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First three months of anticoagulation for venous thromboembolism in non-cancer patients: LMWH VS. VKAs. Findings from the RIETE registry

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ABSTRACT

Background: The use of low-molecular-weight heparin (LMWH) for long-term therapy of venous thromboembolism (VTE) in patients without cancer has not been consistently evaluated.
Methods: We used the data in the RIETE registry to compare the 3-month outcomes (VTE recurrences, major bleeding or death) in non-cancer patients with VTE, according to long-term therapy with LMWH or vitamin K antagonists (VKAs).
Results: As of March 2018, 14,582 non-cancer patients with VTE had received initial therapy with LMWH and then switched to VKAs, while 9151 were prescribed LMWH for initial and long-term therapy. Overall, 11,494 had initially presented with pulmonary embolism (PE) and 12,239 with isolated deep vein thrombosis (DVT). Among 11,494 patients initially presenting with PE, 84 had VTE recurrences, 204 major bleeding and 406 died. Among 12,239 patients with isolated DVT, 133 developed VTE recurrences, 137 bled and 289 died. On propensity score analysis, PE patients on long-term LMWH therapy were at increased risk for PE recurrences (OR: 3.30; 95%CI: 1.67–6.48), major bleeding (OR: 1.68; 95%CI: 1.21–2.32) or death (OR: 3.16; 95%CI: 2.43–4.09) compared with those receiving VKAs. In patients with DVT, those on long-term LMWH also were at increased risk for PE recurrences (OR: 2.31; 95%CI: 1.13–4.73), major bleeding (OR 2.28; 95%CI: 1.51–3.44) or death (OR: 2.32; 95%CI: 1.54–3.51).
Conclusions: In the RIETE non-cancer patients with VTE, long-term therapy with VKAs was associated with a lower risk for recurrences, major bleeding or death.

1. Introduction

Current guidelines of antithrombotic therapy recommend the use of low-molecular-weight heparin (LMWH) for long-term therapy of venous thromboembolism (VTE) in patients with active cancer [1–3]. For patients without cancer, they recommend the use of direct oral anticoagulants (DOACs) or vitamin K antagonists (VKAs). A number of studies and systematic reviews comparing long-term therapy with LMWH vs. VKAs failed to find differences in terms of VTE recurrences of VTE, bleeding or mortality [4–7], but available data in this area are limited.

RIETE is an ongoing international registry of consecutive patients with objectively confirmed, acute VTE (Clinicaltrials.gov NCT:

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02832245). It started in Spain in 2001, and 6 years later the database was translated into English with the aim to expand the registry to other countries, ultimately allowing physicians worldwide to use the database to select the most appropriate therapy for their patients. 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 [8–12]. In the current study, we used the data from RIETE to compare the rates of VTE recurrences, major bleeding or death in non-cancer patients with VTE, according to long-term therapy with LMWH vs. VKAs.

2. Methods

2.1. Patients

Consecutive patients with symptomatic, acute deep vein thrombosis (DVT) or pulmonary embolism (PE) that were confirmed by objective tests (compression ultrasonography or contrast venography for DVT; ventilation-perfusion lung scintigraphy, helical CT-scan 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).

2.2. Study design

We included all VTE patients without cancer (either active cancer or with a history of cancer prior to the diagnosis of VTE) recruited in RIETE from March 2001 to March 2018. We selected those that received initial therapy with LMWH for at least 5 days and then: 1) switched to long-term therapy with VKAs, or 2) kept receiving LMWH for at least the first 3 months of therapy. All patients receiving unfractionated heparin, fondaparinux, direct oral anticoagulants or thrombolytics, and those undergoing inferior vena cava filter placement were excluded.

Each episode of clinically suspected recurrent VTE was investigated by repeat compression ultrasonography, lung scanning, helical-CT scan or pulmonary angiography, as appropriate. 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. Fatal PE, in the absence of autopsy, was defined as any death appearing within 10 days of a PE event, in the absence of any alternative cause of death.

