagulation agents may exhibit differences in efficacy and safety, the present study only focused on the use of tinzaparin. The current analysis evaluated a total of 407 patients who received thromboprophylaxis with tinzaparin.

Statistical analysis. The open source programme R (version 4.0.4) was used for statistical analysis. Data were collected using the Excel 2007 spreadsheet (Microsoft Corporation), and were subsequently conditioned and preprocessed, specifically: missing or erroneous entries were easily identified and subsequently filled or corrected and additional variables, such as patient age were calculated from birth date and study inclusion date. The descriptive statistics for the arithmetic data are presented as the mean value ± standard deviation. Categorical data are presented as frequencies with relative percentages. Comparisons among groups for the arithmetic variables were performed using the Mann Whitney (MW) U test. Non-parametric data were identified using the Kolmogorov-Smirnoff test. Categorical variables were examined using the chi-square test or Fisher's exact test, depending on the number of expected cases within the groups under comparison. Moreover, in order to allow for confounders that exhibited a role in the anticoagulation dose, the odds ratios (ORs) were adjusted, and a forward selection logistic regression model was used on all variables that were employed during the univariate approach. P<0.05 was considered to indicate a statistical significance, and all tests were two sided.

Results

Patient characteristics. In total, 407 patients with active Ca receiving thromboprophylaxis with tinzaparin were included in the current cohort. Their baseline characteristics, the risk factors associated with each patient, Ca type, treatment and biomarkers are displayed in Table I, and are classified according to the Khorana score (<2 or ≥2).

In the present cohort, the majority of patients who received primary prophylaxis with tinzaparin had metastatic disease (69.5%), and 270 (66.3%) patients were being treated with HTBAs. Out of all patients in the study, 178 (43.7%) exhibited a Khorana score <2. Among them, 121 (68.0%) had metastatic disease, and 94 (52.8%) were being treated with HTBAs.

Notably, 30 of the patients in the group with a Khorana score <2 (16.9%) had a high-risk for thrombosis Ca type and metastatic disease, and were also being administered HTBAs. The coexistence of metastatic disease together with HTBA administration was observed in 29 (16.3%) patients. The number of patients with metastatic disease who were receiving HTBAs and exhibited a Khorana score <2 was 27.5%, compared with 3.1% in the Khorana ≥2 group (P<0.0001). Similarly, the number of patients with non-metastatic disease who were receiving HTBAs was 13.5% in the Khorana score <2 group, compared with 3.1% in the Khorana score ≥2 group (P=0.0052). The coexistence of Ca and treatment-associated risk factors are displayed in Fig. 1.

The distribution of patients with a Khorana score of either <2 or ≥2, along with the Ca type, is displayed in Fig. 2. The risk factors associated with thrombosis and Ca, and the corresponding treatment for patients with a Khorana score <2 are displayed in Fig. 3.

Thromboprophylaxis duration. On average, thromboprophylaxis with tinzaparin was administered for 5.0±3.1 months. Patients with a Khorana score ≥2 received prophylaxis for a longer period of time (5.2±3.1 months), compared to patients with a Khorana score <2. The latter patients were receiving tinzaparin for 4.7±3.0 months; however, no statistical significance was observed (MW test: P=0.0893). The average duration of anticoagulation per Ca primary site is demonstrated in Fig. 4.

Thromboprophylaxis dose. A total of 213 (52.4%) patients received an InterD of 8,000-12,000 Anti-Xa IU, once daily. An InterD was administered to 56.2% of the patients with a Khorana score <2, and 49.6% of patients with a Khorana score ≥2 (OR, 0.76; 95% CI, 0.51-1.14; P=0.1918).

