Prognosis of venous thromboembolism in orthopaedic surgery or trauma patients.

Abstract:

Background*: There is scarce evidence about venous thromboembolism (VTE) after non-major joint surgery and in patients suffering injuries not requiring surgery.*

Methods*: We used the RIETE database (Registro Informatizado Enfermedad TromboEmbólica) to compare* ***the prophylaxis and prognosis*** *of VTE developing after elective hip or knee arthroplasty; hip fracture; non-major orthopaedic surgery, or trauma not requiring surgery (most lower limb trauma).*

Results: *From March 2001 to March 2015, 61,789 patients were enrolled in RIETE. Of these, 943 (1.52%) developed VTE after elective arthroplasty , 445 (0.72%) after hip fracture, 1045 (1.69%) after non-major orthopaedic surgery and 2136 (3.46%) after non-surgical trauma. Overall, 2,283 patients (50%) initially presented with pulmonary embolism (PE). Within the first 90 days of therapy, 30 patients (0.66%; 95%CI: 0.45%-0.93%) died of PE. The rate of fatal PE after elective arthroplasty (0.53%) was similar to the rate after non-major orthopaedic surgery (0.48%) or non-surgical trauma (0.51%). The rate of fatal PE after hip fracture was higher than in the remaining subgroups (2.02%). Overall, one in every 3 patients dying of PE had suffered non-surgical trauma (11 of 30,* ***36.6 %****) or had received VTE prophylaxis (12 of 30,* ***40 %****).*

Conclusions: *The amount of fatal PEs after non-major orthopaedic surgery or non-surgical trauma, exceeds the amount after elective arthroplasty. Further research is needed to identify which of these patients would benefit from VTE prophylaxis.*

Resumen:

Introducción: *Hay escasa evidencia sobre la enfermedad tromboembólica venosa (ETV) en los pacientes intervenidos de cirugía ortopédica menor y en pacientes con traumatismos sin cirugía.*

Métodos: *Se usó el regisgtro RIETE (Resgistro Informatizado Enfermedad Tromboembólica) para comparar el pronóstico y la profilaxis de la ETV desarrollada tras la artroplastia de cadera y rodilla; cirugía de fractura de cadera; cirugía ortopédica menor o traumatismo sin cirugía (la mayoría traumatismos de extremidad inferior).*

Resultados*: Se reclutaron 61789 pacientes en Riete desde marzo de 2001 a marzo de 2015. De estos 943 (1.52%) desarrollaron ETV tras la artroplastia electiva , 445 (0.72%) tras fractura de*

cadera, 1045 (1.69%) tras cirugía ortopédica menor y 2136 (3.46%) después de traumatismo no quirúrgico. 2283 pacientes (50%) se presentaron inicialmente como embolismo pulmonar (EP). En los primeros 90 días de tratamiento, 30 pacientes (0.66%; 95%CI: 0.45%-0.93%) murieron de EP. La tasa de EP fatal tras artroplastia electiva (0.53%) fue similar a la encontrada en relación a la cirugía ortopédica menor (0.48%) y con el traumatismo sin cirugía (0.51). La tasa de EP fatal en la cirugía de fractura de cadera fue mayor que en el resto de los grupos (2.02). Uno de cada tres pacientes que murió de EP fatal había sufrido un traumatismo sin cirugía (11 de 30, ***36.6 %****) y solo 1 de cada 3 había recibido tromboprofilaxis (12 de 30,* ***40*** *%).*

Conclusiones: *El número de pacientes que falleció por EP fatal tras traumatismo sin cirugía o cirugía ortopédica menor fue superior al número de fallecidos tras artroplastia electiva.*
Se requieren más estudios de investigación para identificar cuáles de esos pacientes podrían beneficiarse de profilaxis tromboembólica.

Keywords: Trombosis venosa profunda; embolismo pulmonar; sangrado mayor; tromboembolismo recurrente; cirugía ortopédica menor; traumatismo sin cirugía.

Keywords: *Deep-vein thrombosis; pulmonary embolism; major bleeding; recurrent thromboembolism; non-major orthopaedic surgery; trauma not requiring surgery.*

Introduction

Venous thromboembolism (VTE) is a common complication in patients undergoing major joint surgery (elective arthroplasty of hip or knee or hip fracture surgery), with significant morbidity and mortality (1-3). However, there is scarce evidence of the frequency and severity of VTE events developing after non-major joint surgery (patients without major joint surgery) or in patients suffering injuries not requiring surgery. These injuries include bone fractures, contusions, sprained ankle and tendon or muscle ruptures, and options for treatment include immobilization with or without a plaster cast or brace. A considerable amount of literature has shown that VTE prophylaxis is both effective and safe in patients undergoing major joint surgery , but there is scarce evidence of its efficacy and safety in patients undergoing non-major joint surgery or who present injuries which do not require surgery. Based on the results of six randomized trials in patients who required lower-leg immobilization for at least one week (4-9) the American College of Chest Physicians guidelines suggested it would be preferable not to prescribe pharmacologic VTE prophylaxis in patients with isolated lower-leg injuries (1). Other guidelines or expert recommendations did suggest the use of prophylaxis,(10-15) but a recent trial seem to confirm that prophylaxis may not be effective (16).

