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Regular Article

Fondaparinux in the initial and long-term treatment of venous thromboembolism

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ABSTRACT

Background: Even in the absence of evidence on its long-term efficacy and safety, a number of patients with venous thromboembolism (VTE) receive long-term therapy with fondaparinux alone in everyday practice.
Methods: We used the Registro Informatizado de Enfermedad Tromboembólica (RIETE) registry to compare the rate of VTE recurrences and major bleeding at 10 and 90 days in patients with and without cancer. For long-term therapy, fondaparinux was compared with vitamin K antagonists (VKA) in patients without cancer and with low-molecular-weight heparin (LMWH) in those with cancer Results
Of 47,378 patients recruited, 46,513 were initially treated with heparin, 865 with fondaparinux. Then, 263 patients (78 with cancer) were treated for at least 3 months with fondaparinux. After propensity-score matching, there were no differences between patients receiving initial therapy with heparin or fondaparinux. Among patients with cancer, there were no differences between fondaparinux and LMWH. Among patients without cancer, the long-term use of fondaparinux was associated with an increased risk of major bleeding (3.24 % vs. 0.95 %, $p < 0.05$).
Conclusions: An unexpected high rate of major bleeding was observed in non-cancer patients treated with long-term fondaparinux. Our small sample does not allow to derive relevant conclusions on the use of fondaparinux in cancer patients.

Introduction

Venous thromboembolism (VTE) is a commonly diagnosed condition with significant morbidity and mortality. Based on the results of randomized clinical trials and several meta-analyses [1–8], most available guidelines on antithrombotic therapy recommend patients with VTE to be initially treated with low-molecular-weight heparin (LMWH), fondaparinux or unfractionated heparin (UFH) [9–11]. As for long-term treatment, most guidelines recommend the use of vitamin K antagonists (VKA) in patients without cancer, and LMWH for those with active cancer [3,8–23]. No study so far has evaluated the efficacy and safety of fondaparinux for long-term treatment of VTE. A randomised controlled trial comparing fondaparinux with VKA in patients without cancer, or with LMWH in those with active cancer would be the ideal study design, but the expected low event rates requiring a very large sample size would prohibitively increase its costs. Moreover, in the era of the direct oral anticoagulants, feasibility and funding of such studies remains a challenging task.

However, in real life a number of patients with VTE do receive long-term treatment with fondaparinux, irrespective of the guidelines recommendations. The reasons for treating VTE with fondaparinux alone

Abbreviations: VTE, venous thromboembolism; LMWH, low molecular weight heparin; UFH, unfractioned heparin; VKA, vitamin k antagonists; RIETE, Registro Informatizado de Enfermedad TromboEmbólica; DVT, deep vein thrombosis; PE, pulmonary embolism; CUS, compressive ultrasonography; IU, international units; SD, standard deviation; CrCl, creatinine clearance; CI, confidence intervals

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may probably include no need for serial platelet counts, only one fixed dose per day, a perceived safer profile due to the highly selected anti-Xa activity [24,25].

The RIETE (Registro Informatizado de Enfermedad TromboEmbólica) is an ongoing, multi-centre, international (Spain, Argentina, Belgium, Brazil, Canada, Chile, Czech Republic, Ecuador, France, Germany, Greece, Hungary, Ireland, Israel, Italy, Poland, Portugal, Republic of Macedonia, Slovak Republic, Switzerland, Turkey, United States, and Venezuela), observational registry of consecutive patients with symptomatic, objectively confirmed, acute VTE [26,27]. Data from this registry have been used to evaluate outcomes during the first 3 months of anticoagulant therapy in patients with or without cancer. We used the RIETE database to compare the efficacy and safety of long-term treatment of VTE with fondaparinux in a large "real-life" population enrolled in the RIETE registry. Specific objectives of the study were to compare the efficacy and safety of fondaparinux with VKA in patients without cancer, and with LMWH in those with active cancer.