A detailed univariate analysis between patients that received a ProD of ≤4,500 IU compared with those who received an InterD of tinzaparin was performed. A total of 21.6% of patients who received an InterD had a body mass index (BMI) ≥30, compared with 10.8% of those who received a ProD (x^2 test: P=0.0043). Moreover, a significant difference was observed between the doses administered for patients with a BMI ≥35 (Table SI). Similarly, 69.1% of patients who received an InterD were smokers or had a previous history of smoking, compared with 53% of those who received a ProD (χ^2 test: P=0.0011). In the ProD group, 54.6% of patients had a history of surgery, compared with 34% in the InterD group. A total of 77% of patients who received an InterD were suffering with metastatic disease, compared with 61.1% of those who received a ProD (χ^2 test: P=0.0007). A total of 26% of those in the InterD group were administered erythropoietin, compared with 9.2% in the ProD group (χ^2 test: P<0.0001). The results are presented in Table SI. Finally, the percentages of tinzaparin dose administered per primary Ca site is graphically depicted in Fig. 5.

In addition to the aforementioned univariate analysis, a multivariate analysis was performed using the logistic regression method. The results obtained were similar to those obtained using the univariate analysis. However, the results demonstrated that a BMI cut-off value of 35 Kgr/m^2 exerted no significant effects, and an InterD was more frequently administered to patients who did not have low hemoglobin levels (OR, 0.4; 95% CI, 0.2-0.8; P=0.013).

Thromboprophylaxis efficacy. Although arterial complications in patients with Ca are less common than VTE, their incidence is continually observed in a number of cases; therefore, both VTEs and arterial complications were considered in the present study.

A total of 14 patients experienced thrombotic events (3.4%; 95% CI, 2.1-5.7%); 8 experienced deep vein thrombosis,

Table I. Baseline characteristics organized into risk categories contributing to thrombotic burden related to patients, cancer and treatment.

Risk factor	All cases (n=407)	Khorana score <2 (n=178; 43.7%)	Khorana score ≥2 (n=229; 56.3%)
Patient			
Sex (male), n (%)	220 (54.1)	81 (45.5)	139 (60.7)
Age, mean ± SD (% ≥65)	65.2±11.3 (58.2)	65.6±11.7 (43.9)	64.9±10.9 (56.2)
BMI >35 kg/m^2, n (%)	25 (6.1)	3 (1.7)	22 (9.6)
Smoking (ex or current), n (%)	244 (60.0)	95 (53.4)	149 (65.1)
Previous surgical operation, n (%)	180 (44.3)	91 (51.4)	89 (38.9)
Comorbidities, n (%)	109 (26.9)	43 (24.2)	66 (28.8)
Severe renal insufficiency, n (%)	15 (3.7)	8 (4.5)	7 (3.1)
History of trauma, (%)	13 (3.2)	12 (6.9)	1 (0.5)
History of immobility, n (%)	61 (15.0)	37 (20.8)	24 (10.5)
History of thrombosis, n (%)	7 (1.7)	6 (3.4)	1 (0.5)
History of bleeding, n (%)	2 (0.5)	1 (0.6)	1 (0.4)
Ca, n (%)			
Lung	102 (25.1)	33 (32.4)	69 (67.7)
Pancreas	58 (14.3)	0 (0.0)	58 (100.0)
Breast	37 (9.1)	35 (94.6)	2 (5.4)
Stomach	34 (8.4)	0 (0.0)	34 (100.0)
Colorectal	32 (7.9)	26 (81.2)	6 (18.8)
Ovarian	31 (7.6)	15 (48.4)	16 (51.6)
Bladder	22 (5.4)	9 (40.9)	13 (59.1)
Prostate	14 (3.4)	13 (92.9)	1 (7.1)
Sarcomas	11 (2.7)	6 (54.5)	5 (45.5)
Liver	5 (1.2)	3 (60.0)	2 (40.0)
Testis	5 (1.2)	1 (20.0)	4 (80.0)
Cholangiocarcinoma	4 (1.0)	4 (100.0)	0 (0.0)
Larynx	4 (1.0)	3 (75.0)	1 (25.0)
Endometrial	3 (0.7)	0 (0.0)	3 (100.0)
Renal	3 (0.7)	3 (100.0)	0 (0.0)
Cervical	2 (0.5)	2 (100.0)	0 (0.0)
Oesophageal	2 (0.5)	2 (100.0)	0 (0.0)
Other[a]	38 (9.3)	23 (60.5)	15 (39.5)
Metastatic disease	283 (69.5)	121 (68.0)	162 (70.7)
Treatment, n (%)			
HTBAs	270 (66.3)	94 (52.8)	176 (76.9)
Platinum	210 (51.6)	87 (48.9)	123 (53.7)
Antimetabolites	202 (49.6)	73 (41.0)	129 (56.3)
Anti-angiogenesis	32 (7.9)	23 (12.9)	9 (3.9)
Immunotherapy	20 (4.9)	6 (3.4)	14 (6.1)
Erythropoietin	71 (17.4)	25 (14.0)	46 (20.1)
Biomarker, n (%)			
Anemia (Hg <10 g/l)	85 (20.9)	14 (7.9)	71 (31.0)
PLT count ≥350x10^9/liter	153 (37.6)	16 (9.0)	137 (59.8)
Leucocyte count >11x10^9/liter	95 (23.3)	5 (2.8)	90 (39.3)

