REGULAR ARTICLE

blood advances

Comparing low-molecular-weight heparin dosing for treatment of venous thromboembolism in patients with obesity (RIETE registry)

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Key Points

- This is the first study to compare clinical outcomes of treatment dosing strategies for LMWH in patients with obesity.
- Dosing of LMWH by body weight in patients with obesity may lead to increased rates of the composite of bleeding, VTE recurrence, and death.

Because of the absence of comparative evidence, current guidelines and product monographs diverge in the dosing of low-molecular-weight heparin (LMWH) for obese patients with venous thromboembolism (VTE). We used the RIETE registry to compare the primary composite outcomes (VTE recurrence, major bleeding, or death) in patients with VTE who weighed >100 kg during LMWH therapy with capped doses of LMWH (18 000 IU/d) vs uncapped doses (>18 000 IU/d). Multivariable logistic regression analysis was used to account for possible confounders. A total of 2846 patients who weighed >100 kg were included: 454 (16%) received capped doses of LMWH, and the remaining 2392 received uncapped doses. Mean (standard deviation) LMWH treatment duration was 14.8 (20.6) and 14.3 (32.3) days, respectively. Thirty-one patients (1.9%) had VTE recurrences, 38 (1.3%) had bleeding episodes, 65 (2.3%) died, and 122 (4.3%) had at least 1 of the composite outcomes. Unadjusted outcome rates revealed that capped dosing was associated with a decrease in the composite outcome (rate ratio, 0.22; 95% confidence interval [CI], 0.04-0.75). Multivariable analysis confirmed that patients who received capped doses had significantly lower rates of the composite outcome (odds ratio, 0.16; 95% CI, 0.04-0.68) while receiving LMWH. These retrospective observational data suggest that capped dosing of LMWH is an acceptable alternative to uncapped dosing based on body weight, given the significantly lower composite event rate of VTE recurrence, major bleeding, and all-cause death.

Introduction

Obesity is a growing epidemic affecting up to 11% of adults worldwide and 38% of Americans.[1] Obese people are at an increased risk of venous thromboembolism (VTE), compared with individuals of normal weight.[2] Putative mechanisms include stasis secondary to decreased mobility and compression of intra-abdominal and femoral vessels,[3] inflammation secondary to adipokines,[4] and endothelial damage secondary to associated metabolic diseases, including diabetes and hypertension.[5] With predictable pharmacokinetics and near 100% bioavailability, low-molecular-weight heparins (LMWHs) have been routinely used in the initial treatment of VTE, before transition to an oral agent.[6-8] However, the most appropriate LMWH dosing in patients with obesity remains unclear.

LMWHs are hydrophilic and therefore largely remain in the intravascular compartment. In obese individuals with disproportionately more adipose tissue, there is a concern about overdose and bleeding

Submitted 20 December 2019; accepted 25 April 2020; published online 4 June 2020. DOI 10.1182/bloodadvances.2019001373.

All materials will be made available on e-mail request to the corresponding author.

The full-text version of this article contains a data supplement.

when treatment with standard dosing by actual body weight is applied.[7] The alternative strategy, capping at a maximum dose regardless of actual body weight, may cause an underdose.[9] There are no rigorous trials or observational studies comparing therapeutic LMWH dosing strategies in obese patients with VTE that examine clinical end points.[10] The Canadian drug product monographs recommend capped dosing, given that LMWH preferentially distributes to plasma[11-13]; however, practice patterns and the 2018 American Society of Hematology guidelines conditionally recommend uncapped LMWH doses[14] because of concerns about underdosing and the danger of treatment failure. The 2018 American Society of Hematology guidelines conditionally recommend capped LMWH based on evidence of very low certainty.[14] The evidence is based on a meta-analysis of 5 studies, none of which directly compared dosing strategies, revealing no difference in benefit or harm between indirect comparison of dosing strategies. Concerns about underdosing and the serious consequences of therapeutic failure are cited as justification for the recommendation.

Methods

Database

The RIETE (Registro Informatizado Enfermedad TromboEmbólica) database is an ongoing, multinational, observational registry of consecutive patients with objectively confirmed, acute VTE (registered at www.clinicaltrials.gov as #NCT02832245). The database was founded in Spain in 2001 and has expanded to >15 countries since then. The rationale and methodology of RIETE has been published.[15] Patients are excluded if they are currently participating in a therapeutic clinical trial with a blinded therapy. All patients (or their relatives) provide written or oral consent for participation in the registry, in accordance with local ethics committee requirements.