Patients and Methods

Consecutive patients with symptomatic, acute deep vein thrombosis (DVT) or pulmonary embolism (PE), confirmed by objective tests (contrast venography or ultrasonography for suspected DVT; pulmonary angiography, lung scintigraphy, or helical computed tomography scan for suspected PE), were enrolled in RIETE. Patients were excluded if they did not receive any anticoagulant therapy or were currently participating in a therapeutic clinical trial with a blinded therapy. All patients provided consent to their participation in the registry, in accordance with local Ethics Committee on human research requirements. In the RIETE registry, participating physicians ensured that eligible patients were consecutively enrolled. Data were recorded on a computer-based case report form at each participating hospital and submitted to a centralized coordinating centre through a secure website. The study-coordinating centre assigned patients with 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 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, and made sure that consecutive patients had been recruited into RIETE.

For this analysis, we considered patients without or with active cancer (defined as newly diagnosed cancer or cancer that is being treated, i.e. surgery, chemotherapy, radiotherapy, hormonal, support therapy, or combined treatments). Patients were categorised into subgroups according to the presence or absence of cancer, type of therapy and its duration (i.e.: 10-day or 90-day duration).

Study Outcomes

The occurrence of an objectively confirmed PE or DVT, major bleeding, fatal bleeding, fatal PE and overall death were the outcomes of interest that were analysed during a 10-day and 90-day follow-up period. A composite outcome including all these outcomes was included in the analysis.

In patients with acute symptoms suggesting PE, symptomatic PE was confirmed if it was documented objectively (positive helical computed tomography scan, high-probability ventilation–perfusion lung scan, positive pulmonary angiography, visualization of thrombus in right ventricle or right atrium on echocardiography, or intermediate-probability ventilation–perfusion lung scan associated with DVT in the lower limbs confirmed by compression ultrasonography or contrast venography). If the patient died, death was considered to be due to PE if this diagnosis had been documented at autopsy, or if the patient died shortly (less than 10 days) after objectively confirmed symptomatic PE and no reasonable alternative diagnosis. New or recurrent DVT were diagnosed by the appearance of a new non-compressible vein segment, or a 4-mm or more increase in the diameter of a vein previously occluded by thrombus on compressive ultrasonography (CUS) [28]. Fatal bleeding was defined as any death occurring within 7 days of a major bleeding episode and no reasonable alternative cause of death. Major bleeding was defined as an overt bleed that required a transfusion of two or more units of red blood cells, or if it was retroperitoneal, spinal or intracranial, or fatal. The attending physicians assigned the causes of death.

Baseline Variables

The baseline variables registered in RIETE have been described elsewhere [26,27,29,30]. Data were recorded when the qualifying episode of VTE was diagnosed.

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 and dose of anticoagulant therapy, as was the insertion of an inferior vena cava filter, were recorded. After discharge, all patients were followed for up to 3 months in the outpatient clinic. During each visit, any signs or symptoms suggesting either DVT or PE recurrences or bleeding complications were noted. Most outcomes (VTE recurrences, major bleeding and causes of death) were classified as reported by the clinical centres. However, if the staff at the coordinating centre was in disagreement on how to classify a reported outcome, a central adjudicating committee reviewed that event (less than 10% of events).

Patients who had major bleeding or recurrent VTE within 3 months of enrolment remained under surveillance until 3 months of follow-up was completed.

Statistical Analysis

Categorical variables were reported as percentages and compared using the chi-square test (two-sided) and Fisher´s exact test as appropriate. Continuous variables were compared with a Student t test. A p value lower than 0.05 was considered statistically significant.

Because patients with an objectively confirmed acute VTE event were not randomly assigned to an initial treatment with heparin (either UFH or LMWH) or fondaparinux, we used propensity score matching to adjust for differences in baseline characteristics. We constructed a logistic regression model in which the initial treatment at baseline (heparin or fondaparinux) was a dependent variable, while the variables eventually related to the major bleeding, recurrent VTE or overall death were independent variables. This model made it possible to calculate a propensity score, indicating the likelihood that any individual patient would have received treatment with heparin or fondaparinux given all other known covariates.

Due to the disproportion of patients in both treatment groups, we used the nearest neighbour 4:1 matching method for the previously calculated propensity scores in order to make comparable patients in which heparin or fondaparinux treatment was initiated as acute anticoagulant therapy. After matching, we estimated covariate balance between patients treated with heparin or fondaparinux using absolute standardized differences [31], which directly quantifies the bias in the means and proportions of covariates across the groups, expressed as a percentage of the pooled standard deviations. We used matched univariate logistic regression analysis to estimate associations of initial therapy (heparin or fondaparinux) with various outcomes at 10 days. Propensity score matching was performed using the "psmatching" program for IBM SPSS [32].