2.3. Baseline variables

The following parameters were recorded when the qualifying episode of VTE was diagnosed: patient's gender, age and body weight; presence of coexisting conditions such as chronic heart or lung disease; recent (<30 days prior to VTE) major bleeding; presence of risk factors for VTE; prior VTE; concomitant medications and laboratory data at baseline, including whole blood counts and serum creatinine levels.

2.4. 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. The decision to treat patients in hospital or at home was left to the attending physicians. Patients were followed-up in the outpatient clinic (or telephone interviews in patients who could not show up for a clinic visit). 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).

2.5. Statistical analysis

Continuous variables were analyzed using the mean, standard deviation, median and interquartile range, and categorical variables were analyzed using absolute frequencies and percentages. All analyses were separately performed for patients initially presenting with DVT and for those with PE. Differences between groups (LMWH vs. VKAs) were compared using a Chi-squared test for categorical variables and a *t*-test for continuous data. Besides, we used the Cramer's V and Cohen's D tests to measure the effect of size. Univariate and multivariate logistic regression analysis were used to identify independent predictors of events (VTE recurrences, major bleeding or death) during the first 90 days of therapy. Variables entering in the multivariate analyses were: age, sex, body weight, chronic lung disease or heart failure, recent major bleeding, initial VTE presentation (DVT or PE), prior VTE, anemia, creatinine clearance levels at baseline and therapy with LMWH alone (vs. LMWH then VKAs). Adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were estimated.

Subsequently, a propensity matched analysis was applied in 7104 patients with PE and 10,012 with DVT. All the populations studied were divided into two subgroups according to the treatment received: 1) LMWH less than 6 days, followed by VKAs (standard therapy); and 2) only LMWH therapy. All clinical outcomes were analyzed on Day 90 of treatment: VTE recurrences, major bleeding and mortality occurring during the course of anticoagulant therapy. To reduce selection bias due differences in baseline characteristics between the subgroups and to made outcomes comparable, we conducted 1:1 propensity score matching. And a new univariate and multivariate logistic regression was performed with matched data. A SPSS software (version 19, SPSS Inc., Chicago, Illinois) and R version 3.6.1 was used for the statistical management of the data, and a two-sided $p < 0.05$ was considered to be statistically significant.

3. Results

As of March 2018, there were 76,943 patients recruited in RIETE, of whom 23,733 (30%) did not have cancer, and they had no treatment with fibrinolysis, fondaparinux, unfractionated heparin, or direct oral anticoagulants. Of these, 14,582 had received initial therapy with LMWH and then switched to VKAs, while 9151 were prescribed LMWH for initial and for long-term therapy. Overall, 11,494 patients had initially presented with acute PE (with or without concomitant DVT) and 12,239 with isolated DVT (Fig. 1).

Patients receiving LMWH for long-term therapy (irrespectively of initial presentation as PE or DVT) were more likely women, 2 years older, weighed less, were more likely to have concomitant diseases (chronic heart or liver failure, anemia, thrombocytopenia or renal insufficiency), recent immobilization or surgery and recent major bleeding, than those who switched to VKAs (Table 1). They also were more likely to receive antiplatelets concomitantly, and less likely to be using estrogens or to have unprovoked VTE. Interestingly, patients initially presenting with PE were less likely to keep receiving long-term LMWH than those with DVT (32% vs. 44%; odds ratio (OR): 0.60; 95%CI: 0.57–0.63).