Due to this scarce evidence in the current analysis, we used the RIETE database to compare the prognosis of VTE developing after: 1) elective hip or knee arthroplasty; 2) hip fracture); 3) non-major orthopedic surgery, and 4) trauma not requiring surgery and the adherence to the guides in relation to the thromboprophylaxis.

Methods

The RIETE (Registro Informatizado Enfermedad TromboEmbólica) (**17)** is an ongoing, **observational and** international, multicentre prospective registry of consecutive patients presenting with acute, symptomatic VTE. (Spain, Andorra, Belgium, France, Italy, Greece, Portugal, Israel, Germany, Switzerland, Republic of Macedonia, Latvia, Czech Republic, USA, Canada, Ecuador, Argentina, Nicaragua and Brazil). The registry started in Spain in 2001, and some years later the database was translated into English with the aim of expanding 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 VTE, such as the frequency of recurrent VTE, major bleeding and mortality, and predictors for such outcomes (17-19).

Consecutive outpatients with symptomatic acute pulmonary embolism (PE) or deep vein thrombosis (DVT) confirmed by objective tests (ventilation-perfusion lung scan, helical CT-scan or angiography for suspected PE, compression ultrasonography or contrast venography for suspected DVT) 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 inclusion in the registry, in accordance with local ethics committee requirements.

In the RIETE registry, participating physicians ensured that eligible patients were consecutively enrolled. Data were recorded on an electronic form at each participating hospital and submitted to a centralized coordinating center through a secure website. The study-coordinating center assigned patients an unique identification number in order to maintain patient confidentiality and assumed responsibility for all data management. Data quality was regularly monitored electronically, including checks designed to detect inconsistencies or errors, which were subsequently resolved by contacting the local coordinators. Data quality was also monitored by periodic visits to participating hospitals by contract research organizations that compared medical records with the submitted data.

From March 2001 to March 2015, 61,789 patients were enrolled in RIETE to compare the prognosis of VTE developing after: 1) elective hip or knee arthroplasty; 2) hip fracture); 3) non-major orthopedic surgery, and 4) trauma not requiring surgery.

-Major orthopaedic surgery is: elective arthroplasty of hip or knee or hip fracture surgery.
-Non major orthopaedic surgery is the remaning orthopaedic surgery.

Study design

The most significant outcome result was fatal PE (either the initial PE event or recurrent PE appearing within the first 3 months of anticoagulant therapy). Fatal PE, in the absence of autopsy, was defined as any death occurring within 10 days of a confirmed PE diagnosis, in the absence of an alternative cause of death.

Baseline variables

The following parameters were recorded when the qualifying episode of VTE was diagnosed: patient's sex, age, and body weight; presence of coexisting conditions such as chronic heart or lung disease; recent major bleeding(<30 days prior to VTE); presence of risk factors for VTE including active cancer, recent immobilization (defined as non-surgical patients who were confined to bed with bathroom privileges for ≥4 days in the 2 months prior to PE diagnosis), surgery (defined as those who had undergone surgery in the 2 months prior to PE) and laboratory data, including whole blood counts and serum creatinine clearance (CrCl) levels at baseline. CrCl levels were measured according to the Cockcroft and Gault formula.

Treatment and Follow-up

Patients were managed according to the current 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 taken by the attending physicians. Each episode of symptomatic recurrent PE was investigated by repeat lung scanning, helical-CT scan or pulmonary angiography as appropriate. 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 case was reviewed by a central adjudicating committee (less than 10% of cases).

Statistical analysis

We used Student's t test and X^2 test (or Fisher's exact test where appropriate) to compare continuous or categorical variables. SPSS software (version 20, SPSS Inc. Chicago, Illinois) and Epidat 3.1 (Xunta de Galicia, OPS. Coruña, Washington, DC; 2006) were used for the statistical management of the data, and a two-sided $p < 0.05$ was considered to be statistically significant.