[a]Other not-listed solid tumors: Skin brain, unknown primary site, etc. Total and grouped into a Khorana score <2 and ≥2. Ca, Cancer; Hg, hemoglobin; HTBAs, high thrombotic burden agents; PLT, platelet.

4 experienced pulmonary embolism and 2 exhibited arterial thrombosis events. Of these, a total of four events were incidental and 10 were symptomatic. In association with the primary Ca site, five events were reported for patients with

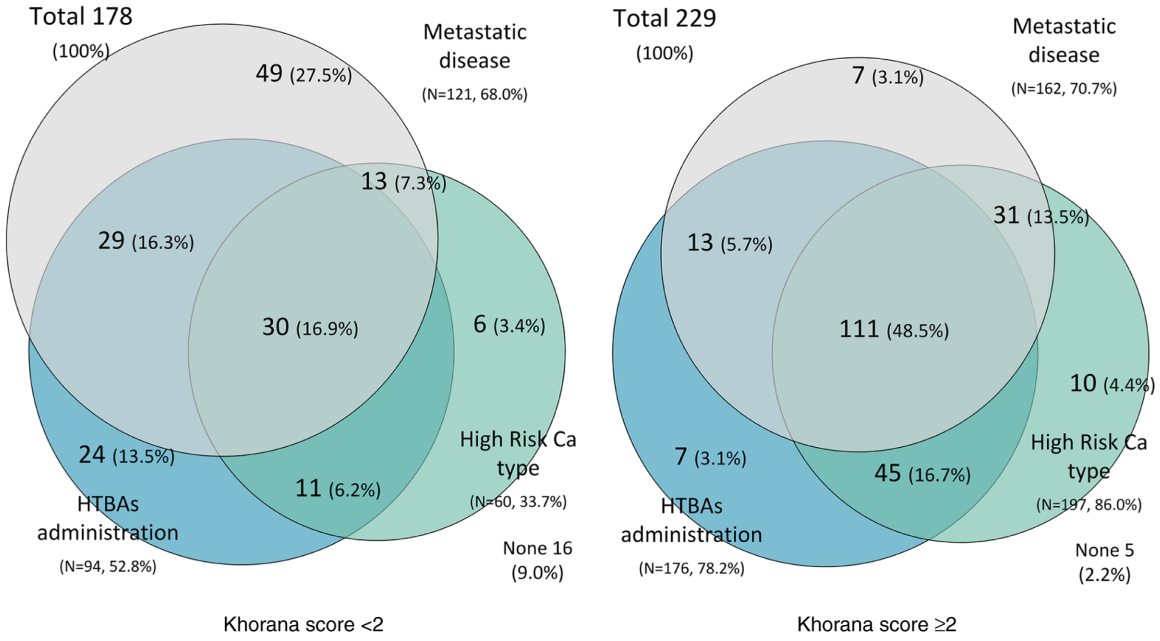

Figure 1. Venn diagrams of coexistence of cancer and treatment-related risk factors: High risk Ca type (included in the Khorana risk assesment model) along with metastatic disease and HTBAs. Ca, cancer; HTBAs, high thrombotic burden agents.