During the first 3 months of therapy, there were 84 VTE recurrences (55 as PE, 29 as DVT), 204 major bleeds and 406 deaths in patients initially presenting with PE, and 133 VTE recurrences (PE 38, DVT 95), 137 major bleeds and 289 deaths in those with DVT. PE patients receiving long-term LMWH therapy had a higher rate of PE recurrences (OR: 4.34; 95%CI: 2.49–7.79), major bleeding (OR: 2.35; 95%CI: 1.78–3.11) or death (OR: 4.51; 95%CI: 2.67–4.16) than those on VKAs, but a similar rate of DVT recurrences (OR: 1.48; 95%CI: 0.69–3.11), as

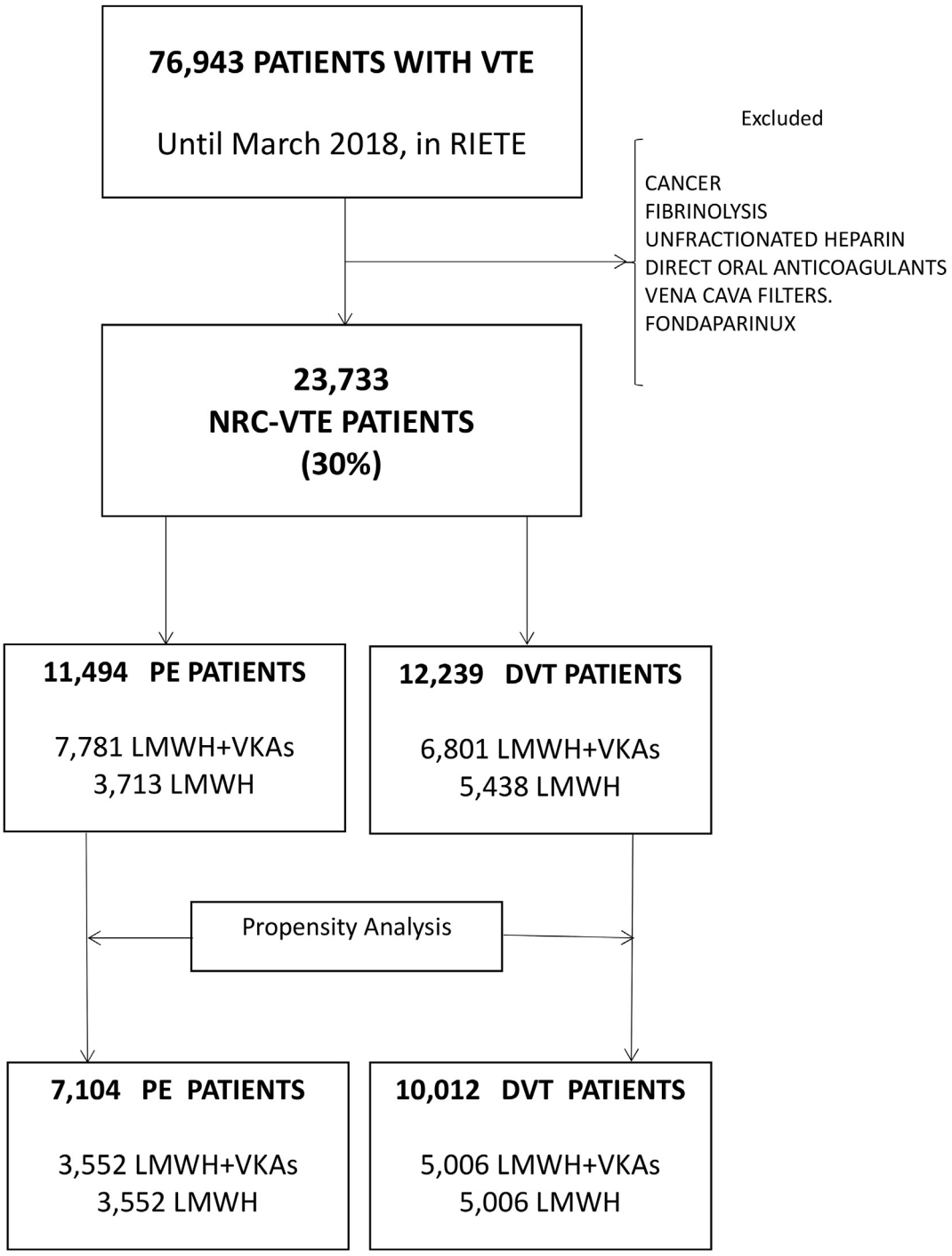

Fig. 1. Study flowchart.

shown in Table 2. DVT patients on long-term LMWH therapy also had a higher rate of PE recurrences (OR: 2.72; 95%CI: 1.39–5.58), major bleeding (OR: 3.07; 95%CI: 2.13–4.48) or death (OR: 4.73; 95%CI: 3.38–6.32) than those on VKAs and a similar rate of DVT recurrences (OR: 0.91; 95%CI: 0.60–1.37) (Fig. 2; Table 2)).