We also compared cancer patients on long-term therapy with LMWH and non-cancer patients on long-term therapy with VKA, as usually recommended, with fondaparinux. We evaluated various outcomes at 90 days. We used the same methods as reported above to calculate

the propensity score and to compare both groups of patients, with and without cancer. Statistical analyses were conducted with SPSS for Mac Release 20.0 (IBM SPSS, Inc., Chicago, IL).

Results

As of May 2014, 47,378 patients were recruited into the RIETE registry. Of these, 46,513 were initially treated with LMWH or UFH and 865 with fondaparinux. In all, 23,972 patients (50%) initially presented with PE (with or without concomitant DVT). Their clinical characteristics are shown in Table 1. Most (82%) patients treated with fondaparinux received a daily dose of 7.5 mg, 8.6% 10 mg, 6.1% 5 mg, and 3.3% received 2.5 mg. Most patients initially treated with heparin (94%) received LMWH, at a mean daily dose of 189 ± 65 IU/Kg, as shown in Table 1. New onset thrombocytopenia was reported in three patients (0.3%) receiving initial therapy with fondaparinux and in 114 (0.2%) receiving heparin.

A more detailed description of new onset thrombocytopenia, including heparin-induced thrombocytopenia (HIT), was not scheduled. After the first week, 263 patients were treated for at least 3 months with fondaparinux, usually maintaining the same initial dose. Of these, 78 had active cancer. Among the remaining patients, 31,386 without cancer received VKA for at least 3 months, and 3,928 with cancer received LMWH for at least 3 months. Among patients without cancer receiving long-term fondaparinux 72% received a daily dose of 7.5 mg, 5.41% 10 mg, 10% 5 mg, and 12 % received 2.5 mg. Among patients with cancer receiving long-term fondaparinux the values were 65%, 5.13%, 22% and 7.69%, respectively. Among patients treated with long-term-LMWH, mean daily dose was 177 ± 60 IU/Kg. No significant differences in the rates of new onset thrombocytopenia were observed: in patients without cancer, a new onset thrombocytopenia was reported in one patient (0.5%) receiving long-term fondaparinux and in 49 (0.2%) receiving long-term VKA. In cancer patients the diagnosis was reported in one (1.3%) receiving long-term fondaparinux and in 75 (1.9%) receiving LMWH.

Their clinical characteristics and data related to the initial therapy, according to the type of injective anticoagulant are shown in Table 2. The 10-day outcomes are shown in Table 3. After propensity score matching, the rates of recurrent VTE and major bleeding were similar between patients treated with fondaparinux and those treated with heparin. A slight but statistically significant higher incidence of fatal PE was noted in patients treated with heparin. The 90-day outcomes are shown in Table 4. Considering non-cancer patients after propensity score matching, the rate of VTE recurrences was similar between patients treated with fondaparinux and those with VKA, while the rate of major bleeding and the composite outcome were significantly higher in patients receiving fondaparinux (3.24% vs. 0.95%, $P < 0.05$ and 7.03% vs. 3.39%, $P < 0.05$, respectively). Considering cancer patients after propensity score matching, the rates of VTE recurrences and major bleeding were similar in patients treated with fondaparinux and those treated with LMWH. The distribution of outcomes, according to the dose chosen for long-term fondaparinux and the presence or absence of cancer are summarised in Tables 5 and 6. Among non-cancer patients, the highest rates of both PE recurrences and major bleeding were reported in patients treated with 2.5 mg (both 8.7%). Among cancer patients, no significant differences were found in the rate of VTE recurrences, but the highest rate of major bleeding was found in patients receiving 5 mg (5.9%) and the highest mortality was found in patients treated with 2.5 mg (50%).

Table 1
Clinical characteristics of patients, according to initial therapy with heparin (LMWH or UFH) or fondaparinux.

