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ORIGINAL ARTICLE

Comparative safety of enoxaparin versus other low-molecular-weight heparins in cancer-associated venous thromboembolism: a real-world cohort study from RIETE

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Abstract

Background: Low-molecular-weight heparins (LMWHs) are widely used in the treatment of cancer-associated venous thromboembolism (VTE), yet their long-term safety profiles remain insufficiently compared in clinical practice.

Objectives: The primary outcome was major bleeding over a 6-month follow-up. Secondary outcomes included VTE recurrence, non-major clinically relevant bleeding, and all-cause mortality.

Methods: We analyzed 7287 patients with active cancer and acute VTE from the RIETE registry (2009-2022) who were treated with full-dose enoxaparin (*n* = 5628) or tinzaparin/dalteparin (*n* = 1659). Analyses were adjusted using multivariable Cox

A full list of the RIETE Investigators is given in the Appendix.

models, Fine-Gray competing risk models, frailty models clustered by center, and propensity score approaches.

Results: Major bleeding occurred in 3.84% of patients receiving enoxaparin versus 2.53% in the tinzaparin/dalteparin group (adjusted hazard ratio [aHR] 1.56; 95% CI: 1.11-2.19), with consistent findings across all sensitivity analyses. Enoxaparin was also associated with higher all-cause mortality (28.3% vs 25.1%; aHR 1.22; 95% CI: 1.09-1.37). No significant differences were observed in VTE recurrence (3.59% vs 3.07%) or non-major bleeding (3.98% vs 3.25%). Importantly, during the first 10 days of therapy, major bleeding occurred in 1.2% of patients treated with enoxaparin twice-daily, compared to 0.4% with once-daily dosing and 0.1% in the tinzaparin/dalteparin group ($P < .001$).

Conclusion: In this large, observational study, enoxaparin, particularly in twice-daily regimens, was associated with significantly increased risks of bleeding and mortality compared to tinzaparin/dalteparin. These findings may help refine LMWH selection and dosing strategies in patients with cancer-associated VTE and warrant further investigation in prospective studies.

KEYWORDS
bleeding, cancer, low-molecular-weight heparins, mortality, recurrences, venous thromboembolism

Essentials

- Some anticoagulants may cause more bleeding in cancer patients with blood clots.
- We studied 7287 patients from the RIETE registry with cancer and a blood clot (venous thromboembolism).
- Enoxaparin given twice daily led to more early bleeding than once-daily alternatives.
- Tinzaparin or dalteparin were linked to fewer bleeds and deaths than enoxaparin.

1 | INTRODUCTION

Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), is a frequent and potentially life-threatening complication in patients with active cancer. The prothrombotic state induced by malignancy and its treatment, together with patient-related factors such as immobility, age, and comorbidities, contribute to increased risks of both recurrent VTE and bleeding [1–7]. As a result, managing cancer-associated VTE presents a clinical challenge, requiring individualized anticoagulation strategies that balance efficacy and safety.

Current international guidelines recommend extended anticoagulation for cancer-associated VTE to minimize recurrence [8,9]. Among available options, low-molecular-weight heparins (LMWHs) have long been a mainstay of therapy due to their predictable pharmacokinetics, ease of subcutaneous administration, and low potential for drug interactions with chemotherapy or other medications. The most used LMWHs include enoxaparin, dalteparin, and tinzaparin. While their efficacy has been established in randomized controlled trials (RCTs) comparing them with vitamin K antagonists (VKAs) or direct oral anticoagulants (DOACs) [10–15], there are no head-to-head trials comparing these LMWHs directly [16]. In the absence of such trials, real-world data derived from observational cohorts may help address this gap and guide clinical decision making.

The initial RIETECAT study identified a higher incidence of bleeding in cancer patients treated with enoxaparin than that in those with tinzaparin or dalteparin [17]. However, its limited sample size and short follow-up period constrained the generalizability of its findings. To expand upon these results, we conducted the RIETECAT-II study, leveraging a larger, contemporary cohort of patients from the RIETE registry and extending the observation period to 6 months. This study aimed to provide a more robust and nuanced assessment of the comparative safety of enoxaparin vs other LMWHs (dalteparin or tinzaparin) in cancer-associated VTE. Furthermore, RIETECAT-II captures contemporary treatment patterns, including once- and twice-daily dosing, allowing exploration of the impact of dosing regimens on clinical outcomes.

2 | METHODS

2.1 | Study design and setting

RIETECAT-II is a multinational, observational cohort study using prospectively collected data from the RIETE registry, which includes consecutive patients with objectively confirmed VTE. The RIETE registry has been previously described in detail [18–20] and captures comprehensive clinical data on demographics, cancer characteristics, risk factors, VTE presentation, comorbidities, laboratory data, treatments, and outcomes. All participating centers obtained local ethics approval, and all patients provided informed consent as required by national regulations.