Multivariate analysis confirmed that PE patients on long-term LMWH were at an increased risk for PE recurrences (OR: 4.34; 95%CI: CI: 2.47–7.64), major bleeding (OR: 1.38; 95%CI: 1.20–1.60) or death (OR: 3.33; 95%CI: 2.67–4.16). DVT patients receiving long-term LMWH also were at increased risk for PE recurrences (OR: 3,05; 95%CI: 1.53–6.07), major bleeding (OR: 2.20; 95%CI: 1.50–3.22) or death (OR: 2.79; 95%CI: 2.08–3.76). The risk for DVT recurrences was not significantly higher in PE and in DVT patients (Table 2).

Propensity matched score analysis included 3552 pairs of patients with PE and 5006 with DVT (Table 3). The majority of variables were well balanced, with the only exception of patient's age (Table 3). PE patients receiving long-term LMWH therapy were at increased risk for PE recurrences (OR: 3.30; 95%CI: 1.67–6.48), major bleeding (OR: 1.68; 95%CI: 1.21–2.32) or death (OR: 3.16; 95%CI: 2.43–4.09). Among patients initially presenting with DVT, those on long-term LMWH also were at increased risk for PE recurrences (OR: 2.31; 95% CI: 1.13–4.73), major bleeding (OR 2.28; 95%CI: 1.51–3.44) or death (OR: 2.32; 95%CI: 1.54–3.51) compared to those who switched to VKAs.

Table 1
Clinical characteristics of the patients, according to initial VTE presentation and long-term therapy with LMWH vs. VKAs.

	Pulmonary embolism			Deep vein thrombosis		
	LMWH	VKAs	Effect size	LMWH	VKAs	Effect size
Patients, N	***3713***	***7781***		***5438***	***6801***	
Clinical characteristics,						
Gender (male)	1424 (38%)‡	3452 (44%)	0.057	2383 (44%)‡	3603 (53%)	0.091
Age (mean years±SD)	69 ± 19‡	67 ± 18	0.120	64 ± 20‡	62 ± 19	0.140
Age >80 years	1259 (34%)‡	1871 (24%)	0.104	1462 (27%)‡	1181 (17%)	0.115
Body weight (mean kg±SD)	73 ± 16‡	77 ± 16	0.240	73 ± 16‡	76 ± 15	0.180
Underlying conditions,						
Chronic lung disease	514 (14%)	1065 (14%)	0.002	446 (8.2%)	575 (8.5%)	0.005
Chronic heart failure	401 (11%)‡	625 (8.0%)	0.045	306 (5.6%)‡	258 (3.8%)	0.043
Chronic liver failure	33 (0.9%)*	44 (0.6%)	0.019	73 (1.3%)‡	38 (0.6%)	0.041
CrCl levels <60 mL/min	1763 (47%)‡	2978 (38%)	0.087	2120 (39%)‡	2021 (30%)	0.097
CrCl levels <30 mL/min	373 (10.0%)‡	392 (5.0%)	0.094	466 (8.6%)‡	275 (4.0%)	0.094
Anemia	1440 (28%)‡	1722 (22%)	0.174	2242 (41%)‡	1625 (24%)	0.097
Platelet count <100,000/μL	73 (2.0%)‡	79 (1.0%)	0.039	110 (2.0%)†	89 (1.3%)	0.028
Recent major bleeding	204 (5.5%)‡	57 (0.7%)	0.149	204 (3.8%)‡	36 (0.5%)	0.115
Risk factors for VTE,						
Surgery	495 (13%)‡	836 (11%)	0.038	662 (12%)‡	638 (9.4%)	0.045
Immobilization ≥4 days	1224 (33%)‡	1619 (21%)	0.132	1959 (36%)‡	1580 (23%)	0.140
Estrogen use	156 (4.2%)‡	477 (6.1%)	0.040	242 (4.5%)‡	462 (6.8%)	0.050
Pregnancy or postpartum	130 (3.5%)‡	45 (0.6%)	0.112	340 (6.3%)‡	54 (0.8%)	0.154
None of the above	1798 (48%)	4927 (63%)	0.141	2389 (44%)‡	4198 (62%)	0.177
Concomitant drugs,						
Antiplatelets	720 (19%)‡	1307 (17%)	0.032	792 (15%)‡	765 (11%)	0.049
NSAIDs	247 (6.7%)	518 (6.7%)	0.000	373 (6.9%)†	378 (5.6%)	0.027
Corticosteroids	317 (8.5%)‡	492 (6.3%)	0.040	398 (7.3%)‡	382 (4.8%)	0.053
Initial LMWH therapy,						
Mean doses (IU/kg/day)	176 ± 43‡	184 ± 35	0.220	165 ± 46‡	179 ± 38	0.320
Median doses (IU/kg/day)	185 (44)	193 (28)		165 (64)	190 (37)	

