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ORIGINAL ARTICLE

Once versus twice daily enoxaparin for the initial treatment of acute venous thromboembolism

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Essentials

- In venous thromboembolism (VTE), it is uncertain if enoxaparin should be given twice or once daily.
- We compared the 15- and 30-day outcomes in VTE patients on enoxaparin twice vs. once daily.
- Patients on enoxaparin once daily had fewer major bleeds and deaths than those on twice daily.
- The rate of VTE recurrences was similar in both subgroups.

Summary. *Background:* In patients with acute venous thromboembolism (VTE), it is uncertain whether enoxaparin should be administered twice or once daily. *Methods:* We used the RIETE Registry data to compare the 15- and 30-day rates of VTE recurrence, major bleeding and death between patients receiving enoxaparin twice daily and those receiving it once daily. We used propensity score matching to adjust for confounding variables. *Results:* The study included 4730 patients: 3786 (80%) received enoxaparin twice daily and 944 once daily. During the first 15 days, patients on enoxaparin once daily had a trend towards more VTE recurrences (odds ratio [OR], 1.79; 95% confidence interval [CI], 0.55–5.88), fewer major bleeds (OR, 0.42; 95% CI, 0.17–1.08) and fewer deaths (OR, 0.32; 95% CI, 0.13–0.78) than those on enoxaparin twice daily. At day 30, patients on enoxaparin once daily had more VTE recurrences (OR, 2.5; 95% CI, 1.03–5.88), fewer major bleeds (OR, 0.40; 95% CI, 0.17–0.94) and fewer deaths (OR, 0.58; 95% CI, 0.33–1.00). On propensity analysis, patients on enoxaparin once daily had fewer major bleeds at 15 (hazard ratio [HR], 0.30; 95% CI, 0.10–0.88) and at 30 days (HR, 0.16; 95% CI, 0.04–0.68) and also fewer deaths at 15 (HR, 0.37; 95% CI, 0.14–0.99) and at 30 days (HR, 0.19; 95% CI, 0.07–0.54) than those on enoxaparin twice daily. *Conclusions:* Our findings confirm that enoxaparin prescribed once daily results in fewer major bleeds than enoxaparin twice daily, as suggested in a meta-analysis of controlled clinical trials.

Keywords: bleeding; enoxaparin; mortality; recurrences; regimen; venous thromboembolism.

Introduction

In patients with acute venous thromboembolism (VTE), it is uncertain whether low-molecular-weight heparin (LMWH) should be administered twice or once daily. A single daily injection of LMWH is more convenient for people and may optimize home therapy. However, it is conceivable that twice-daily LMWH results in a more stable level of anticoagulation and thus in fewer complications. The American College of Chest Physicians (ACCP) guidelines suggest once daily over twice daily

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administration (Grade 2C) [1], but this recommendation only applies when the approved once daily regimen uses the same daily dose as the twice daily regimen (i.e. the once daily injection contains twice the dose of each twice daily injection). This is not the case for enoxaparin, where the once daily dose is a dose only 50% (1.5 mg kg^{-1}) higher than each twice daily injection (1.0 mg kg^{-1}).

The RIETE (Registro Informatizado de Enfermedad TromboEmbólica) Registry is an ongoing, multicenter, international (Spain, Italy, France, Israel, Portugal, Germany, Switzerland, Czech Republic, Republic of Macedonia, Greece, Canada and Ecuador), observational registry of patients with symptomatic, objectively confirmed, acute VTE (ClinicalTrials.gov identifier: NCT02832245). Data from this registry have been used to evaluate outcomes after acute VTE, such as the frequency of recurrent VTE, bleeding and mortality, and risk factors for these outcomes [2–6]. In the current analysis, we compared the effectiveness and safety of the two different dosing strategies of enoxaparin (once vs. twice daily) in the initial therapy of patients with acute VTE.

Patients and methods

Inclusion criteria

Consecutive patients with symptomatic, acute 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), were enrolled in RIETE. Patients were excluded if they were currently participating in a therapeutic clinical trial with a blinded therapy. All patients (or their relatives) provided written or oral consent for participation in the registry, in accordance with local ethics committee requirements. This analysis was approved by the Ethics Committee of the Hospital Universitari Germans Trias i Pujol (Badalona, Spain) and by the Institutional Review Board of NorthShore University Health System (Evanston, Illinois, USA).

Physicians participating in the RIETE registry made all efforts to enroll consecutive patients. Data were recorded on to a computer-based case report form at each participating hospital and submitted to a centralized coordinating center through a secure website. The coordinating center assigned patients a unique identification number to maintain patient confidentiality and was responsible for all data management. Data quality was regularly monitored electronically, including checks to detect inconsistencies or errors, which were resolved by contacting the local coordinators. Data quality was also monitored by periodic visits to participating hospitals by contract research organizations that compared medical records with the submitted data.

Study design

This is an observational, retrospective, cohort study to assess the effectiveness and safety of 1.5 mg kg^{-1} enoxaparin once daily compared with 1 mg kg^{-1} enoxaparin twice daily for treatment of acute VTE, based on the RIETE registry. Only patients receiving an initial dose of 1.2–1.8 mg kg^{-1} once daily or 0.8–1.2 mg kg^{-1} twice daily (that is, within $\pm$ 20% of the theoretical dose) were included in the analysis. The study was conducted using data collected from February 2012 until June 2015. This period corresponds to the time when the dosing regimen of enoxaparin (and other drugs) was recorded in RIETE.

The primary outcome was the rate of VTE recurrences, major bleeding and all-cause death within the first 15 days. The secondary outcome was the rate of VTE recurrences, major bleeding and death within the first 30 days. Major bleeding was defined as an overt bleed that required a transfusion of two or more units of blood, was retroperitoneal, spinal or intracranial, or was fatal. Fatal bleeding was defined as any death occurring within 10 days of a major bleeding episode, in the absence of an alternative cause of death.