2.2 | Study population

We included adult patients (≥18 years) with active cancer and acute symptomatic VTE (proximal lower-limb DVT, upper-limb DVT, or PE) diagnosed between January 1, 2009, and December 31, 2022. Active cancer was defined as malignancy diagnosed within 6 months prior, metastatic disease, hematological malignancy not in remission, or recent cancer therapy (chemotherapy, radiotherapy, hormonal therapy, or surgical treatment) within the past 6 months.

Patients were eligible if they initiated full-dose LMWH (enoxaparin, tinzaparin, or dalteparin) within 48 hours of VTE diagnosis. Patients were excluded if they had received VTE treatment within the past year, were treated with anticoagulants other than LMWH (eg, VKAs or DOACs), or initiated anticoagulation after 48 hours from VTE diagnosis.

Patients were followed for up to 180 days (6 months) after index VTE. Follow-up data included treatment modifications, recurrence of VTE, bleeding events, and all-cause mortality. Patients who discontinued LMWH, switched to DOACs or VKAs, or were lost to follow-up were censored at the time of treatment change or last known visit. Patients who switched between LMWH types (eg, from enoxaparin to dalteparin) were excluded from comparative analyses to maintain consistency.

2.3 | Exposure groups

Patients were stratified by LMWH type: enoxaparin (administered once daily or twice daily) vs dalteparin or tinzaparin (collectively referred to as other LMWHs). Treatment doses followed the standard recommendations for each LMWH. Specifically, enoxaparin was administered as 1 mg/kg (±20%) twice daily or 1.5 mg/kg (±20%) once daily; dalteparin as 200 IU/kg (±20%) once daily for the first month, followed by 150 IU/kg (±20%) once daily; and tinzaparin as175 IU/kg (±20%) once daily.

Patients who switched between twice daily and once daily enoxaparin were identified, and their outcomes were assessed separately in subgroup analyses. Patients transitioning from LMWH to DOACs or discontinuing anticoagulation were censored at the time of treatment change. Temporary interruptions (<3 days) were not considered discontinuations. Details of the timing, reasons, and patterns of switching or discontinuation were captured and reported descriptively.

2.4 | Outcomes

The primary outcome was the cumulative proportions of major bleeding within 6 months of initiating LMWH. Major bleeding was defined according to standard criteria as overt bleeding requiring transfusion of 2 units or more of blood or occurring in a critical site (eg, retroperitoneal, spinal, intracranial, intrathecal, intrapericardial, or intraocular bleeding) or contributing to death. Secondary outcomes included symptomatic, objectively proven VTE recurrences; nonmajor clinically relevant bleeding; and all-cause mortality. Cause-specific deaths (eg, fatal PE and fatal bleeding) were adjudicated by investigators when sufficient clinical information was available.

2.5 | Statistical analysis

Baseline characteristics were summarized using means (±SDs) or frequencies (percentages). Group comparisons used chi-squared or Fisher exact tests for categorical variables, and *t*-tests or Mann-Whitney *U*-tests for continuous variables, as appropriate.

To minimize confounding, 2 approaches were used: (1) frequency matching based on initial PE presentation and tumor-related bleeding risk (high vs low risk) and (2) propensity score matching using nearest-neighbor algorithms without replacement. Propensity scores were derived from logistic regression including age, sex, cancer type, metastases, renal function, anemia, platelet count, recent surgery, concomitant medications, and hospital size.

Multivariable Cox regression was used to estimate adjusted hazard ratios (aHRs) for clinical outcomes, accounting for residual baseline imbalances (standardized mean difference >0.1) and year of treatment. Competing risk analyses using Fine-Gray models treated death as a competing event. To account for center-level variation, we performed 2 additional models: Fine-Gray models with cluster-robust standard errors by center and frailty models with random effects clustered by center.

Sensitivity analyses included propensity score–adjusted models and competing risk frameworks. Centers with <10 patients were grouped for model stability. All analyses were conducted using SPSS Statistics (version 25.0; IBM) and R software (The R Foundation).