Abbreviations: PE, pulmonary embolism; DVT, deep vein thrombosis; LMWH, low-molecular-weight heparin; VKAs, vitamin K antagonists; SD, standard deviation; VTE, venous thromboembolism; CrCl, creatinine clearance; NSAIDs, non-steroidal anti-inflammatory drugs.
Effect size: *$p < 0.05$; †$p < 0.01$; ‡$p < 0.001$.

Table 2
All patients: analysis of recurrences, major bleeding and death during the first 3 months.

	PE recurrences	DVT recurrences	Major bleeding	Death
PE patients, N	55 (0.48%)	29 (0.25%)	204 (1.77%)	406 (3.53%)
VKAs	18 (0.23%)	17 (0.22%)	97 (1.25%)	134 (1.72%)
LMWH	37 (1.00%)	12 (0.32%)	107 (2.88%)	272 (7.33%)
Crude OR (95%CI)	4.34 (2.49–7.79)	1.48 (0.69–3.11)	2.35 (1.78–3.11)	4.51 (3.66–5.58)
Adjusted HR (95% CI)	4.34 (2.47–7.64)	1.48 (0.71–3.10)	1.38 (1.20–1.60)	3.33 (2.67–4.16)
DVT patients, N	***38 (0.31%)***	***95 (0.78%)***	***137 (1.12%)***	***289 (2.36%)***
VKAs	12 (0.18%)	55 (0.81%)	40 (0.59%)	62 (0.91%)
LMWH	26 (0.48%)	40 (0.74%)	97 (1.78%)	227 (4.17%)
Crude OR (95%CI)	2.72 (1.39–5.58)	0.91 (0.60–1.37)	3.07 (2.13–4.48)	4.73 (3.38–6.32)
Adjusted HR (95% CI)	3.05 (1.53–6.07)	0.91 (0.60–1.37)	2.20 (1.50–3.22)	2.79 (2.08–3.76)

Abbreviations: PE, pulmonary embolism; DVT, deep vein thrombosis; LMWH, low-molecular-weight heparin; VKAs, vitamin K antagonists.

4. Discussion

A number of practical considerations involving mainly patient preferences may influence the choice of long-term LMWH. The major disadvantages of VKA therapy compared with LMWH are the need for regular laboratory monitoring and some major drug interactions. Our findings reveal that in real life, 32% of non-cancer patients with PE and 44% of those with DVT, were prescribed long-term LMWH at least during the first 3 months. This is against the recommendations of the current guidelines of antithrombotic therapy, and may be partly explained because these patients were older and more likely to be immobilized or to have concomitant disorders. Other explanation for this important percentage is that most of the members of RIETE come from Spain, and in our country, the health authorities are very restrictive with the use of direct oral anticoagulants, which are not financed by the public health system, for what its use is minority. Therefore, in our country, most patients with VTE receive long term treatment with two options: standard or LMWH.