Population

The study population included patients registered in the RIETE registry who met 4 criteria: age ≥18 years; diagnosis of acute, objectively confirmed deep vein thrombosis (DVT) or pulmonary embolism (PE); obesity; and initial therapy with LMWH for any treatment duration. Our concern in specifying a minimum for treatment duration was the risk of excluding patients who experienced adverse events and therefore had LMWH discontinued. Obesity was defined as body weight >100 kg, a value used by other studies[10] as a pragmatic proxy, because height and body mass index (BMI) are not always recorded in clinical practice. For individual patients, the longest treatment phase on LMWH following the qualifying VTE was chosen for analysis. Patients treated with thrombolytics were excluded from analysis.

Exposure groups

We compared capped dosing (chosen as a dose of 18 000 IU/d, the typical suggested capped dose for LMWH) to noncapped LMWH dosing (any dose equivalent to >18 000 IU/d). Only patients treated with enoxaparin, dalteparin, or tinzaparin were included, given that the recommended capped dose is 18 000 IU for all 3 drugs in the Canadian product monographs.[11-13]

Baseline variables

The following parameters were collected when the qualifying episode of VTE was diagnosed: sex, age, body weight, and, in most cases, height; risk factors for VTE: recent immobility (ie, total bed rest with bathroom privileges for ≥4 days in the 2-month period before VTE diagnosis), recent surgery (in the 2 months before VTE), active cancer (defined as newly diagnosed cancer, metastatic cancer, or cancer that was receiving treatment), hormonal therapy, pregnancy, recent birth prior VTE, and recent travel; and presence of coexisting conditions: chronic heart or lung disease, concomitant therapies, recent (<30 days before enrollment in RIETE) major bleeding, and laboratory data (also at baseline), including complete blood counts and serum creatinine levels.

Treatment and follow-up

Patients were treated according to the clinical practice of each participating hospital (ie, there was no standardized therapy). The drug, dose, and duration of therapy were recorded. The decision on the type and duration of anticoagulant therapy was left to the attending physicians. Patients were followed up in the outpatient clinic (or by telephone interview if they could not visit the clinic). During each visit, any signs or symptoms suggesting VTE recurrences or major bleeding were noted.

Outcome definitions

The primary outcome was the composite of recurrent VTE, major bleeding, or all-cause death attributable to LMWH treatment. The secondary outcome was the composite outcome at 15 days, whether the patient had transitioned from LMWH to another anticoagulant or not.

Major bleeding was defined as overt bleeding requiring a transfusion of 2 or more units of blood or retroperitoneal, spinal, intracranial, or fatal bleeding episodes. Bleeding was attributed to LMWH therapy when it occurred during LMWH treatment or within 3 days of discontinuation of LMWH. Our decision to include up to 3 days after discontinuation was based on 3 factors: (1) there may be a delay in the diagnosis of bleeding; (2) the half-life of LMWH is increased when the glomerular filtration rate is reduced; (3) doses in this population are at and above the upper limits of the studied doses and therefore may be associated with altered kinetics and dynamics.

Each episode of suspected recurrent VTE was investigated by repeat compression ultrasonography, lung scan, computed tomographic pulmonary angiography or pulmonary angiography, as chosen by the treating physician. Most outcomes were classified as reported by the clinical centers; there was no central adjudication of outcome events. VTE recurrences were attributed to LMWH if they occurred while the patient was receiving therapy or during or within 7 days of discontinuation of treatment. Attributing clots within 7 days of discontinuation encompasses cases in which there is delayed diagnosis.

Similarly, deaths were considered attributable to LMWH therapy if they occurred during therapy or within 7 days of treatment discontinuation.

Statistical analysis

All calculations were performed with SPSS Statistics (IBM). Differences in patient and treatment variables were assessed with the χ^2 test for categorical variables; the independent Student *t* test for normally distributed, continuous variables; and the Mann-Whitney *U* test for continuous variables without normal distribution.