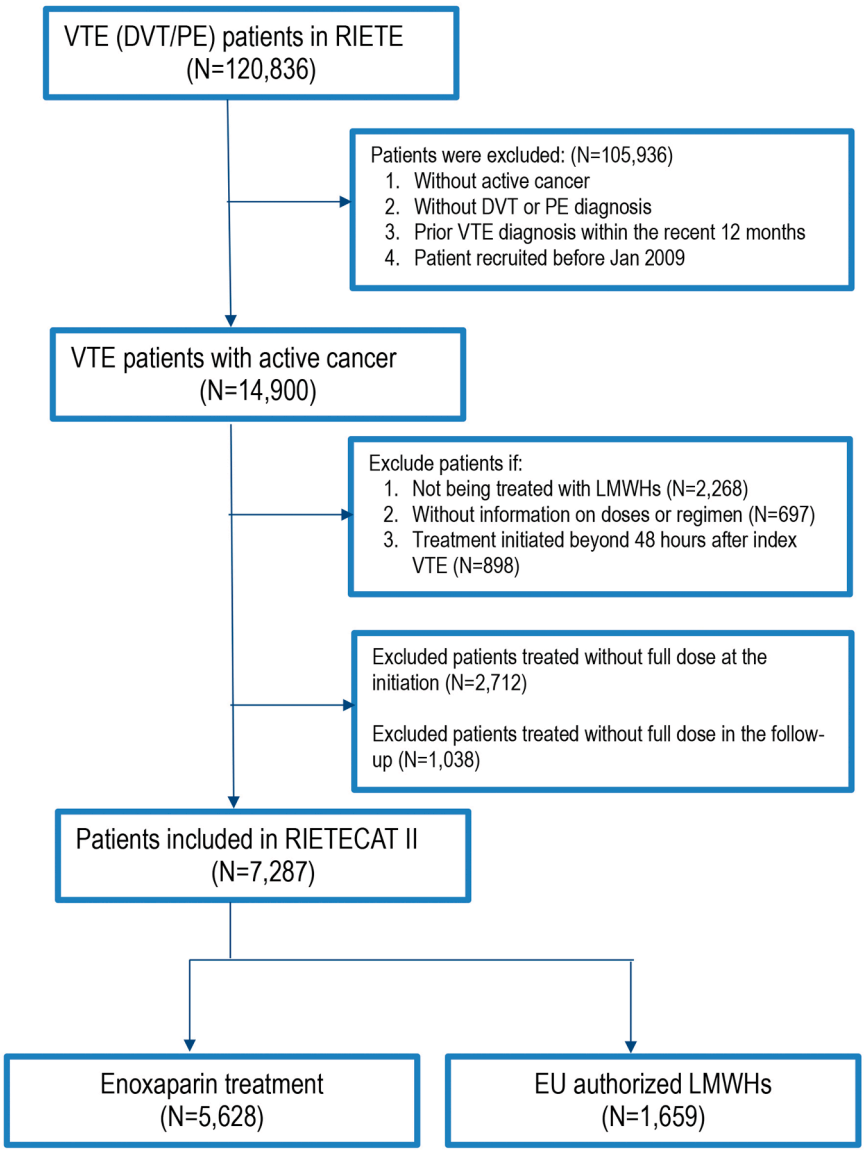

FIGURE 1 Flow chart of the patients. DVT, deep vein thrombosis; EU, European Union; LMWH, low-molecular-weight heparin; PE, pulmonary embolism; VTE, venous thromboembolism.

3 | RESULTS

3.1 | Study population and baseline characteristics

Among 14,900 screened patients from January 2009 to December 2022, a total of 7287 met the inclusion criteria (Figure 1). Of these, 5628 (77%) received enoxaparin, while 1659 (23%) received tinzaparin (n = 1483) or dalteparin (n = 176). Baseline characteristics were broadly similar between the groups. However, patients treated with enoxaparin were more likely to present with PE (63.1% vs 56.1%; $P < .001$) and had slightly higher rates of immobility and anemia. Lung, colorectal, and breast cancers were the most frequent tumor types in both groups (Tables 1 and 2).

3.2 | Treatment characteristics

Most patients in the tinzaparin/dalteparin group remained on once-daily dosing throughout follow-up, while 29.1% of enoxaparin-treated patients required dose modifications, most commonly switching from twice-daily to once-daily regimens (Supplementary Table 1). Overall, 55.6% of patients on enoxaparin started treatment with twice daily dosing. Median duration of treatment was similar across groups (145-148 days). Transition to a DOAC during follow-up occurred in 14.9% of all patients (14.1% in the enoxaparin group vs 17.7% in the other LMWH group).

TABLE 1 Baseline characteristics of patients with cancer-associated venous thromboembolism by LMWH group.

Characteristic	Enoxaparin	Tinzaparin/dalteparin	*P*
Patients (*n*)	5628	1659	
Demographics			
Female	2691 (47.8)	814 (49.1)	.3700
Age (y), mean (SD)	68 (13.0)	67 (13.0)	.0103
Body weight (kg), mean (SD)	73 (14.2)	73 (14.5)	.2491
Initial VTE presentation			
Deep vein thrombosis	2078 (36.9)	728 (43.9)	<.0001
Proximal	1617 (77.8)	465 (63.9)	<.0001
Bilateral lower limb	100 (4.8)	48 (6.6)	.0643
Upper limb	482 (23.2)	267 (36.7)	<.0001
Pulmonary embolism	3550 (63.1)	931 (56.1)	<.0001
SBP levels <100 mm Hg	305 (8.7)	60 (6.6)	.0370
Additional risk factors for VTE			
Postoperative	722 (12.8)	185 (11.2)	.0689
Immobility	835 (14.8)	199 (12.0)	.0036
Prior VTE	407 (7.2)	152 (9.2)	.0094
Comorbidities			
Recent major bleeding	106 (1.9)	22 (1.3)	.1288
Chronic heart disease	261 (4.7)	69 (4.2)	.4065
Atrial fibrillation	200 (4.7)	68 (5.3)	.3881
Chronic lung disease	681 (12.1)	167 (10.1)	.0232
Dementia	154 (2.7)	28 (1.7)	.0162
Depression	398 (7.1)	94 (5.7)	.0449
Liver cirrhosis	40 (0.7)	9 (0.5)	.4612
Blood tests			
Anemia	3259 (57.9)	1021 (61.5)	.0082
CrCl levels 30-60 mL/min	1349 (24.0)	370 (22.3)	.1599
CrCl levels <30 mL/min	183 (3.3)	55 (3.3)	.8980
Platelet count <100/mm^3	247 (4.4)	72 (4.3)	.9350
Concomitant drugs			
Corticosteroids	871 (16.9)	251 (16.5)	.7026
Antiplatelets	833 (16.2)	210 (13.8)	.0281
NSAIDs	416 (8.1)	108 (7.2)	.2329

Values are *n* (%) unless specified.