	Fondaparinux	LMWH or UFH	*p* value
Patients, N	*865*	*46,513*	
Clinical characteristics,			
Gender (males)	408 (47%)	22,734 (49%)	0.32
Mean age (years ± SD)	60 ± 19	66 ± 17	<0.001
Body weight (kg ± SD)	78 ± 17	75 ± 15	<0.001
Inpatients	228 (26%)	12,938 (28%)	0.34
Underlying conditions,			
Chronic heart failure	46 (5.3%)	3,195 (6.9%)	0.07
Chronic lung disease	87 (9.0%)	5,252 (11%)	0.04
CrCl levels (mL/min)	92 ± 48	73 ± 35	<0.001
Recent major bleeding	11 (1.3%)	963 (2.1%)	0.10
Anaemia	220 (25%)	15,994 (34%)	<0.001
Platelet count <100 x10^9/L.	34 (3.9%)	1096 (2.4%)	0.003
Platelet count >450 x10^9/L.	21 (2.4%)	1700 (3.7%)	0.06
Risk factors for VTE,			
Postoperative	100 (12%)	5,339 (12%)	0.94
Immobility ≥4 days	152 (18%)	11,235 (24%)	<0.001
Cancer	91 (11%)	6,683 (14%)	0.001
Oestrogen use	83 (9.6%)	2,165 (4.6%)	<0.001
Pregnancy or puerperium	5 (0.6%)	620 (1.3%)	0.054
None of the above	506 (59%)	27,571 (59%)	0.64
Prior VTE	229 (27%)	7,209 (16%)	<0.001
Initial VTE presentation,			
Pulmonary embolism	398 (46%)	23,574 (51%)	0.006
In patients with PE,			
SBP levels <100 mm Hg	9 (2.3%)	1,705 (7.2%)	<0.001
Heart rate >100 bpm	77 (21%)	8,291 (36%)	<0.001
Sat O_2 < 90%	44 (19%)	4,585 (28%)	0.001
In patients with DVT,	467	22,939	
Proximal DVT	293 (63%)	17,242 (75%)	<0.001
Distal DVT	106 (23%)	3532 (15%)	<0.001
Upper limb DVT	38 (8.1%)	916 (4%)	<0.001
Bilateral lower limb DVT	21 (4%)	643 (3 %)	0.03
Catheter-related arm DVT	9 (1.9%)	606 (3 %)	0.34
Cancer characteristics,			
Metastases	59 (45%)	4,449 (45%)	0.91
Diagnosis <3 months earlier	34 (3.9%)	2,522 (5.4%)	0.054
Initial therapy,			
Low-molecular-weight heparin	-	43,548 (94%)	-
Mean LMWH dose (IU/kg/day)	-	189 ± 65	-
Unfractionated heparin	-	2,965 (6.37%)	-
Mean UFH dose (IU/kg/day)	-	362 ± 116	-
Fondaparinux dose (mg/d),			
2.5 mg/d	29 (3.35%)	-	-
5 mg/d	53 (6.13%)	-	-
7.5 mg/d	708 (82%)	-	-
10 mg/d	75 (8.67%)	-	-
New onset thrombocytopenia	3 (0.3%)	114 (0.2%)	0.55

Discussion

The results of our study confirm that the rates of VTE recurrences and major bleeding appearing in VTE patients receiving fondaparinux as initial therapy are similar to the rates in patients treated with LMWH or UFH, as expected [5,6]. Rather unexpectedly, long-term treatment with fondaparinux in patients without cancer was associated with a significant higher rate of major bleeding compared to that with VKA, while in cancer patients it was as effective and safe as the current recommended treatment with LMWH [16]. Our results should be interpreted with caution, as the reasons why clinicians chose to treat their patients with fondaparinux alone is not retrievable from the registry database. Nevertheless, our analysis could be of interest, as the prescription of long-term fondaparinux in VTE patients is increasing albeit it is not included among the currently authorized indications. The similar efficacy and safety of short and long-term treatment with fondaparinux versus LMWH in patients with cancer seems reassuring, as these subjects are at higher risk of both VTE and bleeding [29,30]. Cancer patients treated with long-term fondaparinux had a significant higher prevalence of lower platelets count and initial distal lower limb DVT and lower prevalence of either initial PE or proximal DVT. Such a clinical profile, characterized by less severe VTE and more frequent concomitant thrombocytopenia might have favoured the choice of fondaparinux, possibly for the lower risk of HIT among other reasons.

Table 2
Clinical characteristics according to the presence or absence of cancer and long-term therapy.*p <0.05; †p <0.01; ‡p <0.001.