Baseline variables

The following parameters were recorded when the qualifying episode of VTE was diagnosed: patient's gender, age and bodyweight, presence of coexisting conditions such as diabetes, prior artery disease, chronic lung disease, chronic heart failure, mental disorders, chronic liver disease, recent (< 30 days prior to VTE) major bleeding, concomitant drugs (corticosteroids, non-steroidal anti-inflammatory drugs or antiplatelet agents), alcohol abuse and laboratory data, including whole blood counts and serum creatinine clearance (CrCl) levels at baseline. CrCl levels were measured according to the Cockcroft and Gault formula [7].

Treatment and follow-up

Patients were managed according to the clinical practice of each participating hospital (i.e. there was no standardization of treatment). The type, dose and duration of anticoagulant therapy were recorded. After discharge, all patients were followed-up in the outpatient clinic. During each visit, any signs or symptoms suggesting VTE recurrences or major bleeding were noted. Most outcomes were classified as reported by the clinical centers. However, if staff at the coordinating center were uncertain how to classify a reported outcome, that event was reviewed by a central adjudicating committee (less than 10% of events).

Statistical analysis

Clinical characteristics, risk factors for VTE and initial VTE presentation were analyzed using descriptive

statistics for continuous variables and frequency counts and percentages for categorical variables. Odds ratios (ORs) with 95% confidence intervals (CIs), as well as *P*-values (Mann–Whitney test or *t*-test for continuous variables and Cochran-Mantel-Haenszel tests for categorical variables) were presented for each variable analyzed. All outcomes were analyzed in the short term (0–15 days) and in the overall follow-up period (0–30 days). Univariate analysis was conducted yielding odds ratios with 95% CI, as well as *P*-values (Cochran-Mantel-Haenszel tests) for each outcome. Kaplan–Meier survival analysis was conducted to investigate the risk of outcomes by treatment dosage for the overall period (0–30 days). We also compared the influence of the two enoxaparin regimens on the 30-day outcome in four subgroups of patients: (i) those aged > 75 years; (ii) those with active cancer; (iii) those with a body mass index (BMI) > 30; and (iv) those with CrCl levels < 30 mL min^{-1}.

Cox proportional hazard models were used to compare the rates of VTE recurrences, major bleeding and death of the two dosing strategies in the 15- and 30-day follow-up periods using twice daily as the reference dosage. Crude and adjusted hazard ratios (HRs) as well as their 95% CI were estimated. The interaction term of study treatment regimen and covariates of interest was examined. The hazard was assumed to be a constant ratio in between two regimen groups. Covariates included in the adjusted model were those for which a statistically significant difference (a threshold *P*-value of 0.1 was set to assess significance of differences) was found between the two dosing regimens, and a backward selection was used for the covariate selection in the multivariate model. For both Kaplan–Meier survival analyses and the Cox regression analyses, if a patient did not have a study outcome of interest before the cut-off time of 30 days or if they died (except for the analysis where death is the outcome), then the time-to-event was censored.

A propensity score was calculated based on the covariates that were clinically considered to be associated with an outcome: age, gender, bodyweight, CrCl levels, presence of cancer, year, underlying conditions, risk factors for VTE, co-morbidities and initial VTE presentation. Propensity score matching was carried out. The nearest neighbor (NN) method was used, with a ratio of 2 : 1 and 3 : 1 for enoxaparin twice daily vs. once daily and different calipers (corresponding to 0.1 and 0.2 value of standard deviation). Imbalance among covariates was measured with the standardized differences of mean for both continuous and categorical variables. A matched analysis was subsequently conducted using Cox proportional hazard models stratifying the matched pairs [8]. All analyses were conducted using SPSS version 20 (Chicago, IL, USA) and the psmatching3 v3.0.4 extension bundle [9].

Results

From February 2012 to June 2015, 6048 patients with acute VTE received initial therapy with enoxaparin: 4627 (76.5%) twice daily and 1421 once daily. The twice daily regimen was used in 72% of patients in Spain and in 94% in other countries (Table S1). Overall, 950 patients were excluded from the study because they received doses above or below ± 20% of the theoretical dose, were treated for less than 3 consecutive days ($n = 248$), started enoxaparin over 3 days after VTE diagnosis ($n = 67$) or experienced an outcome between VTE diagnosis and start of enoxaparin ($n = 11$), as depicted in Fig. 1. Thus, the study included 4730 patients (3786 on twice daily and 944 on once daily enoxaparin).

Patients receiving once daily enoxaparin were more likely to have severe renal insufficiency, anemia, chronic heart disease, esophagitis, gastric erosions, hiatal hernia or chronic liver disease at baseline than those on enoxaparin twice daily, but less likely to have suffered recent major bleeding (Table 1). They also were more likely to have recent immobility or cancer and more likely to receive corticosteroids or non-steroidal anti-inflammatory drugs at baseline than patients on twice daily enoxaparin. The duration of therapy was longer in patients on once daily enoxaparin (7.3 ± 2.9 vs. 6.8 ± 3.1 days) and the mean daily dose was lower (151.5 ± 15.4 vs. 195.6 ± 16.5 IU kg^{-1} day^{-1}), as shown in Table 2.