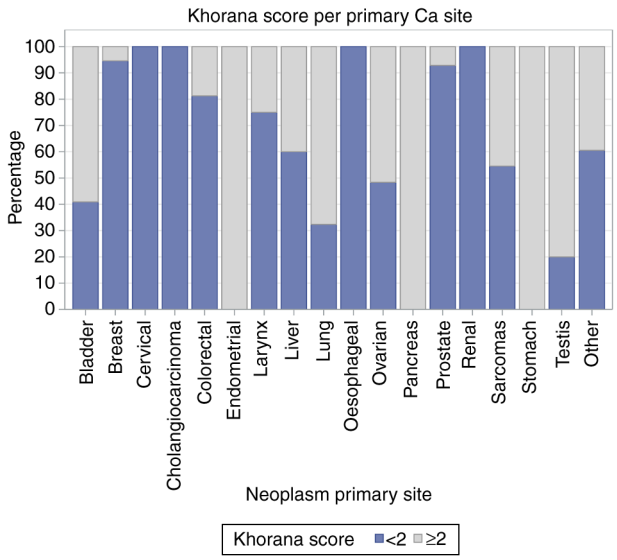

Figure 2. Distribution of patients with a Khorana score <2 vs. ≥2 per primary Ca site. Ca, cancer.

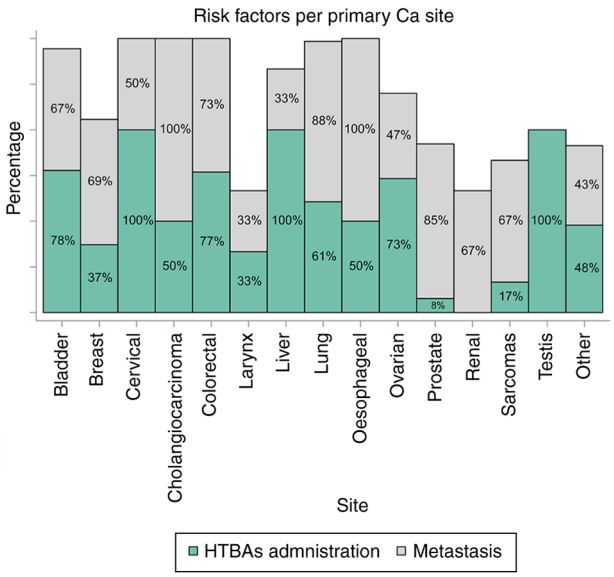

Figure 3. Risk factors contributing to thrombotic burden related to Ca and treatment for patients with a Khorana score <2. The numbers within blocks indicate the percentage of cases per primary site with the specific risk factor. Ca, cancer; HTBAs, high thrombotic burden agents.

lung Ca, two were reported for patients with breast Ca, while one event was reported in each patient with either stomach, colorectal, cervical or bladder Ca. Moreover, one case was reported in a patient with sarcoma and two cases were reported for patients with Ca in other sites. Notably, a high BMI was a significant risk factor. A total of 21% of patients who experienced thrombotic events were grouped in class 2 (obese; BMI ≥35 kg/m^2), compared with 6% of patients who did not experience thrombotic events, who were grouped in class 2 (obese; OR, 4.6; 95% CI, 1.2-17.7; P=0.0476). Moreover, in association with previous medical history, any type of trauma was associated with thrombotic events (OR, 5.7; 95% CI, 1.1-28.8; P=0.0169). Additionally, in terms of co-morbidities, 2 patients had cardiological issues, 1 exhibited respiratory problems and 1 was suffering from a metabolic disease. In total, 9 had metastatic disease. Regarding those receiving treatment, 9 out of these 14 patients were being treated with HTBAs.