Table 1. Patient demographics and treatment variables

	Capped dose	Uncapped dose	*P*
Patients, n	454	2392	
Male sex, n (%)	309 (68)	1641 (69)	.826
Age, mean ± SD, y	56.8 ± 15.8	54.8 ± 15	.011
Body weight, mean ± SD, kg	106.9 ± 8.6	111.3 ± 13.5	<.001
Body height (n = 2010), mean ± SD, cm	173 ± 9.9	173 ± 10	<.987
Body mass index (n = 2010), mean ± SD	36 ± 5.1	38 ± 6.1	<.001
Body mass index >30 (n = 2010), n (%)	320 (93)	1581 (95)	.241
VTE risk factor, n (%)			
Recent immobility ≥4 d	74 (16)	430 (18)	.421
Recent surgery	42 (9.3)	255 (11)	.403
Active cancer	83 (18)	279 (12)	<.001
Metastatic cancer	31 (6.8)	105 (4.4)	.571
Estrogen use	26 (5.7)	115 (4.8)	.409
Pregnancy or postpartum	2 (0.44)	18 (0.75)	.758
None of the above (unprovoked)	272 (60)	1,462 (61)	.637
Prior VTE	88 (19)	386 (16)	.099
Underlying disease, n (%)			
Major bleeding in the past month	5 (1.1)	16 (0.67)	.363
Chronic lung disease	54 (12)	295 (12)	.876
Chronic heart failure	21 (4.6)	119 (5.0)	.814
Anemia	102 (22)	505 (21)	.532
Platelet count <100 × $10^3/\mu L$	8 (1.8)	34 (1.4)	.528
Creatinine clearance level <60 mL/min	22 (4.8)	96 (4.0)	.440
Creatinine clearance level <30 mL/min	2 (0.44)	10 (0.42)	>.99
Initial VTE presentation, n (%)			
Deep vein thrombosis	252 (56)	939 (39)	<.001
Upper limb DVT	20 (4.4)	62 (2.6)	.045
Lower limb proximal DVT	191 (42)	746 (31)	<.001
Lower limb distal DVT	37 (8.1)	124 (5.2)	.015
Pulmonary embolism, n (%)	124 (27)	949 (40)	<.001
DVT and PE, n (%)	78 (17)	504 (21)	.066

SD, standard deviation.

Unadjusted rates of the primary and secondary outcomes were calculated during LMWH therapy. Binary multivariable logistic regression was used to calculate adjusted odds ratios [ORs] for the association of treatment (capped vs uncapped) with the primary composite outcome during LMWH therapy and also at 15 days from initiation of therapy (regardless of transition to another agent) as a secondary outcome. Potential confounders were entered into the multivariable model based on associations from the literature.[16,17] Variables were kept in the model if they were associated with the outcome ($P < .1$). The following variables were entered as potential confounders: age, sex, history of chronic heart or lung disease, recent immobility, cancer, metastatic cancer, recent major bleeding, anemia, thrombocytopenia, renal insufficiency, initial presentation of VTE, type of LMWH used for initial therapy, concomitant therapy with antiplatelets, and long-term therapy with vitamin K antagonists. We planned to compare the effect of dosing strategy in patients with and without metastatic cancer. Of the variables included, 3 had missing data: concomitant antiplatelets (208 missing values) and platelet and hemoglobin count (3 missing values for both counts). The missing data were imputed by the mode value.

Results

A total of 2846 patients weighing >100 kg were included: 454 (16%) received capped doses (18 000 IU/d), and the remaining 2392 received uncapped doses (mean, 20 865 IU/d). Mean treatment duration was 14.8 ± 20.6 and 14.3 ± 32.3 days, respectively. Patients were followed up for a median of 300 days and a mean of 501 days, respectively. Patients who received capped doses were slightly older (56.8 ± 15.8 and 54.8 ± 15.0 years, respectively), weighed less (106.9 ± 8.6 and 111.3 ± 13.5 kg), and were more likely to have active cancer and to initially present with DVT (vs PE) than those receiving uncapped doses (Table 1). In addition, patients who received capped doses of LMWH were more likely to be prescribed tinzaparin or dalteparin, but less likely to receive