During the first 15 days of therapy, 13 patients (0.27%) experienced recurrent VTE, 52 (1.10%) had major bleeding and 68 (1.44%) died. Patients on once daily enoxaparin had a non-significantly higher rate of VTE recurrences (OR, 1.79; 95% CI, 0.55–5.88), a non-significantly lower rate of major bleeding (OR, 0.42; 95% CI, 0.17–1.08) and a lower mortality (OR, 0.32; 95% CI,

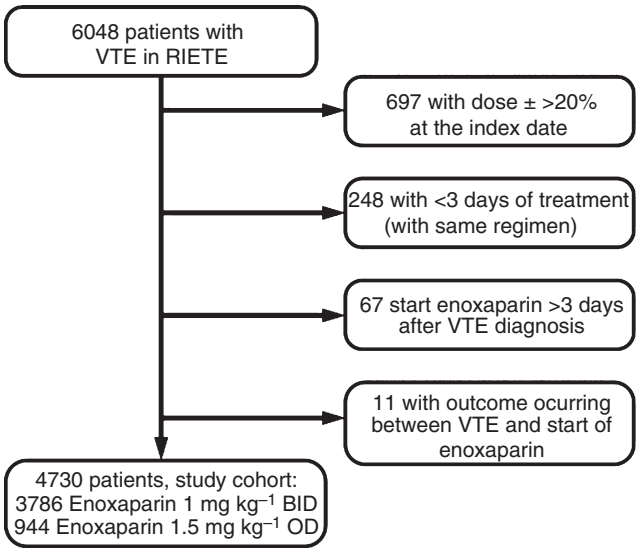

Fig. 1. Flow-chart of patients. VTE, venous thromboembolism.

Table 1 Patients demographics, clinical characteristics and underlying conditions

	Enoxaparin 1.5 mg kg^{-1} od	Enoxaparin 1 mg kg^{-1} bid	Odds ratio (95% CI)	*P* value
Patients, *N*	944	3786		
Clinical characteristics				
Male gender	449 (48%)	1940 (51%)	0.86 (0.75–1.00)	0.04
Age (years)	65 ± 16	66 ± 18		0.27
Bodyweight (kg)	76 ± 14	77 ± 16		0.17
Underlying conditions				
Chronic lung disease	113 (12%)	480 (13%)	0.93 (0.75–1.16)	0.56
Chronic heart disease	44 (4.7%)	241 (6.4%)	0.72 (0.52–1.00)	0.049
Gastroduodenal ulcer	20 (2.1%)	56 (1.5%)	1.45 (0.86–2.44)	0.16
Esophagitis	21 (2.2%)	29 (0.77%)	2.94 (1.67–5.26)	< 0.001
Gastric erosions	17 (1.8%)	35 (0.92%)	1.96 (1.10–3.57)	0.02
Hiatal hernia	68 (7.2%)	143 (3.8%)	1.96 (1.47–2.63)	< 0.001
Liver cirrhosis	8 (0.85%)	13 (0.34%)	2.50 (1.02–5.88)	0.04
Chronic liver disease (other)	17 (1.8%)	38 (1.0%)	1.82 (1.02–3.23)	0.04
CrCl levels (mL min^{-1})	80 ± 37	85 ± 42		< 0.001
CrCl levels 30–50 mL min^{-1}	152 (16%)	592 (16%)	1.11 (0.90–1.37)	0.73
CrCl levels < 30 mL min^{-1}	59 (6.2%)	163 (4.3%)	1.56 (1.14–2.13)	0.01
Recent major bleeding	5 (0.53%)	69 (1.8%)	0.29 (0.12–0.71)	0.004
Anemia	347 (37%)	1147 (30%)	1.33 (1.15–1.56)	< 0.001
Risk factors for VTE				
Postoperative	77 (8.2%)	349 (9.2%)	0.88 (0.68–1.14)	0.31
Immobility ≥ 4 days	222 (23%)	727 (19%)	1.27 (1.08–1.52)	0.005
Cancer	244 (26%)	708 (19%)	1.52 (1.28–1.79)	< 0.001
Concomitant therapies				
Corticosteroids	124 (13%)	356 (9.4%)	1.45 (1.18–1.82)	0.003
Antiplatelets	164 (17%)	680 (18%)	0.96 (0.79–1.16)	0.34
NSAIDs	121 (13%)	302 (8.0%)	1.69 (1.35–2.13)	< 0.001
Initial VTE presentation				
Pulmonary embolism	450	2549		
SBP levels < 100 mm Hg	26 (5.8%)	183 (7.2%)	0.79 (0.52–1.20)	0.27
Heart rate > 100 bpm	110 (24%)	752 (29%)	0.78 (0.61–0.97)	0.01
Sat O_2 levels < 90%	65 (14%)	377 (15%)	0.97 (0.73–1.30)	< 0.001
Deep vein thrombosis	494	1237		
Proximal	395 (80%)	928 (75%)	1.33 (1.03–1.72)	0.02
Bilateral lower limb	14 (2.8%)	19 (1.5%)	1.85 (0.93–3.70)	0.16
Upper limb	41 (8.3%)	120 (9.7%)	0.84 (0.58–1.22)	0.21

od, once daily; bd, twice daily; CI, confidence intervals; CrCl, creatinine clearance; VTE, venous thromboembolism; NSAIDs, non-steroidal anti-inflammatory drugs; SBP, systolic blood pressure; bpm, beats per minute.

0.13–0.78) than those on enoxaparin twice daily (Table 3). During the first 30 days of therapy, 21 patients (0.44%) had recurrent VTE, 65 (1.37%) bled and 118 (2.49%) died. Patients on once daily enoxaparin had a significantly higher rate of VTE recurrences (OR, 2.50; 95% CI, 1.03–5.88), a lower rate of major bleeding (OR, 0.40; 95% CI, 0.17–0.94) and a lower mortality (OR, 0.58; 95% CI, 0.33–1.00) than those on twice daily enoxaparin. There were no differences in the rate of fatal PE events (0.21% vs. 0.29%), but there were no fatal bleeds among patients receiving once daily enoxaparin. The number needed to treat at 30 days for the different outcomes appears in Table S2.