Interestingly however, patients on long term LMWH in our cohort were at an increased risk for PE recurrences, major bleeding or death. These findings were consistently found in patients initially presenting with PE or DVT, and persisted after adjusting for a number of potential confounders on multivariable analysis, and on propensity score matched analysis as well.

In our cohort, patients that later were prescribed long-term LMWH received initial therapy with slightly lower doses of LMWH per body weight, and this may partly explain the higher risk for PE recurrences. However, this could not justify the 2-fold higher risk for major bleeding, or the over 2-fold higher risk to die. Our results do not coincide with those in a meta-analysis of 16 randomized clinical trials comparing the efficacy and safety of long-term LMWH vs. VKAs in 3299 patients with symptomatic VTE [7]. In that study, there were no differences in the risk for VTE recurrences or death during the first 3 months, but patients on long-term LMWH therapy had half the risk for major bleeding than those on VKAs. Interestingly, the rate of VTE recurrences in this meta-analysis (4.4% in patients with LMWH, 5.1% in those on VKAs) was higher than in our cohort, while the rate of major bleeding (1.6% vs. 2.9%, respectively)

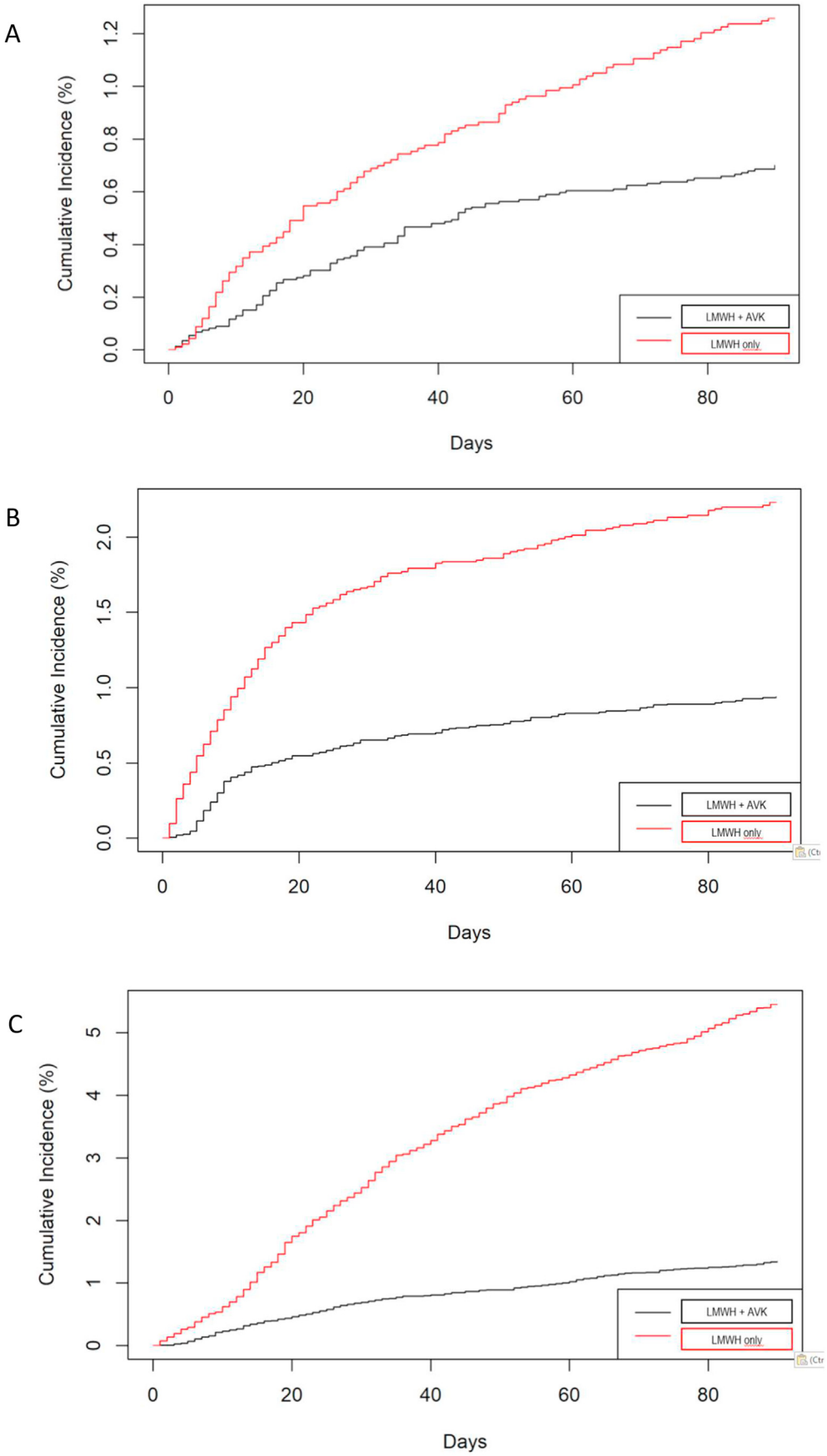

Fig. 2. Cumulative incidence. A: Recurrent VTE. B: Major Bleeding. C: Death.

Table 3
Clinical characteristics of patients with PE, after propensity match score, according to therapy.

	Pulmonary embolism			Deep vein thrombosis		
	LMWH	VKAs	Effect size	LMWH	VKAs	Effect size
Patients, N	***3552***	***3552***		***5006***	***5006***	