CrCl, creatinine clearance; LMWH, low-molecular-weight heparin; NSAID, nonsteroidal anti-inflammatory drug; SBP, systolic blood pressure; VTE, venous thromboembolism.

3.3 | Primary outcome: major bleeding

Major bleeding occurred in 221 patients (3.84%) receiving enoxaparin, compared with 44 patients (2.53%) receiving tinzaparin or dalteparin (Table 3). After adjustment for baseline variables using frequency matching and multivariable Cox regression, enoxaparin was associated with a significantly higher risk of major bleeding (aHR, 1.56; 95% CI, 1.11-2.19; *P* = .001) (Table 4). A similar association was observed in the

TABLE 2 Tumor characteristics among study participants.

Characteristic	Enoxaparin	Tinzaparin/dalteparin	*P*
Patients (*n*)	5628	1659	
Cancer sites			
Lung	983 (17.5)	281 (16.9)	.6175
Colorectal	789 (14.0)	250 (15.1)	.2823
Breast	693 (12.3)	237 (14.3)	.0344
Hematological	437 (7.8)	104 (6.3)	.0411
Prostate	434 (7.7)	93 (5.6)	.0036
Pancreas	286 (5.1)	102 (6.1)	.0891
Bladder	275 (4.9)	93 (5.6)	.2395
Stomach	218 (3.9)	53 (3.2)	.1991
Ovary	208 (3.7)	76 (4.6)	.1016
Uterus	206 (3.7)	69 (4.2)	.3487
Brain	197 (3.5)	40 (2.4)	.0279
Kidney	152 (2.7)	46 (2.8)	.8741
Oropharynx/larynx	106 (1.9)	35 (2.1)	.5566
Unknown	75 (1.3)	22 (1.3)	.9837
Esophagus	65 (1.2)	17 (1.0)	.6585
Others	504 (9.0)	141 (8.5)	.5654
Time since cancer diagnosis (mo)			
Mean (SD)	24 (48.1)	24 (46.0)	.8381
Median (Q1-Q3)	4 (1-24)	6 (2-25)	<.001
Cancer stage			
With metastases	2875 (51.1)	991 (59.7)	<.0001
Current cancer therapy			
Chemotherapy	2316 (48.2)	921 (64.0)	<.0001
Radiotherapy	736 (15.3)	179 (12.4)	.0065
Hormonal	596 (12.4)	168 (11.7)	.4530
Other	202 (4.2)	70 (4.9)	.2843
None	1707 (35.6)	329 (22.9)	<.0001

Values are *n* (%) unless specified.
LMWH, low-molecular-weight heparin.

propensity score-adjusted analysis (aHR, 1.53; 95% CI, 1.08-2.17). These findings remained consistent in sensitivity analyses, including Fine-Gray models accounting for death as a competing risk (aHR, 1.51; 95% CI, 1.08-2.10) and frailty models clustered by treatment center (aHR, 1.73; 95% CI, 1.20-2.51). Kaplan-Meier curves revealed a more rapid decline in major bleeding-free survival among patients treated with enoxaparin (Figure 2).

3.4 | Secondary outcomes

The rate of recurrent VTE did not differ significantly between groups (3.59% with enoxaparin vs 3.07% with tinzaparin/dalteparin; aHR, 1.26; 95% CI, 0.91-1.74; $P = .167$). Similarly, rates of nonmajor clinically relevant bleeding were comparable (3.98% vs 3.25%; aHR, 1.32; 95% CI, 0.95-1.83; $P = .094$). However, all-cause mortality was significantly higher in the enoxaparin group (28.3% vs 25.1%; aHR, of 1.22; 95% CI, 1.09-1.37; $P = .001$) than that in other groups. Rates of fatal PE and fatal bleeding were low and did not significantly differ between groups.

3.5 | Early major bleeding events (first 10 days)

During the first 10 days of treatment, major bleeding occurred in 1.2% of patients receiving enoxaparin twice daily, 0.4% of those on enoxaparin once daily, and 0.1% of patients treated with other LMWHs ($P < .001$). Most early bleeding events involved gastrointestinal, retroperitoneal, or intracranial sites (Supplementary Table 2). Pairwise comparisons showed a significantly higher early bleeding rate with enoxaparin twice daily than that with other LMWHs ($P < .001$), while rates of enoxaparin once daily did not differ significantly from tinzaparin/dalteparin ($P = .154$).