On multivariable analysis, there were no differences in outcome during the first 15 days, but patients on once daily enoxaparin had a significantly lower risk of major bleeding (HR, 0.30; 95% CI, 0.12–0.75) and all-cause death (HR, 0.23; 95% CI, 0.11–0.44) at 30 days, with no differences in VTE recurrences (HR, 1.36; 95% CI, 0.55–3.36). We performed four matching analyses with ratios of 2 : 1 and 3 : 1 and two caliper widths (0.1 and 0.2 of standard deviation of propensity score). We finally chose the nearest neighbor matching approach with a 2 : 1 ratio and caliper of 0.1 because it did not show imbalance among covariates. Results of the propensity score matching involved 1407 patients on twice daily enoxaparin and 864 on once daily enoxaparin. The matched sample was well balanced in all variables, except in the proportion of PE patients with systolic blood pressure levels < 100 mm Hg (8.8% vs. 6.3%). During the first 15 days of therapy, the matched analysis (with a ratio 2 : 1 and caliper of 0.1 of standard deviation) revealed a similar rate of VTE recurrences (HR, 1.26; 95% CI, 0.25–6.36) and a lower rate of major bleeding (HR, 0.30; 95% CI, 0.10–0.88) and all-cause death (HR, 0.37; 95% CI, 0.14–0.99) in patients on enoxaparin once daily (Table S3). At 30 days, patients

Table 2 Treatment details.

	Enoxaparin 1.5 mg kg^{-1} od	Enoxaparin 1 mg kg^{-1} bid	*P*-value
Enoxaparin therapy			
Patients, *n*	944	3786	
Duration of therapy (days)			
Mean (SD)	7.3 (2.9)	6.8 (3.1)	0.0002
Median	7	6	
Min-Max	2–14	0–14	
Average dosing* (IU kg^{-1} day^{-1})			
Mean (SD)	151.5 (15.4)	195.6 (16.5)	N/A
Median	151.5	200	
Min-Max	120–179.1	160–240	
VKA therapy			
Patients, *n*	458	2664	
Duration of therapy (days)			
Mean (SD)	210.5 (210.8)	181.3 (165.6)	0.0050
Median	160	141	
INR in therapeutic range† (%)			
Mean (SD)	36.9 (47.9)	32.4 (46.0)	0.2843

od, once daily; bd, twice daily; SD, standard deviation; VKA, vitamin K antagonists; INR, international normalized ratio. *Average dosing per day per patient during therapy. †During the first 15 days of treatment.

on enoxaparin once daily also had a lower rate of major bleeding (HR, 0.16; 95% CI, 0.04–0.68) and a lower mortality (HR, 0.19; 95% CI, 0.07–0.54) than those on enoxaparin twice daily. Other matching ratios and calipers showed similar results (Figs. 2 and 3). There also was a trend towards more VTE recurrences with enoxaparin once daily that lessened after propensity score matching.

On multivariable analysis, patients aged > 75 years treated once daily had a lower rate of major bleeding (adjusted HR, 0.12; 95% CI, 0.03–0.52) and all-cause death (adjusted HR, 0.10; 95% CI, 0.04–0.28) than those treated twice daily, with no differences in the rate of VTE recurrences (Table 4). Patients with active cancer on enoxaparin once daily also had a lower mortality rate (adjusted HR, 0.40; 95% CI, 0.20–0.81) than those on enoxaparin twice daily, with no differences in the rate of VTE recurrences or major bleeding. Patients with BMI > 30 had no differences in outcome. Finally, patients with CrCl levels < 30 mL min^{-1} receiving enoxaparin once daily had a lower mortality rate (adjusted HR, 0.13; 95% CI, 0.03–0.56) than those on enoxaparin twice daily.

Discussion

Initially, most studies comparing LMWH vs. unfractionated heparin in the treatment of VTE used a twice daily regimen [10–12]. Once daily administration has lately been compared with a twice daily regimen, and some studies found it to be as effective and safe as twice daily dosing [13–18]. Because it seems more convenient for people and may optimize home therapy, the ACCP guidelines on antithrombotic therapy suggested that once daily administration should be preferred over twice daily administration [1]. However, all randomized trials comparing the new direct oral anticoagulants (DOACs) vs. standard therapy used enoxaparin twice daily [19–21].

Our data, obtained from a large series of patients with acute VTE, reveal that in real life most of these patients (72% in Spain, 94% outside Spain) received enoxaparin twice daily. From a theoretical point of view, it is conceivable that twice daily LMWH results in a more stable level of anticoagulation and thus in fewer bleeding events [22]. This may explain why the twice daily regimen was preferred in most centers. Unexpectedly, however, patients on once daily enoxaparin therapy had less than half the rate of major bleeding and half the mortality rate, both at 15 and at 30 days, compared with patients on enoxaparin twice daily. Interestingly, the trend or significant differences between the two doses for the occurrence of endpoints at 15 days was confirmed or changed to significance at day 30 while on VKA. There were no differences in the rate of gastroduodenal bleeds, but no patient receiving once daily enoxaparin suffered retroperitoneal, cerebral or fatal bleeding. There also was a trend towards more VTE recurrences with enoxaparin once daily that lessened after propensity score matching. Our findings confirm those obtained in a Cochrane review of trials, suggesting that twice daily LMWH results in a non-significantly lower rate of VTE recurrences (OR, 0.82; 95% CI, 0.49–1.39) and a non-significantly higher rate of major bleeding (OR, 1.29; 95% CI, 0.79–2.50) compared with once daily LMWH [23].

This lower bleeding rate in patients on once daily enoxaparin may be because they received lower daily doses (151.5 ± 15.4 IU kg^{-1} day^{-1}) than those on twice daily enoxaparin (195.6 ± 16.5 IU kg^{-1} day^{-1}). Certainly, patients receiving once daily enoxaparin had a higher rate of VTE recurrences, although these differences disappeared on multivariable analysis. Most importantly, the mortality rate at 15 and at 30 days was significantly lower in patients treated with enoxaparin once daily.