In total, 50% patients who experienced thrombosis exhibited a Khorana score ≥2; 5 of them were administered with a ProD, while 2 received an InterD of tinzaparin. Out of the remaining 7 patients with a Khorana score <2, 5 received a ProD and 2 received an InterD. Patients who received an InterD were less likely to experience a thrombotic event,

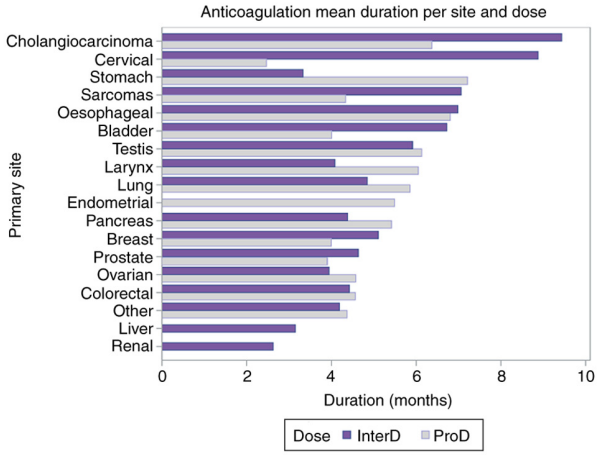

Figure 4. Average duration (in months) of tinzaparin administration per Ca primary site and dose. InterD, intermediate dose; ProD, prophylactic dose.

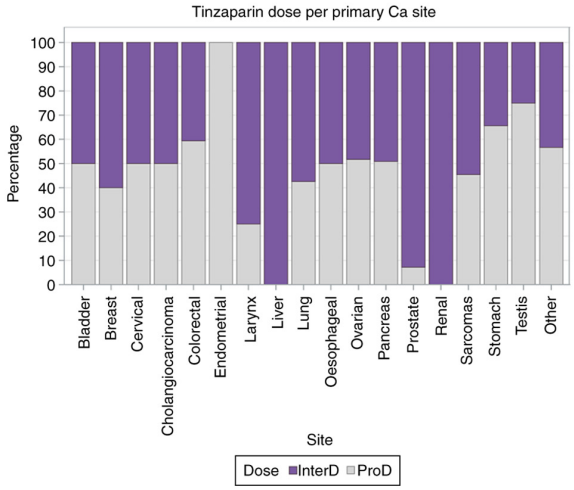

Figure 5. Administration (%) of ProD vs. InterD tinzaparin per primary Ca site. Ca, cancer InterD, intermediate dose; ProD, prophylactic dose.

compared with those who received a ProD (OR, 0.4; 95% CI, 0.1-1.1; P=0.0701). However, this result was not statistically significant. When only VTE events are considered, the OR becomes statistically significant (OR, 0.2; 95% CI, 0.04-0.81; P=0.0126).

Thromboprophylaxis safety. Out of a total of 407 patients, 6 (1.5%; 95% CI, 0.7-3.1%) experienced a bleeding event, although all of these events were categorized as minor. More specifically, 1 experienced epistaxis, 1 experienced hematuria and 4 hemoptysis events were observed. These events occurred in 0.5% of patients receiving ProD and 2.3% of patients receiving InterD; however, no statistically significant difference was observed. Table II demonstrates the various events in association with Khorana score and the dose administered.

Discussion

In the current cohort, 407 patients with various types of active malignancies were administered tinzaparin as primary prophylaxis. Almost 50% of the cohort population receiving thromboprophylaxis exhibited a Khorana score <2. The justification for using thromboprophylaxis was the presence of metastatic disease, and whether HTBAs were being administered. These factors were present in two thirds and >50% of the patients, respectively. The average duration of prophylaxis was 5.0±3.1 months. In total, 213 (52.4%) received tinzaparin as an InterD (8,000-12,000 Anti-Xa IU; once daily). Notably, the following factors were found to be the main criteria for selection of an InterD: A BMI >30 Kg/m^2, previous history of smoking, the presence of metastatic disease and previous administration of erythropoietin. A total of 14 patients experienced thrombotic events (3.4%), while 6 (1.5%) reported a bleeding event; although all bleeding events were minor.