3.6 | Summary of sensitivity analyses

The primary findings were robust across multiple sensitivity analyses, including models adjusted for residual imbalances after matching, Fine-Gray competing risk models, and frailty models accounting for intercenter variability (Table 4). Across all models, enoxaparin remained significantly associated with increased risks of major bleeding and all-cause mortality.

4 | DISCUSSION

In this large, multicenter observational study of patients with active cancer and acute VTE, treatment with enoxaparin was associated with significantly higher risks of major bleeding and all-cause mortality than tinzaparin or dalteparin. These findings remained consistent across multiple analytical approaches, including frequency and propensity score matching, Fine-Gray competing risk models, and frailty models adjusting for intercenter variability, reinforcing the robustness of our results.

The increased bleeding risk was especially marked during the first 10 days of therapy in patients treated with enoxaparin twice daily, where the early major bleeding rate (1.2%) was significantly higher than that observed with enoxaparin once daily (0.4%) or other

TABLE 3 Clinical outcomes during the 6-month follow-up.

Outcome	Enoxaparin	Tinzaparin/dalteparin	*P*	OR (95% CI)
Patients (*n*)	5628	1659		
Primary				
Major bleeding	216 (3.84)	42 (2.53)	.010	1.54 (1.10-2.15)
Site of bleeding				
Gastrointestinal	90 (1.60)	15 (0.90)	.035	1.78 (1.03-3.09)
Intracranial	33 (0.59)	13 (0.78)	.379	0.75 (0.39-1.42)
Hematoma	18 (0.32)	2 (0.12)	.282	2.66 (0.62-11.5)
Retroperitoneal	18 (0.32)	2 (0.12)	.282	2.66 (0.62-11.5)
Genitourinary	26 (0.46)	5 (0.30)	.520	1.54 (0.59-4.00)
Other	31 (0.55)	6 (0.36)	.433	1.53 (0.64-3.66)
Secondary				
Recurrence of VTE	202 (3.59)	51 (3.07)	.3139	1.17 (0.86-1.60)
Symptomatic DVT	123 (2.19)	23 (1.39)	.0412	1.59 (1.01-2.49)
Symptomatic PE	93 (1.65)	28 (1.69)	.9212	0.98 (0.64-1.50)
Nonmajor bleeding	224 (3.98)	54 (3.25)	.1754	1.23 (0.91-1.67)
All-cause death	1591 (28.3)	416 (25.1)	.0105	1.18 (1.04-1.33)
Cause of death				
Pulmonary embolism	37 (0.66)	10 (0.60)	.8069	1.09 (0.54-2.20)
Bleeding	35 (0.62)	14 (0.84)	.3309	0.74 (0.39-1.37)
Infection	79 (1.40)	16 (0.96)	.1657	1.46 (0.85-2.51)
Respiratory insufficiency	99 (1.76)	11 (0.66)	.0013	2.68 (1.44-5.01)
Sudden unexpected death	17 (0.30)	4 (0.24)	.6840	1.25 (0.42-3.73)
Disseminated malignancy	1092 (19.4)	316 (19.0)	.7473	1.02 (0.89-1.18)
Fatal PE or fatal bleeding	72 (1.28)	24 (1.45)	.5994	0.88 (0.55-1.41)

Values are *n* (%) unless specified.

DVT, deep vein thrombosis; LMWH, low-molecular-weight heparin; OR, odds ratio; PE, pulmonary embolism; VTE, venous thromboembolism.

LMWHs (0.1%). Most of these early events involved critical anatomical sites. Notably, among all regimens, enoxaparin twice daily was the most frequently used (administered in more than half of enoxaparin-treated patients), despite being associated with the highest bleeding risk. This is clinically relevant, as the higher total dose delivered by twice daily administration may lead to greater cumulative anti-Xa exposure and bleeding liability, particularly in patients with impaired renal clearance. Importantly, these findings confirm and extend those from the original RIETECAT study and a prior RIETE analysis comparing twice-daily vs once-daily enoxaparin regimens [21], both of which signaled an elevated bleeding risk with twice-daily dosing.

While VTE recurrence rates were similar across groups, the numerically higher incidence in the enoxaparin cohort (3.6% vs 3.1%), although not statistically significant, warrants careful attention. Our analytical approach considered only first events, meaning VTE recurrence was not simply a consequence of prior bleeding or treatment interruptions. This reinforces the need to balance bleeding and thrombotic risks when selecting anticoagulant regimens in oncology patients.

The elevated all-cause mortality observed in the enoxaparin group (28.3% vs 25.1%) likely reflects a more vulnerable clinical profile. Although we applied frequency matching, multivariable adjustment, and propensity score methods, unmeasured confounding (such as frailty, active cancer progression, or perceived bleeding risk) may have influenced both treatment selection and outcomes. Nevertheless, the consistency of findings across models suggests a potential contribution of enoxaparin dosing strategy to mortality differences.