Our data are of particular interest because physicians' preference for an anticoagulant therapy has been gaining importance as a result of the increasing number of choices for a specific drug, mostly reported for DOACs vs. vitamin K antagonists. Currently, this may also apply for LMWH as once versus twice daily may be preferred for some subgroups of patients. For instance, in cancer patients with multiple therapies once daily injections may reduce discomfort. However, our findings indicate that this may result in an added benefit of statistically lower mortality.

Propensity scores have been used to reduce bias in observational studies in many fields and are becoming more widely used in cardiovascular research [23–26]. The propensity score for an individual is the probability of being treated conditionally on (or only on the basis of)

Table 3 Fifteen-day and 30-day outcomes

	Enoxaparin 1.5 mg kg^{-1} od	Enoxaparin 1 mg kg^{-1} bid	Odds ratio (95% CI)
Patients, *n*	944	3786	
15-day outcome			
DVT recurrences	1 (0.11%)	2 (0.05%)	2.00 (0.07–2.50)
PE recurrences	3 (0.32%)	7 (0.18%)	1.72 (0.36–6.67)
DVT or PE recurrences	4 (0.42%)	9 (0.24%)	1.79 (0.55–5.88)
Major bleeding	5 (0.53%)	47 (1.24%)	0.42 (0.17–1.08)
Sites of bleeding			
Hematoma	0	19 (0.50%)	–
Gastroduodenal	3 (0.32%)	7 (0.18%)	1.72 (0.36–2.00)
Retroperitoneal	0	8 (0.21%)	–
Cerebral	0	2 (0.05%)	–
Genitourinary	0	2 (0.05%)	–
Other	2 (0.21%)	9 (0.24%)	0.89 (0.13–3.70)
Death	5 (0.53%)	63 (1.66%)	0.32 (0.13–0.78)
Causes of death			
Pulmonary embolism	2 (0.21%)	11 (0.29%)	0.73 (0.11–2.94)
Bleeding	0	6 (0.16%)	–
Disseminated cancer	1 (0.11%)	10 (0.26%)	0.40 (0.02–2.38)
Respiratory insufficiency	0	10 (0.26%)	–
Sudden, unexpected	0	6 (0.16%)	–
Other/unknown	2 (0.21%)	20 (0.53%)	0.L40 (0.06–1.47)
30-day outcome			
DVT recurrences	4 (0.42%)	5 (0.13%)	3.23 (0.77–12.5)
PE recurrences	4 (0.42%)	8 (0.21%)	2.00 (0.53–6.67)
DVT or PE recurrences	8 (0.85%)	13 (0.34%)	2.50 (1.03–5.88)
Major bleeding	6 (0.64%)	59 (1.56%)	0.40 (0.17–0.94)
Sites of bleeding			
Hematoma	0	21 (0.55%)	–
Gastroduodenal	4 (0.42%)	10 (0.26%)	1.61 (0.44–5.00)
Retroperitoneal	0	9 (0.24%)	–
Cerebral	0	3 (0.08%)	–
Genitourinary	0	3 (0.08%)	–
Other	2 (0.21%)	13 (0.34%)	0.62 (0.09–2.41)
Death	15 (1.6%)	103 (2.7%)	0.58 (0.33–1.00)
Causes of death			
Pulmonary embolism	2 (0.21%)	11 (0.29%)	0.73 (0.11–2.94)
Bleeding	0	10 (0.26%)	–
Disseminated cancer	7 (0.74%)	21 (0.55%)	1.33 (0.55–3.13)
Respiratory insufficiency	1 (0.11%)	13 (0.34%)	0.31 (0.01–1.75)
Sudden, unexpected	0	7 (0.18%)	–
Other/unknown	5 (0.53%)	41 (1.1%)	0.49 (0.17–1.16)

od, once daily; bd, twice daily; CI, confidence intervals; DVT, deep vein thrombosis; PE, pulmonary embolism.

the individual's covariate values. The propensity score method can be used if the treatment assignment can be associated with covariate values but not be related to outcome values once the covariates are controlled for. In practice, the success of the propensity score modeling is judged by whether balance on covariate values is achieved between the treatment groups after its use, and in the current study both groups (once daily and twice daily) were well balanced.

The present study has potential limitations. First, data from registries are susceptible to selection bias if a nonrepresentative sample of patients is selected for analysis. However, the RIETE registry captures a broad range of consecutive patients with symptomatic VTE from multiple medical centers, countries and treatment settings, making it less likely that the study cohort is made up of a skewed population. Second, the study sample may have received LMWH therapy based on certain baseline and prognostic characteristics, and this could significantly bias the study findings. The selection of propensity score-matched cohorts for direct comparison allowed us to address the imbalance in distribution of characteristics that existed between patients receiving once or twice daily enoxaparin. Third, the major weakness of propensity scores is unmeasured bias not accounted for in the score that may explain the association found in a retrospective analysis, especially bias by indication. Indeed, even after matching, the two groups of patients may differ on several points,