Table 2. Details of therapy

	Capped dose	Uncapped dose	*P*
Patients, n	454	2392	
Initial therapy			
Enoxaparin, n (%)	127 (28)	2 186 (91)	<.001
Tinzaparin, n (%)	249 (55)	72 (3.0)	<.001
Dalteparin, n (%)	78 (17)	134 (5.6)	<.001
Mean ± SD, d	14.8 ± 20.6	14.3 ± 32.3	.735
Median (IQR), d	11 (8-14)	10 (8-13)	.001
Treatment dose			
Mean LMWH dose, IU/kg per d	169 ± 12	189 ± 17	.001
LMWH dose >18 000 IU/kg per d, n (%)	0 (0)	2 392 (100)	—
Mean dose ± SD per d, n	18 000 ± 0	20 865 ± 2 102	.001
Long-term therapy, n (%)			
LMWH	110 (24)	393 (16)	<.001
Vitamin K antagonists	317 (70)	1 776 (74)	.064
Direct oral anticoagulants	25 (5.5)	191 (8.0)	.081
Fondaparinux	1 (0.22)	6 (0.25)	>.99
Concomitant therapy, n (%)			
Antiplatelets	32 (7.0)	259 (11)	.014
Corticosteroids	27 (5.9)	116 (4.8)	.348

IQR, interquartile range.

enoxaparin, and were also less likely to have concomitant therapy with antiplatelets (Table 2). For long-term therapy, most patients switched to vitamin K antagonists (70% vs 74%), but a higher proportion of those with capped doses (24% vs 16%) continued to receive LMWH for long-term therapy. The breakdown of weights between groups is reported in Table 3.

Forty-nine total events were attributable to LMWH therapy, according to the prespecified rule of counting events if they occurred within 3 or 7 days of discontinuation (Table 4). Two events were counted in the capped-dose group: 2 PEs (0.44%) and 1 death attributable to PE (0.22%). There were no bleeding events. (Only the first event in a single individual was counted toward the composite, therefore

Table 3. Unadjusted outcome rates (uncapped vs capped dosing) at 15 days in patients initiated on LMWH and transitioned to other agents

	Capped dose	Uncapped dose	OR (95% CI)	*P*
Patients, n	454	2392		
15-d outcome, n (%)				
Recurrent PE	2 (0.44)	5 (0.21)	2.11 (0.41-10.9)	.310
Recurrent DVT	0 (0)	4 (0.17)	—	>.99
Recurrent VTE	2 (0.44)	9 (0.38)	1.17 (0.25-5.44)	.691
Major bleeding	0 (0)	26 (1.1)	—	.026
Gastrointestinal	0 (0)	6 (0.25)	—	.598
Hematoma	0 (0)	5 (0.21)	—	>.99
Intracranial	0 (0)	4 (0.17)	—	>.99
Recurrent VTE or major bleeding	2 (0.44)	35 (1.5)	0.30 (0.07-1.24)	.109
Death	1 (0.22)	21 (0.88)	0.25 (0.03-1.86)	.237
Cause of death, n (%)				
Pulmonary embolism	1 (0.22)	9 (0.38)	0.58 (0.07-4.62)	>.99
Sudden, unexpected	0 (0)	2 (0.08)	—	>.99
Bleeding	0 (0)	1 (0.04)	—	>.99
Disseminated cancer	0 (0)	3 (0.13)	—	>.99
Ischemic stroke	0 (0)	2 (0.08)	—	>.99
Composite outcome	2 (0.44)	2 (2.2)	0.20 (0.05-0.82)	.008