	No cancer, Fondaparinux	No cancer, VKA	Cancer, Fondaparinux	Cancer, LMWH
Patients, N	*185*	*31,386*	*78*	*3,928*
Clinical characteristics,				
Gender (males)	86 (47%)	15,526 (50%)	36 (46%)	2,076 (53%)
Mean age (years ± SD)	59 ± 17‡	64 ± 18	66 ± 12	66 ± 13
Body weight (kg ± SD)	76 ± 17	76 ± 15	72 ± 16	71 ± 14
Inpatients	58 (31%)	8,179 (26%)	24 (31%)	1,076 (27%)
Underlying conditions,				
Chronic heart failure	13 (7.0%)	2,072 (6.6%)	5 (6.4%)	134 (3.4%)
Chronic lung disease	14 (7.6%)	3,568 (11%)	9 (12%)	347 (8.8%)
CrCl levels (mL/min)	93 ± 41‡	76 ± 35	76 ± 27	72 ± 32
Recent major bleeding	5 (2.7%)*	362 (1.2%)	1 (1.3%)	94 (2.4%)
Anaemia	60 (32%)*	7,803 (25%)	44 (56%)*	2,704 (69%)
Platelet count <100 x10^9/L	9 (4.9%)	456 (1.5%)	11 (14%)†	241 (6.1%)
Platelet count >450 x10^9/L	6 (3.2%)‡	841 (2.7%)	7 (9.0%)	247 (6.3%)
Risk factors for VTE,				
Postoperative	24 (13%)	3,234 (10%)	12 (15%)	652 (17%)
Immobility ≥4 days	57 (31%)†	6,696 (21%)	17 (22%)	742 (19%)
In cancer patients,				
Metastases	-	-	47 (63%)	2,307 (61%)
Diagnosis <3 months earlier	-	-	24 (31%)	1,213 (31%)
Oestrogen use	9 (4.9%)	1,771 (5.6%)	1 (1.3%)	129 (3.3%)
Pregnancy or puerperium	3 (1.6%)	286 (0.9%)	0	4 (0.1%)
None of the above	92 (50%)	19,452 (62%)‡	49 (63%)	2,474 (63%)
Prior VTE	36 (20%)	5,361 (17%)	14 (18%)	459 (12%)
Initial VTE presentation,				
Pulmonary embolism	52 (28%)‡	16,341 (52%)	23 (30%)‡	1,912 (49%)
In patients with PE,				
SBP levels <100 mm Hg	4 (8.0%)	990 (6.1%)	0	168 (8.8%)
Heart rate >100 bpm	14 (30%)	5,471 (35%)	6 (33%)	732 (40%)
Sat O_2 < 90%	7 (27%)	3,107 (27%)	4 (40%)	286 (24%)
In patients with DVT,	133	15,045	55	2016
Proximal DVT	63 (47%)‡	11,514 (77%)	29 (53%)†	1,363 (68%)
Distal DVT	52 (39%)‡	2528 (17%)	10 (18%)*	169 (8 %)
Upper limb DVT	10 (8%)*	554 (3%)	5 (9%)	144 (7%)
Bilateral lower limb DVT	4 (3%)	290 (2%)	7 (13%)*	106 (5 %)
Catheter-related arm DVT	4 (3%)*	159 (1%)	4 (7%)	234 (12%)
Initial therapy,				
Fondaparinux	119 (64%)‡	563 (1.79%)	50 (64%)	12 (0.31%)
Low-molecular-weight heparin	58 (31%)‡	28,622 (91%)	24 (31%)	3,795 (97%)
Mean LMWH dose (IU/kg/day)	180 ± 100	189 ± 68	176 ± 106	177 ± 60
Unfractionated heparin	8 (4.32%)	2,201 (7.01%)	4 (5.13%)	121 (3.08%)
Mean UFH dose (IU/kg/day)	403 ± 41	358 ± 112	296 ± 261	386 ± 137
Fondaparinux dose (mg/d),				
2.5 mg/d	23 (12%)	-	6 (7.69%)	-
5 mg/d	19 (10%)	-	17 (22%)	-
7.5 mg/d	133 (72%)	-	51 (65%)	-
10 mg/d	10 (5.41%)	-	4 (5.13%)	-
New onset thrombocytopenia	1 (0.5%)	49 (0.2%)	1 (1.3%)	75 (1.9%)

Table 3
10-day outcome, before and after propensity-score matching, according to initial therapy with heparin (LMWH or UFH) or fondaparinux.

