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

Raffaele Pesavento[1¶], Maria Amitrano[2¶], Javier Trujillo-Santos[3], Paolo di Micco[4], Luciano López-Jiménez[5], Conxita Falgá[6], Fernando García-Bragado[7], Chiara Piovella[1], Paolo Prandoni[1] , Manuel Monreal[8], RIETE Investigators.

¶ Both authors contributed equally to this work.

[1] Department of Medicine- DIMED, 2nd Chair of Internal Medicine, University of Padua. Padua, Italy.
[2] Department of Internal Medicine, AORN San Giuseppe Moscati Avellino. Campania, Italy.
[3] Department of Internal Medicine, Hospital General Universitario Santa Lucía. Cartagena, Murcia, Spain.
[4] Emergency Room, Department of Medicine, Ospedale Buonconsiglio Fatebenefratelli. Naples, Italy.
[5] Department of Internal Medicine, Hospital Universitario Reina Sofía. Córdoba, Spain.
[6] Department of Internal Medicine, Consorci Hospitalari de Mataró. Barcelona, Spain.
[7] Department of Internal Medicine, Hospital Universitari de Girona Dr. Josep Trueta. Gerona, Spain.
[8] Department of Internal Medicine, Hospital Universitari Germans Trias i Pujol. Badalona, Barcelona, Spain.

And the RIETE Investigators*
* *A full list of RIETE investigators is given in the appendix*

Corresponding Author:
Dr. Raffaele Pesavento
Dept. of Medicine –DIMED
Clinica Medica 2
University of Padua
Via Giustiniani, 2
3514 Padova, Italy
Phone: +39-049-8218732
Email: raffaele.pesavento@unipd.it

Abstract (250 words)

Background

A number of patients with venous thromboembolism (VTE) are treated with fondaparinux alone for prolonged times, despite no evidence on its long-term efficacy and safety. We evaluated the outcome of long-term treatment with fondaparinux in a large cohort of VTE patients.

Methods

Consecutive patients with symptomatic acute VTE were enrolled in the RIETE registry and divided in subgroups (cancer, type and duration of therapy). The rate of VTE events and major bleeding were assessed during 10-day and 90-day follow-up period. We used propensity score matching to compare the outcomes in patients treated with fondaparinux, unfractioned (UFH) or low molecular weight (LMWH) heparin and/or vitamin K antagonists (VKA).

Results

Of 47378 patients recruited into the RIETE, 46513 were initially treated with LMWH or UFH, 865 with fondaparinux. 263 patients (78 of whom with cancer) were treated for at least 3 months with fondaparinux, 31386 with VKA and 3928 cancer patients with LMWH. After propensity-score matching, the 10-day, in all patients, and the 90-day outcomes in cancer patients were similar between patients treated with fondaparinux and those treated with heparins, while a significant higher rate of major bleeding was observed in non-cancer patients treated with fondaparinux for at least 90 days compared with those treated with VKA (3.24% vs.0.95%,$p< 0.05$).

Conclusions

An unexpected high rate of major bleeding was observed in non-cancer VTE patients treated with long-term fondaparinux. Until evidence from rigorous prospective studies do not become available, long-term treatment with fondaparinux alone should be avoided in non-cancer VTE patients.

Keywords

Venous Thromboembolism, Anticoagulants, Fondaparinux, Drug Therapy, Deep Vein Thrombosis, Pulmonary Embolism

Abbreviations: VTE-venous thromboembolic events, 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

Background

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 LMWHs 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, irrespectively of the guidelines recommendations. The reasons for treating VTE with fondaparinux alone 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, Italy, France, Israel, Portugal, Germany, Switzerland, Czech Republic, Macedonia, United States, Brazil and Ecuador), 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 active 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 deep-vein thrombosis 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 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 group 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, 47378 patients were recruited into the RIETE registry. Of these, 46513 were initially treated with LMWH or UFH and 865 with fondaparinux. In all, 23972 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 equal to 7.5 mg, 8.6% to 10 mg, 6.1% to 5 mg, 3.3% to 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.

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 others, 31386 patients without cancer received VKA for at least 3 months, and 3928 patients with cancer received LMWH for at least 3 months. Of the patients without cancer and treated with long-term fondaparinux 72% received a daily dose of 7.5 mg, 5.41% of 10 mg, 10% of 5 mg, 12 % of 2.5 mg. Of the patients with cancer and treated with long-term fondaparinux the values were 65%, 5.13%, 22% and 7.69%, respectively. Of the patients treated with long-term-LMWH, the mean daily dose was equal to 177 ± 60 IU/Kg. 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 rate of recurrent VTE and of 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 treated with VKA, while both the rate of major bleeding and of composite outcome were significantly higher in patients treated with 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 both VTE recurrences and major bleeding were similar between 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. Considering non-cancer patients the highest rates of both PE recurrence and major bleeding were reported in patients treated with 2.5 mg (both 8.7%). In cancer patients no clear differences were noted regarding VTE recurrences while the highest rate of major bleeding was noted in patients treated with 5 mg (5.9%) and the highest rate of overall death was reported in patients treated with 2.5 mg (50%).