Clinical characteristics,						
Gender (male)	1376 (39%)	1419 (40%)	0.012	2317 (46%)	2447 (49%)	0.026
Age (mean years±SD)	70 ± 18	69 ± 17	0.082	66 ± 20	63 ± 19	0.130
Age >80 years	1232 (35%)	1038 (29%)	0.059	1400 (28%)	1063 (21%)	0.078
Weight (mean kg±SD)	73 ± 16	74 ± 14	0.042	73 ± 16	75 ± 15	0.100
Underlying conditions,						
Chronic lung disease	509 (14%)	502 (14%)	0.003	426 (8.5%)	432 (8.6%)	0.002
Chronic heart failure	395 (11%)	313 (8.8%)	0.039	280 (5.6%)	217 (4.3%)	0.029
Chronic liver failure	31 (0.9%)	21 (0.6%)	0.017	71 (1.4%)	28 (0.6%)	0.043
CrCl levels <60 mL/min	1720 (48%)	1572 (44%)	0.042	2034 (41%)	1693 (34%)	0.070
Anemia	1323 (37%)	1164 (33%)	0.047	1974 (39%)	1542 (31%)	0.090
Platelet count <100,000/μL	71 (2.0%)	39 (1.1%)	0.038	106 (2.1%)	69 (1.4%)	0.028
Recent major bleeding	104 (2.9%)	57 (1.6%)	0.044	89 (1.8%)	36 (0.7%)	0.048
Risk factors for VTE,						
Surgery	450 (13%)	451 (13%)	0.000	593 (12%)	552 (11%)	0.013
Immobilization ≥4 days	1233 (35%)	1042 (29%)	0.058	1839 (37%)	1437 (29%)	0.086
Estrogen use	151 (4.3%)	196 (5.5%)	0.029	217 (4.3%)	377 (7.5%)	0.068
Pregnancy or postpartum	69 (1.9%)	44 (1.2%)	0.028	72 (1.4%)	54 (1.1%)	0.016
None of the above	1776 (50%)	1928 (54%)	0.043	2377 (47%)	2705 (54%)	0.066
Concomitant drugs,						
Antiplatelets	702 (20%)	658 (18%)	0.016	753 (15%)	609 (12%)	0.042
NSAIDs	238 (6.7%)	251 (7.1)	0.007	356 (7.1%)	287 (5.7%)	0.028
Corticosteroids	302 (8.5%)	251 (7.1%)	0.027	372 (7.4%)	271 (5.4%)	0.041
Initial therapy,						
Mean doses (IU/kg/day)	177 ± 42	185 ± 35		166 ± 44	180 ± 38	
Median doses (IU/kg/day)	185 (158–200)	193 (171–200)		171 (136–198)	190 (164–200)	