10-day outcome	Fondaparinux	LMWH or UFH	P value
Patients, N	*865*	*46,513*	
***Before* propensity-score matching**			
Recurrent PE	1 (0.12%)	154 (0.33%)	0.27
Recurrent DVT	0	68 (0.15%)	0.26
Major bleeding	4 (0.46%)	440 (0.95%)	0.14
Overall death	6 (0.69%)	959 (2.06%)	0.005
Fatal PE	0	412 (0.89%)	0.005
Fatal bleeding	1 (0.12%)	65 (0.14%)	0.85
Composite outcome	10 (1.16%)	1,466 (3.15%)	0.001
***After* propensity-score matching**			
Recurrent PE	1 (0.12%)	9 (0.26%)	0.43
Recurrent DVT	0	5 (0.15%)	0.26
Major bleeding	4 (0.46%)	24 (0.70%)	0.45
Overall death	6 (0.70%)	36 (1.05%)	0.35
Fatal PE	0	17 (0.49%)	0.04
Fatal bleeding	1 (0.12%)	4 (0.12%)	1.00
Composite outcome	10 (1.16%)	65 (1.89%)	0.14

Conversely, a prolonged treatment with fondaparinux in VTE patients without cancer seems to expose them to a significant higher risk of bleeding compared to the standard anticoagulant treatment (3.24 % vs. 0.95%, p < 0.05), even if the clinical profile of these patients was characterized by younger age and a normal renal function. However, the higher prevalence of lower platelets count, recent major bleeding, anaemia and the relatively high fraction of patients treated with lower daily doses of fondaparinux (up to 22%) could indicate a pre-treatment higher risk of bleeding. It is unknown whether clinicians preferably treated these patients with fondaparinux because of either higher haemorrhagic risk, a lower risk of HIT at least in some of them or a wrong prescription for an off-label indication. Ko and coll. recently reported the long-term follow-up data of 35 children treated with fondaparinux alone after acute VTE; after a mean duration of therapy of 371 days the rate of major bleeding (5.7%) was quite similar to that reported in literature for other anticoagulants [33]. However, the small sample size and the clear differences between the two cohorts do not allow any kind of comparisons among data. The different outcome related to a specific dose of fondaparinux should be evaluated

Table 4
90-day outcome, before and after propensity-score matching, according to long-term therapy and the presence or absence of cancer.

90-day outcome	No cancer, Fondaparinux	No cancer, VKA	Cancer, Fondaparinux	Cancer, LMWH
Patients, N	*185*	*31,386*	*78*	*3,928*
***Before* propensity-score matching**				
Recurrent PE	2 (1.08%)	144 (0.46%)	0	68 (1.73%)
Recurrent DVT	1 (0.54%)	210 (0.67%)	0	64 (1.63%)
Major bleeding	6 (3.24%)‡	266 (0.85%)	1 (1.28%)	120 (3.05%)
Overall death	4 (2.16%)	394 (1.26%)	8 (10.3%)*	749 (19.1%)
Fatal PE	0	19 (0.06%)	0	25 (0.64%)
Fatal bleeding	0	36 (0.11%)	1 (1.28%)	24 (0.61%)
Composite outcome	13 (7.03%)†	962 (3.07%)	9 (11.5%)*	914 (23.3%)
***After* propensity-score matching**				
Recurrent PE	2 (1.08%)	3 (0.41%)	0	3 (0.98%)
Recurrent DVT	1 (0.54%)	3 (0.41%)	0	6 (1.95%)
Major bleeding	6 (3.24%)*	7 (0.95%)	1 (1.28%)	6 (1.95%)
Overall death	4 (2.16%)	14 (1.90%)	8 (10.3%)	48 (15.6%)
Fatal PE	0	0	0	0
Fatal bleeding	0	2 (0.27%)	1 (1.28%)	2 (0.65%)
Composite outcome	13 (7.03%)*	25 (3.39%)	9 (11.5%)	59 (19.2%)

* $p < 0.05$; † $p < 0.01$; ‡ $p < 0.001$

with caution, given the low number of patients stratified for drug dosage. Nevertheless, it is interestingly enough to note that in patients without cancer the use of a prophylactic dosage was associated with high rates of both VTE recurrences and major bleeding. We can speculate that in these patients the choice of the lowest dose (2.5 mg) could have been influenced by a pre-treatment higher haemorrhagic risk, which would justify the observed high rate of bleeding, or the location of the thrombosis. However, as expected, a too low dose of fondaparinux led to an unacceptable high rate of VTE recurrences. Therefore, clinicians that chose to treat non-cancer VTE patients with sub-therapeutic dose of fondaparinux may expose them to a relevant risk of VTE recurrences without reducing the risk of bleeding. Overall, a daily 2.5 mg prophylactic dose was prescribed in a relatively high proportion (11%) of the 263 patients treated with long-term fondaparinux: the rate of VTE recurrences observed confirm that decisions like this should be avoided in medical practice without strong scientific evidence.