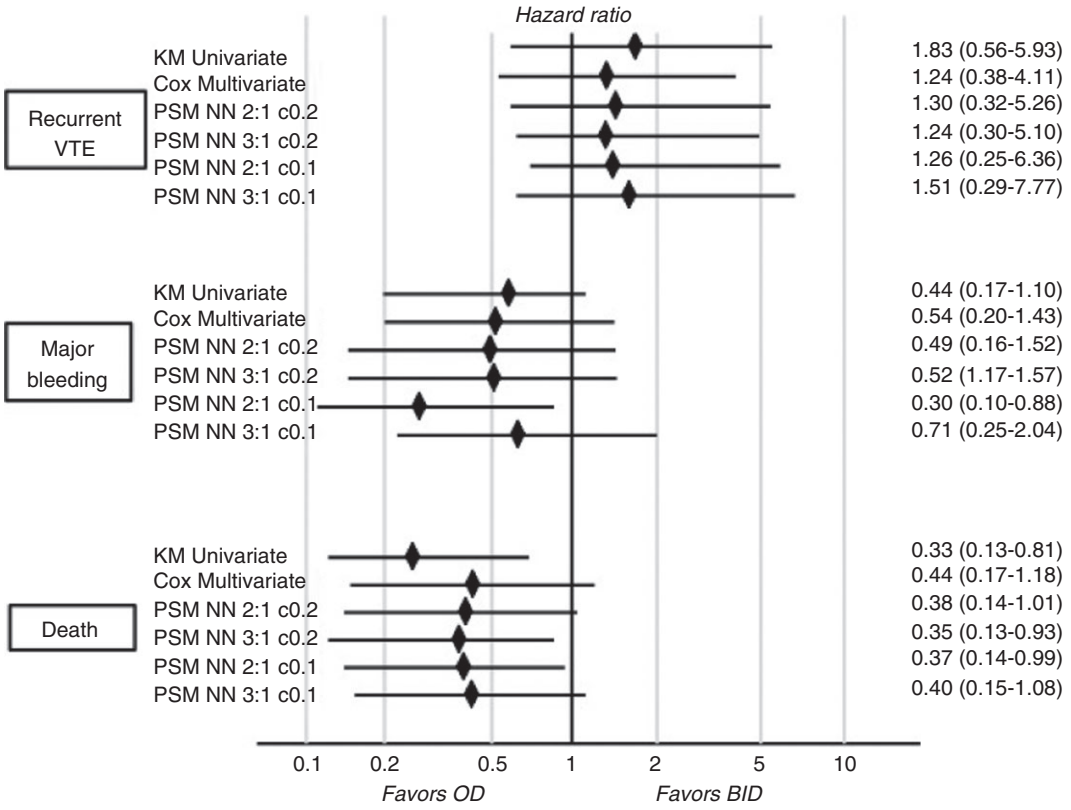

Fig. 2. Clinical outcome at 15 days using different matching ratios and calipers. VTE, venous thromboembolism.

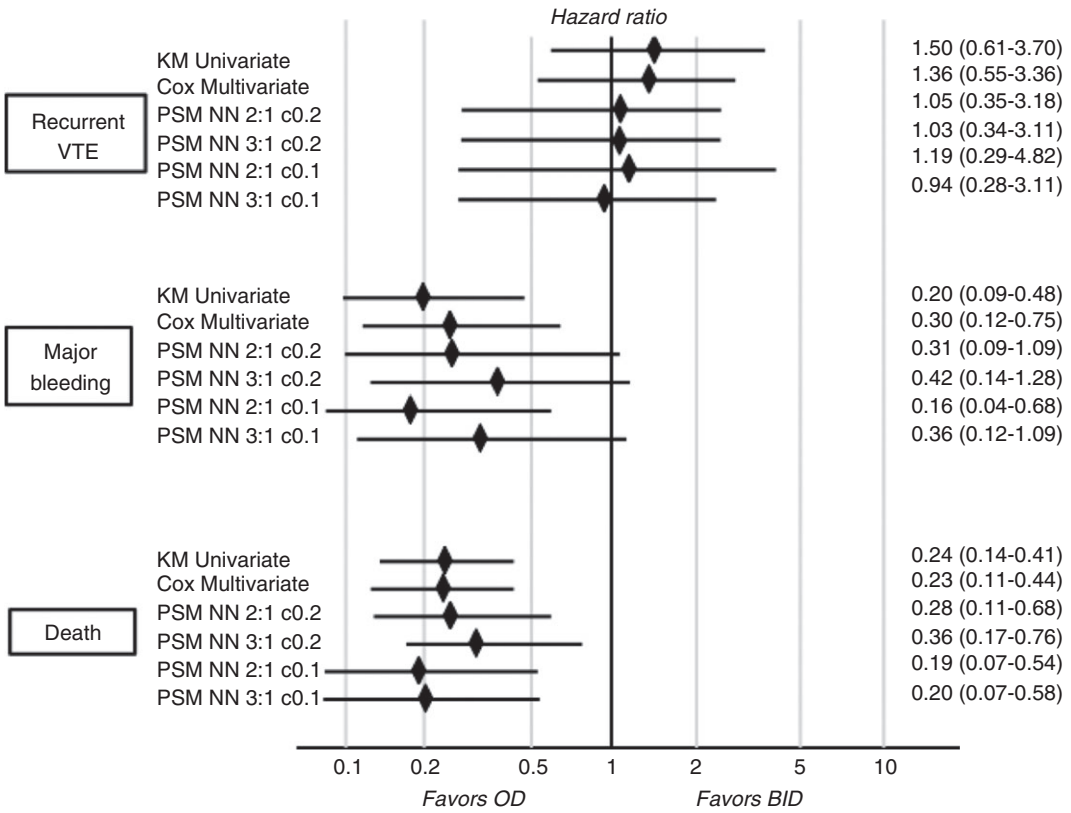

Fig. 3. Clinical outcome at 30 days using different matching ratios and calipers. VTE, venous thromboembolism.