Abbreviations: PE, pulmonary embolism; DVT, deep vein thrombosis; LMWH, low-molecular-weight heparin; VKAs, vitamin K antagonists; SD, standard deviation; VTE, venous thromboembolism; CrCl, creatinine clearance; NSAIDs, non-steroidal anti-inflammatory drugs.
Effect size: Cramer's V and Cohen's D tests.

or death (3.9% vs. 3.5%) were similar [7]. The higher rate of VTE recurrences in the meta-analysis may at least partly be explained because 18% of patients had cancer, the mean age was lower and because in some trials the dose of LMWH was rather low. The similar rate of major bleeding or death in our non-cancer patients might likely be explained because 24% were older than 80 years, 6′3% had CrCl levels <30 mL/min, 2.1% had recent (<30 days before VTE) major bleeding and 1.5% had a platelet count <150,000/μL at baseline. Patients with these co-morbidities are seldom recruited in randomized trials [13,14].

It is well known that fragility may predispose to bleeding and mostly death (risk of major bleeding: OR 1.41, all-cause death: OR 2.02, than the non-fragile). We hypothesize that a significant number of fragile patients could have been included in our study, only in the LMWH treatment group [14]. Unfortunately, there are aspects of fragility not quantified in RIETE. An example of this situation is represented by patients immobilized due to dementia as a predisposing factor of VTE. It is known that with the similar degree of immobility, the vital prognosis of a patient with dementia grade FAST 6 of Reisberg is not the same as that of a patient with grade 7. However, this difference cannot be quantified in RIETE. It can be definitely thought, that there is an important group of patients treated with LMWH alone due to preferences of their physicians based on the comfort and precision provided by an anticoagulant treatment with LMWH in respect to AVK.

We compared conventional treatment against LMWH in the largest cohort of patients with VTE not related to cancer to date: 8558 patients in each treatment group. Our findings represent current clinical practice in more than 20 countries around the world. As a reference, the meta-analysis that included more patients accounted for 1597 patients treated with LMWH and 1702 treated with LMWH and VKAs. After applying the propensity analysis, our groups showed remarkable uniformity. We have not included patients treated with unfractionated heparin, or patients with cancer, and all patients in our cohort were older than 18 years. In contrast, in the meta-analysis by Andras et al., of the 16 publications included, the majority had patients with any of the mentioned characteristics [7].

The present study has a number of limitations. First, our data come from a registry, and selection bias could have conditioned the study, since patients were not randomized, and were treated according to their physician's choice. As explained in the discussion, we cannot rule out the possibility of a bias in the choice of treatment, conditioned by the clinical characteristics of the patients, which have not been quantified in the Registry. However, the wide range of patients from multiple medical centers, countries and treatment settings enrolled in the RIETE registry decreased the likelihood of inclusion of a biased population in this study. Second, propensity analysis is a useful tool to unify populations, but only in those characteristics that are analyzed.

Third, we did not analyze the effect of INR control in our patients, since it is a variable whose value has begun to be registered in the RIETE in recent years. However, in many clinical trials, the time in the therapeutic range was not available through the INR, and in some of them this time was in the infra-therapeutic range [7].

In conclusion, after propensity score analysis in a large cohort of Non-cancer patients with VTE from the RIETE, those undergoing long-term therapy with LMWH only were at an increased risk for recurrent PE, major bleeding or death than those receiving standard therapy with VKAs.

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Registry Coordinating Center

S & H Medical Science Service.

Declaration of competing interest

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