It is also possible that enoxaparin twice daily was preferentially prescribed to more fragile or periprocedural patients, in whom clinicians may favor shorter dosing intervals to allow for greater

TABLE 4 Adjusted HRs for clinical outcomes according to the type of LMWH therapy: multivariable Cox and sensitivity analyses.

Outcome	Model	HR (95% CI)	*P*
Major bleeding	Cox (frequency matching)	1.56 (1.11-2.19)	.010
	Fine-Gray	1.51 (1.08-2.10)	.017
	Fine-Gray (cluster-robust SE)	1.51 (1.04-2.19)	.032
	Frailty (clustered by center)	1.73 (1.20-2.51)	.004
	PS analysis	1.53 (1.08-2.17)	.017
	Fine-Gray (PS adjusted)	1.50 (1.05-2.12)	.024
	Fine-Gray (PS adjusted, clustered)	1.50 (1.00-2.24)	.051
	Frailty (PS adjusted)	1.66 (1.15-2.41)	.007
Nonmajor bleeding	Cox (frequency matching)	1.32 (0.95-1.83)	.094
	Fine-Gray	1.21 (0.89-1.63)	.220
	Fine-Gray (cluster-robust SE)	1.21 (0.82-1.78)	.345
	Frailty (clustered by center)	1.26 (0.90-1.78)	.180
All-cause death	Cox (frequency matching)	1.22 (1.09-1.37)	.001
	Frailty (clustered by center)	1.15 (0.99-1.33)	.067
Fatal bleeding	Cox (frequency matching)	0.80 (0.42-1.50)	.477
	Fine-Gray	0.78 (0.41-1.47)	.440
	Fine-Gray (cluster-robust SE)	0.78 (0.43-1.41)	.412
	Frailty (clustered by center)	1.08 (0.54-2.16)	.830
Fatal PE	Cox (frequency matching)	1.04 (0.48-2.23)	.930
	Fine-Gray	1.00 (0.45-2.22)	.997
	Fine-Gray (cluster-robust SE)	1.00 (0.50-2.03)	.993
	Frailty (clustered by center)	1.11 (0.46-2.66)	.810
Recurrent VTE	Cox (frequency matching)	1.26 (0.91-1.74)	.167
	Fine-Gray	1.25 (0.91-1.73)	.170
	Fine-Gray (cluster-robust SE)	1.25 (0.93-1.68)	.139
	Frailty (clustered by center)	1.23 (0.87-1.75)	.240

Frequency-matching models included covariates used for matching (age and tumor site) plus additional variables with residual imbalance (standardized mean difference > 10%) and the year of LMWH initiation. Variables were retained using stepwise selection ($P < .05$). Frailty and cluster-robust models were adjusted as in the frequency-matching model, with center-level clustering; centers with <10 patients were grouped. PS analyses adjusted for imbalanced covariates and the treatment year; variables selected via stepwise regression ($P < .05$). Competing risk and frailty models based on PS-matched populations, with center-level clustering as in frailty and cluster-robust models.

HR, hazard ratio; LMWH, low-molecular-weight heparin; PE, pulmonary embolism; PS, propensity score; VTE, venous thromboembolism.

flexibility or easier interruption of therapy. Such decisions, based on individualized clinical judgment, are difficult to capture in observational datasets and may have contributed to the observed differences in bleeding and mortality. This confounding by indication cannot be completely eliminated, even with propensity score adjustment.

These findings also raise important questions regarding the role of enoxaparin as a comparator in RCTs. Pivotal RCTs comparing DOACs with standard therapy (both in cancer-associated and general populations) used enoxaparin twice daily as the standard LMWH comparator [13–15]. Those trials consistently demonstrated lower bleeding rates with DOACs, while maintaining noninferior efficacy. However, our findings suggest that if enoxaparin once daily had been used as the control arm, bleeding outcomes might have been different. This possibility warrants consideration when interpreting trial data and in the design of future anticoagulant studies.

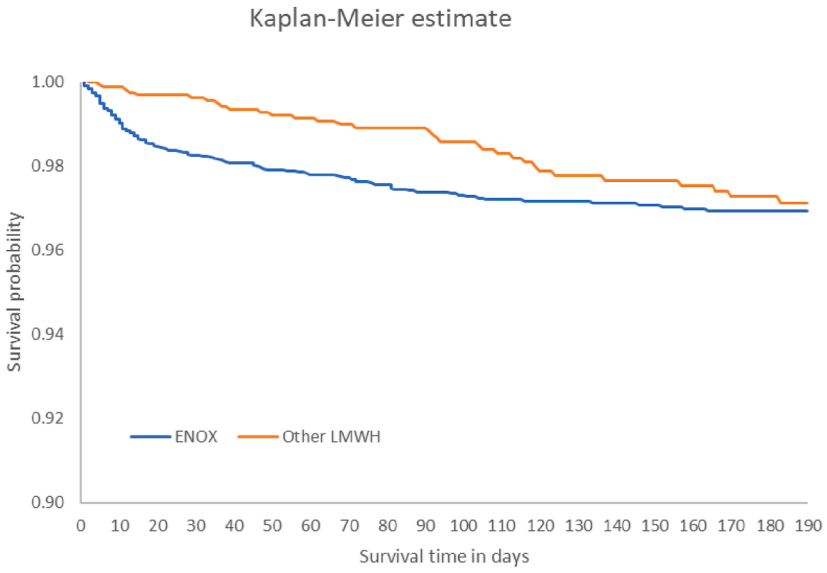

FIGURE 2 Kaplan-Meier survival analysis of time until the first major bleeding event.