Table 4 Regression analyses separately in patients aged > 75 years, with active cancer, with body mass index > 30 and in those with creatinine clearance levels < 30 mL min^{-1}. Results are expressed as hazard ratio and 95% confidence intervals

	Age > 75 years	Cancer	BMI > 30	CrCl < 30 mL min^{-1}
Recurrent VTE				
Pre-PSM	3.42 (0.73–16.1)	2.04 (0.61–6.78)	2.95 (0.51–17.0)	–
Ratio 2 : 1 c0.2	–	–	2.56 (0.23–29.1)	–
Ratio 3 : 1 c0.2	–	1.00 (0.14–7.10)	–	–
Ratio 2 : 1 c0.1	–	–	–	–
Ratio 3 : 1 c0.1	–	–	1.00 (0.06–16.0)	–
Major bleeding				
Pre-PSM	0.12 (0.03–0.52)	0.58 (0.17–1.92)	0.62 (0.15–2.45)	0.31 (0.03–2.06)
Ratio 2 : 1 c0.2	0.02 (0.00–226)	1.41 (0.09–23.6)	1.00 (0.06–16.0)	–
Ratio 3 : 1 c0.2	1.00 (0.09–11.0)	–	–	–
Ratio 2 : 1 c0.1	0.02 (0.001–23.8)	–	–	–
Ratio 3 : 1 c0.1	0.02 (0.001–14.2)	1.00 (0.06–16.0)	–	–
Death				
Pre-PSM	0.10 (0.04–0.28)	0.40 (0.20–0.81)	0.39 (0.12–1.30)	0.13 (0.03–0.56)
Ratio 2 : 1 c0.2	0.02 (0.00–164.8)	0.25 (0.03–2.24)	1.00 (0.06–16.0)	–
Ratio 3 : 1 c0.2	0.02 (0.00–5.73)	0.40 (0.08–2.06)	0.25 (0.03–2.24)	–
Ratio 2 : 1 c0.1	0.02 (0.00–2.53)	0.18 (0.02–1.51)	2.56 (0.23–29.1)	–
Ratio 3 : 1 c0.1	0.02 (0.001–1.40)	0.02 (0.00–10.9)	0.33 (0.04–3.21)	–

VTE, venous thromboembolism; PSM, propensity score matching; c0, caliper; BMI, body mass index; CrCl, creatinine clearance.

leading to a higher risk of recurrence, bleeding or death. Fourth, duration of VTE symptoms prior to initiation of anticoagulant therapy may have predisposed patients to death, but this information is not available in RIETE. Fifth, we studied only the initial 15-day and 30-day periods of treatment because most patients switched to VKA drugs 1 week after VTE diagnosis. Finally, another limitation is that numbers are small and, therefore, the robustness of the findings may be questioned. The main strength of our observation is that the population-based sample we used describes the effects of initial therapy for VTE in 'real-world' clinical care, as opposed to in a protocol-driven randomized trial, and enhances the generalizability of our findings.

In conclusion, in our propensity score matching retrospective study, VTE patients receiving enoxaparin once daily as initial therapy had a significantly lower rate of major bleeding and a lower mortality rate than those on enoxaparin twice daily. Our findings confirm the results of a meta-analysis of controlled clinical trials, which suggested that twice daily LMWH results in a non-significantly lower rate of VTE recurrences and a non-significantly higher rate of major bleeding compared with once daily LMWH. Moreover, specific subgroups of patients benefited from the physician's decision to treat them with LMWH once daily.

Addendum

J. Trujillo-Santos contributed to the design, analysis and interpretation of data, collected patients, performed the statistical analyses and approved the final version of the article. J. F. Bergmann contributed to the design, analysis and interpretation of data and approved the final version of the article. C. Bortoluzzi contributed to the design, analysis and interpretation of data, collected patients and wrote the article. R. López-Reyes contributed to the interpretation of data, collected patients and approved the final version of the article. M. Giorgi-Pierfranceschi contributed to the interpretation of data, collected patients and approved the final version of the article. J. B. López-Sáez contributed to the interpretation of data, collected patients and approved the final version of the article. P. Ferrazzi collected patients and approved the final version of the article. J. Bascuñana collected patients and approved the final version of the article. J. M. Suriñach collected patients and approved the final version of the article. M. Monreal contributed to the design, analysis and interpretation of data, collected patients, wrote the article and obtained funding.

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Disclosure of Conflict of Interests

The authors state that they have no conflict of interest.

Appendix

The RIETE Registry

Coordinator of the RIETE Registry: M. Monreal (Spain).

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Distribution of patients by dosing regimen[1] and countries.

Table S2. Number needed to treat at 30 days for the different outcomes.

Table S3. Cox proportional hazard for the association between venous thromboembolism recurrences, major bleeding and all-cause death during follow-up period (0–15 and 0–30 days) before and after propensity score matching.

References

1 Kearon C, Akl EA, Comerota AJ, Prandoni P, Bounameaux H, Goldhaber SZ, Nelson ME, Wells PS, Gould MK, Dentali F, Crowther M, Kahn SR; American College of Chest Physicians. Antithrombotic therapy for VTE disease: Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012; **141** (2 Suppl): e419S–94S.

2 Ruíz-Giménez N, Suárez C, González R, Nieto JA, Todolí JA, Samperiz AL, Monreal M. Predictive variables for major bleeding events in patients presenting with documented acute venous thromboembolism. Findings from the RIETE Registry. *Thromb Haemost* 2008; **100**: 26–31.

3 Nieto JA, Solano R, Ruiz-Ribó MD, Ruiz-Giménez N, Prandoni P, Kearon C, Monreal M. Fatal bleeding in patients receiving anticoagulant therapy for venous thromboembolism: findings from the RIETE Registry. *J Thromb Haemost* 2010; **8**: 1216–22.

4 Sánchez Muñoz-Torrero JF, Bounameaux H, Pedrajas JM, Lorenzo A, Rubio S, Kearon C, Hernández L, Monreal M. Effects of age on the risk of dying from pulmonary embolism or bleeding during treatment of deep vein thrombosis. *J Vasc Surg* 2011; **54**: 26S–32S.