The risk for VTE was found to increase 6-fold in outpatients receiving chemotherapy, as well as in those with advanced stage of disease (25); however, neither of these elements are included within the Khorana score.

In the present cohort, factors influencing the clinicians' decision to administer prophylaxis, apart from Khorana score, were the presence of metastatic disease in 2 out of 3 patients, and the use of HTBAs in 50% of them.

Ca stage, rather than Ca type, is a dominant risk factor for VTE. Specifically, metastasis is considered to be a key risk factor for VTE (26). Moreover, platinum compounds, 5-flurouracil and bevacizumab (13) were received by ~50% of the patients in the present study cohort, and these have been reported to increase thrombotic risk by up to 18% as single agents (13). The coexistence of Ca and treatment-associated factors further contributes to the risk of thrombotic events.

With regards to patient-associated factors, increased age and a history of smoking, which were found to be present in 1 out of 2 patients with a Khorana score <2, have previously been associated with an increased risk of VTE development (27). Additionally, 1 out of 5 patients with a Khorana score <2 exhibited comorbidities, including cardiovascular, endocrinological, metabolic or respiratory disease, which could also contribute to the overall risk of thrombotic events (4).

The average duration of prophylaxis with tinzaparin lasted 5.0±3.1 months of anticancer treatment. A trend towards the use of prophylaxis for longer periods was found in patients with a Khorana score ≥2 (P=0.0893).

Regarding the dose administered, >50% patients received tinzaparin as an InterD. No significant difference in the selected dose (ProD or InterD) was observed between the groups of patients with a Khorana score <2 or ≥2 (OR, 0.76; 95% CI, 0.51-1.14; P=0.1918). The main selection criteria for the use of an InterD were as follows: a BMI >30 Kg/m^2, previous history of smoking, the presence of metastatic disease and previous administration of erythropoietin. Notably, the administration of InterD was consistent regardless of the aggressiveness of the disease, and an increasing trend for the administration of InterD was observed depending on the systemic anticancer treatment. The percentages of patients receiving InterD were distributed as follows: Preoperative, 23%; adjuvant, 34%; first-line, 50%; second-line, 60%; and third-line, 65% (P=0.0364).

Two main RCTs (Randomized Control Trials) have examined the impact of thromboprophylaxis on LMWHs in various Ca types; namely, SAVE ONCO (28), which looked at the use of semuloparin, and PROTECT (29), which examined the use

Table II. Observed events in relation to tinzaparin dose and Khorana score.

	ProD tinzaparin dose ≤4,500 Anti-Xa IU, once daily (n=194)		InterD tinzaparin dose 8,000-12,000 Anti-Xa IU, once daily (n=213)		Total tinzaparin (n=407)	
Adverse events	Number of events (%)	KS	Number of events (%)	KS	Number of events (%)	KS
Thrombotic events per KS	5 (6.4)	<2 (n=78)	2 (2.0)	<2 (n=100)	7 (3.9)	<2 (n=178)
	5 (4.3)	≥2 (n=116)	2[a] (1.8)	≥2 (n=113)	7 (3.1)	≥2 (n=229)
Total thrombotic events, n (%)	10 (5.2)		4[b] (1.9)		14 (3.4)	
Bleeding events per KS	1 (1.3)	<2 (n=78)	0 (0.0)	<2 (n=100)	1 (0.6)	<2 (n=178)
	0 (0)	≥2 (n=116)	5 (4.4)	≥2 (n=113)	5 (2.2)	≥2 (n=229)
Total bleeding events, n (%)	1 (0.5)		5 (2.3)		6 (1.5)	