		0-30	30-60	60-90	90-120	120-150	150-190
ENOX	PATIENTS AT RISK	4,318	3,677	3,266	2,710	2,169	1,876
	Events	77	16	15	6	2	3
Other LMWH	PATIENTS AT RISK	1,588	1,445	1,307	1,091	871	748
	Events	6	7	3	10	3	4

Differences in pharmacological profiles may further explain the observed safety disparities. Enoxaparin has a higher anti-Xa/anti-IIa ratio and greater renal clearance than tinzaparin/dalteparin, which may lead to accumulation and increased bleeding risk in patients with impaired renal function. By contrast, tinzaparin and dalteparin (administered once daily) were associated with lower bleeding rates, while maintaining similar protection against recurrent VTE, supporting their preferential use in high-risk patients.

The strengths of this study include a large, international, real-world cohort from the RIETE registry, encompassing unselected patients treated in routine clinical practice. Unlike RCTs that often exclude high-risk or complex patients, this study captured a more representative and clinically complex population. The use of granular treatment data, including timing and dosage patterns, allowed for detailed comparisons between LMWHs. Our results also align with current regulatory trends, recognizing real-world evidence as a valuable complement to clinical trials. Guidance form the European Medicines Agency and the US Food and Drug Administration increasingly supports the integration of registry-based data in clinical and regulatory decision making, especially for populations underrepresented in trials [22–24].

However, some limitations should be acknowledged. As with all observational studies, residual confounding may persist despite robust statistical control. We lacked detailed data on oncologic treatment regimens, rationale for dosing decisions, and timing of clinical interventions, which may have influenced outcomes. Additionally, the number of patients receiving enoxaparin once daily was relatively small, limiting definitive conclusions about its safety profile. Finally, we did not have access to detailed cause-specific mortality data, precluding precise attribution of deaths to bleeding, thrombosis, or cancer progression.

In conclusion, enoxaparin therapy over 6 months (particularly with twice daily dosing) is associated with increased bleeding and mortality risk compared with tinzaparin or dalteparin in patients with cancer-associated VTE. These findings reinforce the need to reconsider routine use of twice-daily enoxaparin in this population and support the preferential use of once-daily LMWHs, especially during the early phase of treatment. Future prospective studies and registry-based research should aim to refine anticoagulation strategies by exploring the safety and effectiveness of once-daily enoxaparin or stepdown approaches from twice daily to once daily during the acute phase of VTE therapy in patients with cancer.

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AUTHOR CONTRIBUTIONS

M.M. designed the study, obtained funds, recruited patients, participated in the statistical analyses, and wrote the manuscript. All the remaining coauthors discussed the design of the study with the principal investigator, recruited patients, discussed the manuscript, and provided their comments. Finally, they approved the final version.

RELATIONSHIP DISCLOSURE

M.M., as the principal investigator of the RIETE registry, received an unrestricted grant for research by Sanofi to sponsor the RIETE registry. The remaining coauthors declared that they have no conflicts of interest with the current manuscript.

APPENDIX

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REFERENCES

[1] Heit JA, Silverstein MD, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ. Risk factors for deep vein thrombosis and pulmonary embolism: a population-based case-control study. *Arch Intern Med*. 2000;160:809–15.

[2] Blom JW, Doggen CJM, Osanto S, Rosendaal FR. Malignancies, prothrombotic mutations, and the risk of venous thrombosis. *JAMA*. 2005;293:715–22.

[3] Connolly GC, Khorana AA, Kuderer NM, Culakova E, Francis CW, Lyman GH. Leukocytosis, thrombosis and early mortality in cancer patients initiating chemotherapy. *J Clin Oncol*. 2010;126:113–8.

[4] Ay C, Pabinger I, Cohen AT. Cancer-associated venous thromboembolism: burden, mechanisms, and management. *Thromb Haemost*. 2017;117:219–30.

[5] Zakai NA, Walker RF, MacLehose RF, Alonso A, Adams T, Lutsey PL. Impact of anticoagulant choice on hospitalized bleeding risk when treating cancer-associated venous thromboembolism. *J Thromb Haemost*. 2018;16:2403–12.

[6] López-Núñez JJ, Trujillo-Santos J, Monreal M. Management of venous thromboembolism in cancer patients. *J Thromb Haemost*. 2018;16:2391–6.

[7] Lanting VR, Takada T, Bosch FTM, Marshall A, Grosso MA, Young AM, et al. Risk of recurrent venous thromboembolism in patients with cancer: an individual patient data meta-analysis and development of a prediction model. *Thromb Haemost*. 2025;125:589–96.