5 Muriel A, Jiménez D, Aujesky D, Bertoletti L, Decousus H, Laporte S, Mismetti P, Muñoz FJ, Yusen R, Monreal M. Survival effects of inferior vena cava filter in patients with acute symptomatic venous thromboembolism and a significant bleeding risk. *J Am Coll Cardiol* 2014; **63**: 1675–83.

6 Jiménez D, de Miguel-Díez J, Guijarro R, Trujillo-Santos J, Otero R, Barba R, Muriel A, Meyer G, Yusen RD, Monreal M. Trends in the management and outcomes of acute pulmonary embolism: analysis from the RIETE Registry. *J Am Coll Cardiol* 2016; **67**: 162–70.

7 Cockcroft DW, Gault MH. Predicition of creatinine clearance from serum creatinine. *Nephron* 1976; **16**: 31–41.

8 D'Agostino RB. Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. *Stat Med* 1998; **17**: 2265–81.

9 Thoemmes F, Liao W. http://sourceforge.net/projects/psmspss/files/ accessed on February 10th, 2016.

10 Alhenc-Gelas M, Jestin-Le Guernic C, Vitoux JF, Kher A, Aiach M, Fiessinger JN. Adjusted versus fixed doses of the low-molecular-weight heparin fragmin in the treatment of deep vein thrombosis. Fragmin-Study Group. *Thromb Haemost* 1994; **71**: 698–702.

11 Meyer G, Brenot F, Pacouret G, Simonneau G, Gillet Juvin K, Charbonnier B, Sors H. Subcutaneous low-molecular-weight heparin fragmin versus intravenous unfractionated heparin in the treatment of acute non massive pulmonary embolism: an open randomized pilot study. *Thromb Haemost* 1995; **74**: 1432–5.

12 Levine M, Gent M, Hirsh J, Leclerc J, Anderson D, Weitz J, Ginsberg J, Turpie AG, Demers C, Kovacs M, Geerts W, Kassis J, Desjardins L, Cusson J, Cruickshank M, Powers P, Brien W, Haley S, Willan A. A comparison of low-molecular-weight heparin administered primarily at home with unfractionated heparin

administered in the hospital for proximal deep-vein thrombosis. *N Engl J Med* 1996; **334**: 677–81.
13 Holmström M, Berglund MC, Granqvist S, Bratt G, Törnebohm E, Lockner D. Fragmin once or twice daily subcutaneously in the treatment of deep venous thrombosis of the leg. *Thromb Res* 1992; **67**: 49–55.
14 Partsh H, Kechavarz B, Mostbeck A, Köhn H, Lipp C. Frequency of pulmonary embolism in patients who have iliofemoral deep vein thrombosis and are treated with once- or twice-daily low-molecular-weight heparin. *J Vasc Surg* 1996; **24**: 774–82.
15 Charbonnier BA, Fiessinger JN, Banga JD, Wenzel E, d'Azemar P, Sagnard L; on behalf of the FRAXODI group. Comparison of a once daily with a twice daily subcutaneous low molecular weight heparin regimen in the treatment of deep vein thrombosis. *Thromb Haemost* 1998; **79**: 897–901.
16 Merli G, Spiro TE, Olsson CG, Abilgaard U, Davidson BL, Eldor A, Elias D, Grigg A, Musset D, Rodgers GM, Trowbridge AA, Yusen RD, Zawilska K. Subcutaneous enoxaparin once or twice daily compared with intravenous unfractionated heparin for treatment of venous thromboembolic disease. Enoxaparin Clinical Trial Group. *Ann Intern Med* 2001; **134**: 191–202.
17 Couturaud F, Julian JA, Kearon C. Low molecular weight heparin administered once versus twice daily in patients with venous thromboembolism. A meta-analysis. *Thromb Haemost* 2001; **86**: 980–4.
18 Bhutia S, Wong PF. Once versus twice daily low molecular weight heparin for the initial treatment of venous thromboembolism (Review). *Cochrane Database Syst Rev* 2013; **7**: CD003074.
19 EINSTEIN Investigators. Oral rivaroxaban for symptomatic venous thrombo-embolism. *N Engl J Med* 2010; **363**: 2499–510.
20 EINSTEIN–PE Investigators. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. *N Engl J Med* 2012; **366**: 1287–97.
21 Agnelli G, Buller HR, Cohen A, Curto M, Gallus AS, Johnson M, Masiukiewicz U, Pak R, Thompson J, Raskob GE, Weitz JI. Oral apixaban for the treatment of acute venous thromboembolism. *N Engl J Med* 2013; **369**: 799–808.
22 Vrijens B, Heidbuchel H. Non-vitamin K antagonist oral anticoagulants: considerations on once- vs. twice-daily regimens and their potential impact on medication adherence. *Europace* 2015; **17**: 514–23.
23 Van Dongen CJ, MacGillavry MR, Prins MH. Once versus twice daily LMWH for the initial treatment of venous thromboembolism. *Cochrane Database Syst Rev* 2005; **3**: CD003074.
24 Chertow GM, Normand SL, Silva LR, McNeil BJ. Survival after acute myocardial infarction in patients with end-stage renal disease: results from the cooperative cardiovascular project. *Am J Kidney Dis* 2000; **35**: 1044–51.
25 Chertow GM, Normand SL, McNeil BJ. Renalism: inappropriately low rates of coronary angiography in elderly individuals with renal insufficiency. *J Am Soc Nephrol* 2004; **15**: 2462–8.
26 Trujillo-Santos J, Schellong S, Falga C, Zorrilla V, Gallego P, Barrón M, Monreal M. Low-molecular-weight heparin or unfractionated heparin in venous thromboembolism: the influence of renal function. *Am J Med* 2013; **126**: 425–34e1.