[a]Arterial thrombotic events, [b]two arterial thrombotic events included. InterD, intermediate dose; ProD, prophylactic dose; KS, Khorana Score; Anti-Xa IU, Anti-Xa International Units.

of nadroparin. The percentages of the different malignancies and those of the different stages of the disease (advanced or metastatic) which were included in the aforementioned studies were similar to those included in the present post hoc analysis. In the PROTECT study (29), the median prophylaxis duration was <4 months, and in the SAVE ONCO study (28) this was 3.5 months, compared with the present cohort, in which the average duration was longer (5±3.1 months). With regards to efficacy, thromboembolic events were experienced by 2.0% of the patients treated with nadroparin in the PROTECT study (29), and by 1.2% of the patients receiving semuloparin in the SAVE ONCO study (28). In the present study, this was the case with 5.2% of the patients who received a ProD, and 1.9% of the patients who received an InterD of tinzaparin. In terms of safety, minor bleeding events occurred in 7.4% of patients treated with nadroparin in the PROTECT study, and major events in 0.7% of them. The incidence rate of clinically relevant bleeding in the SAVE ONCO study was 2.8%, and that of major bleeding was 1.2% in the semuloparin group. In the present analysis, all bleeding events reported were minor; specifically, the bleeding incidence was 0.5% in the ProD group and 2.3% in the InterD group. In both the PROTECT and SAVE ONCO trials, the dose used was the prophylactic dose.

A total of two DOAC (Direct Oral Anti-Coagulant) trials examined the use of primary prophylaxis; the AVERT trial (30), in which apixaban was evaluated, and the CASSINI trial (31), in which patients were administered with rivaroxaban. These studies only included patients with a Khorana score ≥2. The comparable population in this cohort (patients with a Khorana score ≥2) were 229 patients (56.3% of the total population). In the AVERT trial (30), the median duration of the prophylaxis period was 5.2 months in the apixaban group, and 4.3 months in the CASSINI trial, which is comparable with the median duration in the present study (5±3.1 months). In the AVERT trial (30), 4.2% cases of VTE were reported, and in the CASSINI trial (31), 6.0% of the patients were diagnosed with VTE. In the present analysis, VTE events were observed in 4.3% of the patients receiving a ProD and in 1.8% of the patients receiving an InterD of tinzaparin. Clinically relevant bleeding events were observed in 9.0% of the patients treated with apixaban in the AVERT study, and in 4.7% of the patients who received rivaroxaban in the CASSINI trial. In the present study, bleeding was not reported in patients who received a ProD, while minor events were reported in 4.4% of the patients who received an InterD.

Both the AVERT and CASSINI trials had excluded patients with severe renal insufficiency [creatinine clearance (CrCl) <30 ml/min]. Patients with chronic kidney disease are at an increased risk of bleeding (32). In this cohort, severe renal insufficiency was reported in 15 patients (3.7%), while one minor bleeding event occurred in a patient with lung Ca. Tinzaparin pharmacokinetics is of the first-order, as there is involvement of both the cellular and renal elimination paths (33). In addition, tinzaparin does not exhibit bioaccumulation, even in the presence of severe renal impairment (34). Results of previous studies demonstrated that tinzaparin does not accumulate in patients with a CrCl as low as 20 ml/min (35). The aforementioned DOAC trial also excluded patients with significant comorbidities, patients with a predisposition for bleeding or a low-platelet count, and patients undergoing chemotherapy, which may interact with DOACs. Notably, in the present cohort, ~80% of the patients received anticancer treatment with potential drug-drug interactions (DDIs) with DOACs. Interactions with chemotherapy may reduce the efficacy of oral anticoagulants or increase the risk of bleeding. Moreover, chemotherapy may cause gastrointestinal disturbances, which may affect oral anticoagulant bioavailability (36,37).