Table 4. Unadjusted clinical outcomes during initial therapy with LMWH

	Capped dose		Uncapped dose		
	n	Events per 100 patient-years	n	Events per 100 patient-years	Rate ratio (95% CI)
Patients, n	454		2392		
Duration of therapy, d					
Mean ± SD	15 ± 21		14 ± 32		0.650
Median (IQR)	11 (8-14)		10 (8-13)		0.001
Event					
Recurrent PE	2	10.9 (1.82-35.9)	3	3.21 (0.82-8.73)	3.39 (0.40-22.8)
Recurrent DVT	0	—	3	3.21 (0.82-8.74)	—
Recurrent VTE	2	10.9 (1.82-35.9)	6	6.43 (2.61-13.4)	1.69 (0.24-8.00)
Major bleeding	0	—	24	25.7 (16.8-37.7)	—
Gastrointestinal	0	—	5	5.35 (1.96-11.8)	—
Hematoma	0	—	4	4.28 (1.36-10.3)	—
Intracranial	0	—	4	4.28 (1.36-10.3)	—
Recurrent VTE or major bleeding	2	11.0 (1.82-35.9)	30	32.2 (22.1-45.4)	0.34 (0.05-1.20)
Death	1	5.43 (0.27-26.8)	21	22.5 (14.3-33.8)	0.24 (0.01-1.30)
Cause of death					
Pulmonary embolism	1	5.43 (0.27-26.8)	9	9.63 (4.70-17.7)	0.56 (0.03-3.43)
Sudden, unexpected	0	—	2	2.14 (0.36-7.06)	—
Respiratory failure	0	—	0	—	—
Bleeding	0	—	2	2.14 (0.36-7.06)	—
Disseminated cancer	0	—	4	4.28 (1.36-10.3)	—
Composite outcome	2	10.9 (1.82-35.9)	47	50.5 (37.6-66.6)	0.22 (0.04-0.75)

the sum of individual events do not match the total.) In the uncapped dose group, there were 47 events: 3 PEs (0.13%), 3 DVTs (0.13%), 24 major bleeding incidents (1%), and 21 deaths (0.88%).

During the first 15 days of anticoagulant therapy (including events not attributable to LMWH by our rule), 11 patients (0.39%) developed VTE recurrences (7 recurrent PE, 4 recurrent DVT), 26 (0.91%) had major bleeding, 22 (0.77%) died (10 died of PE, 1 of bleeding), and 54 (1.9%) had at least 1 of the composite outcomes (Table 5).

We prespecified that patients with metastatic cancer would have a higher risk of death, thrombosis, and bleeding. However, we did not have sufficient power to test statistically for interaction of dosing strategy with metastatic cancer. The composite outcomes of the capped vs uncapped strategy in metastatic cancer at 15 days were 0 vs 11 events (0% vs 10.4%; $P = .051$). Table 6 includes detailed outcomes for this subgroup.

Multivariable binary logistic regression revealed that patients receiving capped doses of LMWH were at a lower risk for composite outcomes, both during LMWH therapy (OR, 0.16; 95% confidence interval [CI], 0.04-0.68) and at 15 days (OR, 0.17; 95% CI, 0.04-0.71; Table 7). This effect was mainly due to a trend toward lower rates of unadjusted major bleeding: no episodes in the capped-dose group vs 24 in the uncapped-dose group (Figure 1).

Discussion

The optimal dose of LMWH therapy for obese patients with acute VTE is guided by limited pharmacokinetic data with no substantiating clinical data. To our knowledge, there are no data in the literature that compare rates of clinical events in obese patients with VTE treated with capped vs uncapped doses. Ours is the first study to compare these 2 therapeutic LMWH dosing strategies on the basis of patient-important clinical outcomes.

Our data, obtained from RIETE, a large registry of patients with VTE, reveal that 1 in every 6 patients (19%) weighing >100 kg was prescribed capped doses of LMWH, whereas the remainder received

Table 5. Multivariable analyses for the composite outcome at 15 days in patients first treated with LMWH and during therapy with LMWH

	15 d, OR (95% CI)	During LMWH therapy, OR (95% CI)
No. of events	54	49
Total sample, n	2846	2843
Capped doses of LMWH	0.17 (0.04-0.71)*	0.16 (0.04-0.68)*
Male sex	0.61 (0.35-1.04)	0.59 (0.33-1.06)
Body weight <106 kg	—	2.55 (1.35-4.81)†
Active cancer	2.52 (1.30-4.87)†	—
Anemia	1.95 (1.10-3.44)*	—
Creatinine clearance level <60 mmol/L	1.97 (0.82-4.73)	—
PE as initial VTE presentation	—	—
Corticosteroids	—	3.06 (1.45-6.47)†

Outcomes at 15 days includes patients who first received LMWH and transitioned to other agents. Outcomes during LMWH therapy include only outcomes attributable to LMWH as described in "Methods." ORs marked with a dash did not reach $P < .1$ in univariable analyses and therefore were not included in multivariable analyses.
*$P < .05$; †$P < .01$.