[8] Farge D, Frere C, Connors JM, Khorana AA, Kakkar A, Ay C, Muñoz A, et al. 2022 International clinical practice guidelines for the treatment and prophylaxis of venous thromboembolism in patients with cancer. *Lancet Oncol*. 2022;23:e334–47.

[9] Key NS, Khorana AA, Kuderer NM, Bohlke K, Lee AYY, Arcelus JI, et al. Venous thromboembolism prophylaxis and treatment in patients with cancer: ASCO Clinical Practice Guideline Update. *J Clin Oncol*. 2020;38:496–520.

[10] Lee AY, Levine MN, Baker RI, Bowden C, Kakkar AK, Prins M, et al. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. *N Engl J Med*. 2003;349:146–53.

[11] Meyer G, Marjanovic Z, Valcke J, Lorcerie B, Gruel Y, Solal-Celiny PS, et al. Comparison of low-molecular-weight heparin and warfarin for secondary prevention of VTE in cancer patients. *Arch Intern Med*. 2002;162:1729–35.

[12] Young AM, Marshall A, Thirlwall J, Chapman O, Lokare A, Hill C, et al. Comparison of an oral factor Xa inhibitor with low molecular weight heparin in patients with cancer with venous thromboembolism: results of a randomized trial (SELECT-D). *J Clin Oncol*. 2018;36:2017–23.

[13] Agnelli G, Becattini C, Meyer G, Muñoz A, Huisman MV, Connors JM, et al. Apixaban for the treatment of venous thromboembolism associated with cancer. *N Engl J Med*. 2020;382:1599–607.

[14] Prins MH, Lensing AW, Brighton TA, Lyons RM, Rehm J, Trajanovic M, et al. Oral rivaroxaban versus enoxaparin with vitamin K antagonist for the treatment of symptomatic venous thromboembolism in patients with cancer (EINSTEIN-DVT and EINSTEIN-PE): a pooled subgroup analysis of two randomised controlled trials. *Lancet Haematol*. 2014;1:e37–46.

[15] Raskob GE, van Es N, Verhamme P, Carrier M, Di Nisio M, Garcia D, et al. Edoxaban for the treatment of cancer-associated venous thromboembolism. *N Engl J Med*. 2018;378:615–24.

[16] Kürzinger ML, El-Haddad C, Gouin-Soboleva T, Fazekas Z, Granados D, Benito-García E, et al. Structured benefit-risk assessment for enoxaparin, in the context of its label extension, for the extended treatment of deep vein thrombosis and pulmonary embolism, and prevention of its recurrence in patients with active cancer. *Pharmacoepidemiol Drug Saf*. 2024;33:e5795.

[17] Trujillo-Santos J, Farge-Bancel D, Pedrajas JM, Gómez-Cuervo C, Ballaz A, Braester A, et al. Enoxaparin versus dalteparin or tinzaparin in patients with cancer and venous thromboembolism: the RIETECAT study. *Res Pract Thromb Haemost*. 2022;6:e12736.

[18] Bikdeli B, Jimenez D, Hawkins M, Ortíz S, Prandoni P, Brenner B, et al. Rationale, design and methodology of the computerized registry of patients with venous thromboembolism (RIETE). *Thromb Haemost*. 2018;118:214–24.

[19] Bertoletti L, Madridano A, Jiménez D, Muriel A, Bikdeli B, Ay C, et al. Cancer-associated thrombosis. Trends in clinical features, treatment, and outcomes from 2001 to 2020. *JACC CardioOncol*. 2023;5:758–72.

[20] Galanaud JP, Trujillo-Santos J, Bikdeli B, Bertoletti L, Di Micco P, Poénou G, et al. Clinical presentation and outcomes of patients with cancer-associated isolated distal deep vein thrombosis. *J Clin Oncol*. 2024;42:529–37.

[21] Trujillo-Santos J, Bergmann JF, Bortoluzzi C, López-Reyes R, Giorgi-Pierfranceschi M, López-Sáez JB, et al. Once versus twice daily enoxaparin for the initial treatment of acute venous thromboembolism. *J Thromb Haemost*. 2017;15:429–38.

[22] Berger ML, Sox H, Wilke RJ, Brixner DL, Eichler HG, Goettsch W, et al. Good practices for real-world data studies of treatment and/or comparative effectiveness: recommendations from the joint SPOR-ISPE Special Task Force on real-world evidence in health care decision making. *Pharmacoepidemiol Drug Saf*. 2017;26:1033–9.

[23] European Medicines Agency: Regulatory science to 2025. https://www.ema.europa.eu/en/documents/regulatory/procedural-guideline/ema-regulatory-science-2025-strategic-reflection_en.pdf; 2024 [accessed November 17, 2025].

[24] US Food and Drug Administration. Real-world Evidence Program. https://www.fda.gov/media/120060/download; 2024 [accessed November 17, 2025].

SUPPLEMENTARY MATERIAL

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