The present analysis demonstrated a potential clinical benefit in the efficacy of thromboprophylaxis with the use of ProD tinzaparin, consistent with the previously published data; InterD of tinzaparin appeared to be more effective (4 thrombotic events) compared with a ProD (10 thrombotic events) and this is supported by marginally statistical significance (OR, 0.4; 95% CI, 0.1-1.1; P=0.0701). Considering only VTE events, patients who received an InterD exhibited an 80% reduced risk of experiencing a thrombotic event (OR, 0.2; 95% CI, 0.04-0.81; P=0.0126). Bleeding is a frequent problem for patients with advanced Ca, with approximately 10% of all

patients having at least one episode (38). Anticoagulation with tinzaparin appeared to offer a balance between the competing risks of clotting and bleeding in those patients, as only six minor bleeding events were observed.

Patients included in this analysis had active Ca, exhibited a high thrombotic burden, renal insufficiency and a type of anticancer treatment. The present study was heavily reliant on data obtained from day-to-day clinical practice and, as such, it is not possible to make direct comparisons between the various groups. An alternative approach is the use of DOACs for thromboprophylaxis in patients with Ca, assuming the absence of significant risk factors associated with bleeding and DDIs (24).

There were certain limitations to the present study, as well as a number of advantages associated with observational studies (39). Notably, the present study involved a broad range of patients with no specific focus on their characteristics. Thus, biases of an unknown nature may have been present. For example, such heterogeneity between patients may lead to a dilution of the beneficial effects of prophylaxis against thrombosis. By contrast, such heterogeneity may have allowed the impact of thrombosis-associated complications and the potential benefits of anticoagulation intervention to be highlighted in various different Ca types. Further limitations may have been present; however, the present study summarized the conditions of a common clinical oncology setting.

The present cohort includes practice-based evidence, and its aim was to summarize the individualized stratification of VTE risk in patients with active Ca.

Future randomized control studies, focusing on more specific patient profiles with a high risk of thromboembolism development, may be an attractive approach to assessing the clinical benefits of thromboprophylaxis in terms of patient outcomes.

In conclusion, personalized treatment is becoming an increasingly attractive approach, and may allow oncologists to consider the positive effects of antineoplastic agents without the interference of challenges, such as thrombosis. The presence of metastatic disease and the use of HTBAs appear to influence oncologists' decisions for the use of thromboprophylaxis in patients with active Ca, regardless of the Khorana score. The results of the present study also demonstrated that an InterD of tinzaparin was administered more frequently to patients with a BMI ≥30 kg/m^2, a previous history of smoking and a history of metastatic disease, along with a previous administration of erythropoietin. Moreover, an InterD of tinzaparin was found to be more efficacious for the prevention of VTE, without compromising safety. Therefore, the administration of tinzaparin appears to offer a promising solution for thromboprophylaxis in patients undergoing a course of anticancer treatment.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

AC, PPapakot, NT and IB conceived the study. AC, ET and IB developed the methodology. AC and IB performed formal analysis. AC, AAr, CP, GK, GPa, PPapakot, NT, CA, GS, PPapakos, GA, NZ, MS, CK, ES, PM, GPe, AAt, HS, AB, AG, EST, IV, ET and IB managed the subject patients included in the study and acquired the data used in the analysis. AC wrote the original draft. IB reviewed and edited the manuscript. IB supervised the study. NT and PPapakot were responsible for project administration. AC, AAr, CP, GK, GPa, PPapakot, NT, CA, GS, PPapakos, GA, NZ, MS, CK, ES, PM, GPe, AAt, HS, AB, AG, EST, IV, ET and IB have critically revised the manuscript for important intellectual content. AC, AAr, CP, GK, GPa, PPapakot, NT, CA, GS, PPapakos, GA, NZ, MS, CK, ES, PM, GPe, AAt, HS, AB, AG, EST, IV, ET and IB agreed to be accountable for all aspects of this work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. AC, AAr and IB confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The study was conformant with the Helsinki Declaration and the relevant amendments and was approved by the Bioethics Committee of 'Saint Andrew' General Hospital (Patras, Greece). Written informed consent was obtained from all subjects involved in the study for their participation.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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