Our study has a number of strengths: the most relevant is that for the first time, to our knowledge, a quite consistent number of VTE patients treated with fondaparinux for at least 3 months was consecutively enrolled in a prospective, international, multicentre registry and their data have been formally analysed. Our study has several limitations: the main is that our results are not derived by predefined experimental data with a randomization process, thus leading to an unbalanced comparison between different populations. However, the propensity score matching analysis we used reduced the bias in the comparison among groups and a high number of observable covariates were included in the model [31]. Most outcomes were assigned by local investigators and less than 10% of them received a central assignment, thus introducing a possible bias on assigning treatments by physicians possibly aware of patients treatments. However, the data quality monitoring by contract research organizations should have reduced the impact of such a reporting bias. Measures of the international normalized ratio and the time in therapeutic range were not reported in patients treated with VKA, therefore we cannot exclude that the low rate of major bleeding observed in that group, albeit unlikely, could be due to under-dosing or an otherwise excellent management of the oral anticoagulant drug. Of note, the rate of major bleeding observed in patients without cancer treated with long-term fondaparinux was similar to that in cancer patients treated with LMWH (3.24% and 3.05%, respectively). As our data are limited to the first three month of anticoagulant treatment, they cannot apply to cancer patients treated with fondaparinux for longer time. Finally, the small sample size of cancer patients treated with long-term fondaparinux and of patients stratified for fondaparinux dose makes it impossible to derive relevant conclusions from our results.

Conclusions

While confirming a similar outcome in patients receiving fondaparinux as initial therapy compared to those treated with heparin, our study found an unexpected higher rate of major bleeding in patients without cancer receiving long-term fondaparinux compared to those treated with VKA. However, in cancer patients, the long-term treatment with fondaparinux was as effective and safe as the recommended treatment with LMWH. Despite some methodological limitations, our study collected for the first time a consistent number of VTE subject treated with fondaparinux alone for a long time and its results have some clinical implications: although not yet recommended for long-term treatment in VTE patients, fondaparinux is increasingly prescribed for several weeks or months in an off-label fashion. Our data show that such decision is potentially dangerous in non-cancer patients and should be avoided, except, perhaps, in highly selected patients. Although our results do not allow to draw any consistent conclusion in cancer patients, in those who had VTE, contraindication of LMWH

Table 5
Clinical outcome according to long-term fondaparinux dose in patients without cancer.

90-day outcome,	2.5 mg N = 23	5 mg N = 19	7.5 mg N = 133	10 mg N = 10
Recurrent PE	2 (8.7%)	0	0	0
Recurrent DVT	0	0	1 (0.8%)	0
Major bleeding	2 (8.7%)	1 (5.3%)	3 (2.3%)	0
Overall death	0	2 (11%)	0	2 (20%)
Fatal PE	0	0	0	0
Fatal bleeding	0	0	0	0
Composite outcome	4 (17%)	3 (16%)	4 (3.0%)	2 (20%)

Table 6
Clinical outcome according to long-term fondaparinux dose in patients with cancer.

90-day outcome	2.5 mg N = 6	5 mg N = 17	7.5 mg N = 51	10 mg N = 4
Recurrent PE	0	0	0	0
Recurrent DVT	0	0	0	0
Major bleeding	0	1 (5.9%)	0	0
Overall death	3 (50%)	4 (24%)	1 (2.0%)	0
Fatal PE	0	0	0	0
Fatal bleeding	0	1 (5.9%)	0	0
Composite outcome	3 (50%)	5 (29%)	1 (2.0%)	0

for other reasons than a bleeding and for whom VKA or an oral direct anticoagulant are not the best alternative choice, a long-term treatment with fondaparinux could be considered.

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Appendix

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