Table 6. Unadjusted outcome rates (uncapped vs capped dosing) in patients with metastatic cancer

	Capped dose	Uncapped dose	OR (95% CI)	*P*
Patients, n	31	105		
15-d outcome, n (%)				
Recurrent PE	0 (0)	0 (0)	—	—
Recurrent DVT	0 (0)	2 (1.9)	—	>.99
Recurrent VTE	0 (0)	2 (1.9)	—	>.99
Major bleeding	0 (0)	2 (1.9)	—	>.99
Retroperitoneal	0 (0)	1 (0.95)	—	>.99
Menorrhagia	0 (0)	1 (0.95)	—	>.99
Death	0 (0)	7 (6.7)	—	.351
Cause of death				
Pulmonary embolism	0 (0)	2 (1.9)	—	>.99
Sudden, unexpected	0 (0)	1 (0.95)	—	>.99
Ischemic stroke	0 (0)	1 (0.95)	—	>.99
Neoplasia	0 (0)	3 (2.9)	—	>.99
Composite outcome	0 (0)	11 (10.4)	—	.051

an uncapped dose. The concern regarding uncapped doses is the subtherapeutic anticoagulant effect resulting in otherwise avoidable thromboembolisms.[9] In our study, 1.5% of patients experienced major bleeding and 1.2% had a VTE when exposed to uncapped dosing, compared with 0.22% and 0.66%, respectively, of those receiving a capped dose at 90 days after therapy initiation (results are not statistically significant for all individual comparisons). After adjustment for multiple potential confounders, patients with obesity who were receiving capped doses were at a lower risk of having the composite outcome of VTE recurrences, major bleeding, or all-cause death at 15 and 90 days.

This study has several significant limitations, broadly categorized as risk of significant bias and problems relating to the analysis. First, data were derived from the RIETE registry, which is a large, prospective case series of patients with VTE and may be subject to selection bias. Second, there were several prognostic differences at baseline between the 2 groups: patients receiving capped doses were significantly more likely to have active and metastatic cancer, to weigh less, and to have DVT (vs PE) and were significantly less likely to have received concomitant antiplatelet therapy. Despite our attempt to control for these potential confounders in multivariable analysis, residual confounding may partially explain the difference in outcomes between capped and uncapped dosing. Moreover, some baseline differences point toward confounding by indication: for example, those who received capped doses typically weighed less and were more likely to receive enoxaparin than those who received capped doses (91% vs 28%). Further, dosing regimens were different for tinzaparin 175 μg/kg per day vs dalteparin 200 IU/kg per day vs enoxaparin 1 mg (~100 IU/kg) twice daily or 1.5 mg daily. A maximum unit threshold that is the same across each drug and dose strategy means that the weights at which a dose should be defined as capped vs not capped can vary, as would the pharmacologic effects. Third, outcome events were not adjudicated centrally. As physicians were aware of treatment allocation, it is possible that their knowledge of dosage influenced their reporting of clinical events. In terms of the multivariable analysis, there was a relatively low number of events, especially in the capped-dose group, which may have led to overfitting in multivariable analysis. In addition, the mean actual dose difference between the 2 groups was small (18 000 vs 20 865 IU/d). Finally, our composite analysis assumed that an episode of VTE, a major bleeding episode, and all-cause death had equal value. Higher doses could cause both more bleeding and decreased VTE, reducing the value of this composite end point.