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 some importance, 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 observed in cancer patients when compared to that with LMWH 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 higher prevalence of abnormal platelet count

and a lower prevalence of either initial PE or proximal DVT; it is possible that the presence of one or more of these factors could have favoured the choice of fondaparinux.

Conversely, a prolonged treatment with fondaparinux in VTE patients without cancer seems to expose them to a significant higher risk of severe bleeding when 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 higher values of creatinine clearance. However, the higher prevalence of recent major bleeding, of 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 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 rate of outcomes related to a specific dose of fondaparinux should be evaluated 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 exposed them to a relevant risk of VTE recurrences without reducing any possible higher bleeding risk. Overall, a daily 2.5 mg prophylactic dose was prescribed in a relatively high fraction (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 reduced the bias in the comparison among groups and a high number of observable covariates were included in the model [31]. 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 of the oral drug. Of note, the rate of major bleeding observed in patients without cancer treated with long-term fondaparinux is very similar to that of 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. At last, 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 conclusion from our results.

Conclusions

While confirming a similar outcome in patients receiving fondaparinux as initial therapy compared to those treated with heparin, our study showed an unexpected significant higher rate of major bleeding in patients without cancer and treated with 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 drawing any consistent conclusion in cancer patients,

in those who had VTE, contraindication of LMWH for other reasons than a bleeding and for whom VKA is not the best alternative choice, a long-term treatment with fondaparinux could be considered.

Author Contributions:

Drs Pesavento, Amitrano and Trujillo-Santos had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Raffaele Pesavento and Maria Amitrano both ex-aequo, Javier Trujillo-Santos.

Acquisition of data: Javier Trujillo-Santos, Paolo di Micco, Paolo Prandoni, and Manuel Monreal.

Analysis and interpretation of data: Raffaele Pesavento, Maria Amitrano, Javier Trujillo-Santos, Paolo di Micco, Paolo Prandoni, Manuel Monreal.

Drafting of the manuscript: Raffaele Pesavento.

Critical revision of the manuscript for important intellectual

Content: Javier Trujillo-Santos, Paolo di Micco, Paolo Prandoni, Manuel Monreal.

Statistical analysis: Javier Trujillo-Santos.

Obtained funding: Manuel Monreal.

Financial Disclosures: None reported. No conflicts of interest that could influence this work were declared.

Role of the Sponsors: The boards of the respective hospitals did not have any specific role in the design and conduct of the study; in the collection, management, analysis, and interpretation of the data; or in the preparation, review, or approval of the manuscript.

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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
Abnormal platelet count	55 (6.4%)	2,796 (6.0%)	0.67
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,			
Proximal DVT	290 (72%)	17,029 (82%)	<0.001
Bilateral lower limb DVT	21 (4.7%)	698 (3.1%)	0.06
Upper limb DVT	49 (11%)	1,571 (6.8%)	0.002
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%)	-	-

SD, standard deviation; CrCl, creatinine clearance; VTE, venous thromboembolism; DVT, deep vein thrombosis; LMWH, low-molecular-weight heparin; IU, international units; CI, confidence intervals.

Table 2. Clinical characteristics according to the presence or absence of cancer and long-term therapy.

	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	83±70	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%)
Abnormal platelet count	15 (8.1%)†	1,297 (4.1%)	18 (23%)†	488 (12%)
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,				
Proximal DVT	61 (53%)‡	11,283 (81%)	33 (75%)†	1,380 (89%)
Bilateral lower limb DVT	4 (3.1%)	302 (2.1%)	7 (13%)	125 (6.4%)
Upper limb DVT	14 (11%)†	750 (5.0%)	10 (18%)	379 (19%)
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%)	-

*p <0.05; †p <0.01; ‡p <0.001

SD, standard deviation; CrCl, creatinine clearance; VTE, venous thromboembolism; DVT, deep vein thrombosis; LMWH, low-molecular-weight heparin; IU, international units; CI, confidence intervals.

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

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

	No cancer, Fondaparinux	No cancer, VKA	Cancer, Fondaparinux	Cancer, LMWH
Patients, N	***185***	***31,386***	***78***	***3,928***
***Before* propensity-score matching**				
90-day outcome,				
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
PE, pulmonary embolism; DVT, deep vein thrombosis; CI, confidence intervals.

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

	2.5 mg N=23	**5 mg N=19**	**7.5 mg N=133**	**10 mg N=10**
90-day outcome,				
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

	2.5 mg N=6	**5 mg N=17**	**7.5 mg N=51**	**10 mg N=4**
90-day outcome,				
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

Highlights

- We evaluated the outcome of long—term therapy with fondaparinux in VTE patients.
- The 10-day outcome was similar with that of patients treated with heparins.
- The 90-day outcome was similar with that of cancer patients treated with VKA.
- A high rate of major bleeding was observed in non-cancer fondaparinux patients.
- Long-term treatment with fondaparinux should be avoided in non-cancer VTE patients.