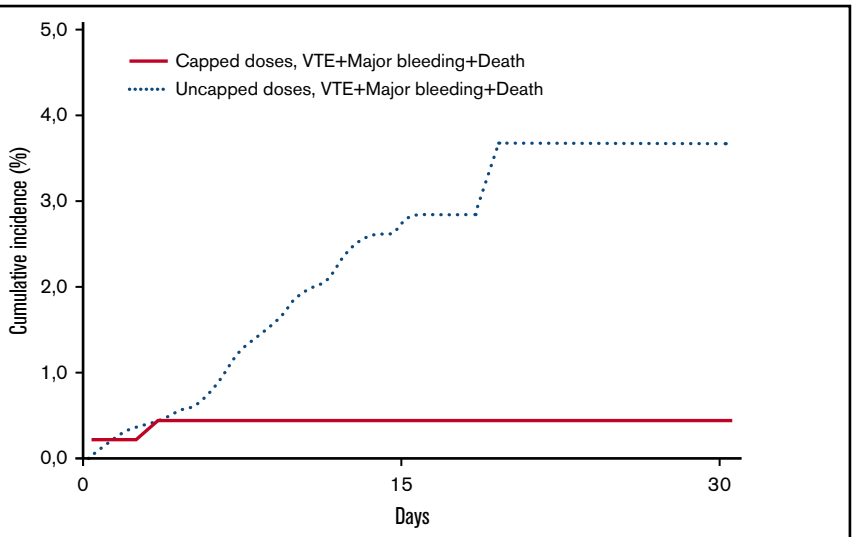
Given the higher percentage of patients with active and metastatic cancer in the capped-dose group and the lower unadjusted event rates in the group, it seems improbable that capped dosing is harmful in either subgroup.

Our results are potentially valuable, however, as they suggest that capped dosing may have a role in obese patients with VTE who are at high risk for bleeding. Indeed, our findings are consistent with

Table 7. Use of capped vs uncapped LMWH doses according to body weight

	Capped dose	Uncapped dose	*P*
Patients, n	454	2392	
100-110 kg	364 (80)	1.526 (64)	<.001
111-120 kg	63 (14)	479 (20)	.002
121-130 kg	20 (4.4)	205 (8.6)	.002
131-140 kg	4 (0.88)	89 (3.7)	<.001
141-150 kg	1 (0.22)	56 (2.3)	<.001
151-160 kg	1 (0.22)	16 (0.67)	.501
161-170 kg	1 (0.22)	10 (0.42)	>.99
171-180 kg	0 (0)	3 (0.13)	>.99
181-190 kg	0 (0)	5 (0.21)	>.99
191-200 kg	0 (0)	0 (0)	0
201-210 kg	0 (0)	2 (0.08)	>.99
211-220 kg	0 (0)	1 (0.04)	>.99

Unless otherwise indicated, values are n (%).



Days		15	30
At risk (Composite outcome)	*Capped doses*	280	67
	Uncapped doses	1,445	288
Composite outcome	*Capped doses*	2 (0.44%)	2 (0.44%)
	Uncapped doses	44 (2.84%)	46 (3.68%)

Figure 1. Cumulative rates of composite outcome (VTE, major bleeding, or death) during the first 30 days of LMWH therapy (uncapped vs capped dosing).

a meta-analysis of the bariatric surgery literature suggesting higher rates of bleeding episodes, without reduction in rates of VTE, using weight-adjusted heparin prophylaxis dosing.[18] We emphasize that our findings are at high risk of bias and should not change current practice, but should spur further investigation in the form of an appropriately powered randomized controlled trial.

Acknowledgments

The RIETE investigators express their gratitude to Sanofi Spain for supporting this registry with an unrestricted educational grant; the RIETE Registry Coordinating Center, S&H Medical Science Service, for quality control data, logistic, and administrative support; and Salvador Ortiz, (Universidad Autónoma Madrid) and Silvia Galindo, Statistical Advisors with S&H Medical Science Service, for providing ongoing statistical analysis and assistance with respect to the data.

The RIETE registry receives funding from Sanofi Spain.

Authorship

Contribution: R.M. conceived and coordinated the study, designed the study, conducted the initial analysis, and wrote the initial draft; R.N. played a central role in formulating the question, conducting statistical analyses, and editing the manuscript. J.J.L.-N., R.B., A.A., C.F., R.I., and E.G. contributed significantly to the interpretation of the findings and the writing of the manuscript, in addition to contributing to the database itself; M.C. helped recruit experts to choose and interpret the outcomes and made major contributions to the text, leading to substantial revisions; and M.M. provided the data, recruited a team that assisted throughout the study, and assisted at each stage of the process.

Conflict-of-interest disclosure: R.I. has participated on an advisory board once with both Apsen Pharmacare and LEOPharma. M.C. is receiving or has received monetary compensation from Bayer, Pfizer, CSL Behring, Servier Canada, Diagnostica Stago, Asahi Kasei, and Alnylam. The remaining authors declare no competing financial interests.

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