Results

From March 2001 to March 2015, 61,789 patients were enrolled in RIETE. Of these, 943 (1.52%) developed VTE after elective arthroplasty (hip 460, knee 483), 445 (0.72%) after hip fracture, 1045 (1.69%) after non-major orthopaedic surgery and 2,136 (3.46%) after non-surgical trauma. The most common reasons for non-major orthopaedic surgery and non-surgical trauma are depicted in Table I. **VTE prophylaxis was higher than 90% in patients with major orthopaedic surgery, 73% in non major orthopaedic surgery patients and 32% in non surgery trauma patients., and did not reduce mortality significantly in the last two groups of patients.**

Overall, 2,283 patients (50%) initially presented as PE (with or without DVT) and 2285 as DVT alone. During the first 90 days of therapy, 30 patients (0.66%; 95%CI: 0.45-0.93) died of PE: 25 died of the initial PE event, 5 died of recurrent PE during the course of anticoagulant therapy.

The rate of fatal PE in patients with VTE after elective arthroplasty (0.53%) was similar to the rate in patients with VTE after non-major orthopaedic surgery (0.48%) or non-surgical trauma (0.51%). However, in absolute numbers the rate is lower: 5 vs. 16 fatal PEs, respectively. The rate of fatal PE in patients with VTE after hip fracture was four times higher than in the remaining subgroups (2.02% vs. 0.51%; odds ratio: 4.03; 95%CI: 1.75-9.26). Overall, one in every 3 patients who died of PE had undergone non-surgical trauma (11 of 30, 36.7%), and only 12 of 30 (40%) had received VTE prophylaxis. Most of these patients had bone fractures, but 2 patients had lower limb contusions and one had a sprained ankle.

Mean age and presence of comorbidities varied among patients in the 4 subgroups, but the severity of the initial PE event (in terms of hypotension, tachycardia or hypoxemia) was similar (Table II). Over 90% of patients with VTE after elective arthroplasty or hip fracture received VTE prophylaxis, but only 32% of those with non-surgical trauma had received prophylaxis.

The majority of patients in all 4 subgroups (86%) were initially treated with low-molecular-weight heparin (LMWH), with no differences in mean doses (Table III). Then, most (64%) switched to vitamin K antagonists (VKA). The 90-day outcome was similar for patients in all subgroups except for those with hip fracture, who had a higher rate of PE recurrences, major bleeding, fatal PE and a higher mortality (Table IV). **The main risk factors for bleeding were (OR 95% CI): PE vs DVT 3.53 (2.02-6.15), chronic heart failure 2.29 (1.19-4.40), CrCla levels <60 ml/min 2.63 (1.64-4.21) and cancer 2.26 (1.19-4.29). The main risk factors for overall death were (OR 95% CI) : hip fracture surgery 3.13 (1.93-5.09), age>80 years 3.07 (2.19-4.29), chronic heart disease 3.54 (2.37-5.31), and cancer 4.98 (3.43-7.23) (Table V).**

Interestingly, PE was the most common cause of death among patients with VTE after elective arthroplasty (5 of 30 deaths, 17%), hip fracture (9 of 65, 14%), non-major orthopaedic surgery (5 of 20, 25%) and non-surgical trauma (11 of 86, 13%).

Discussion

The 9 th American College of Chest Physicians guidelines (2012) for patients undergoing major orthopaedic surgery recommends use of one of the following for a minimum of 10 to 14 days rather than no antithrombotic prophylaxis: low-molecular-weight heparin (LMWH), fondaparinux, apixaban, dabigatran, rivaroxaban, low-dose unfractionated heparin (LDUH), adjusted-dose VKA, or aspirin (all Grade 1B). For patients undergoing knee arthroscopy without a history of prior VTE, suggests no thromboprophylaxis rather than prophylaxis (Grade 2B) and suggests no prophylaxis rather than pharmacologic thromboprophylaxis in patients with isolated lower-leg injuries requiring leg immobilization (Grade 2C). These last recommendations are very generic and with weak evidence. That is why we need to go to other guides such as the European ones that complement it (10,11,25).

Our data reveal that in real life most patients who developed VTE after elective arthroplasty (94%), hip fracture (93%) or non-major orthopaedic surgery (71%) had received VTE prophylaxis, as

recommended by the current guidelines of antithrombotic therapy (1,21,22). Most of the patients received LMWH as thromboembolic prophylaxis and we do not have data on the use of aspirin because it is not collected in our database. However, only one in every three patients (32%) who developed VTE after non-surgical trauma received prophylaxis. Interestingly, the number of patients who died of PE after non-surgical trauma (n=11) doubled the number of patients dying of PE after elective hip or knee arthroplasty (n=5). Its clinical relevance should therefore not be underestimated. This is contrary to data reported in some studies where most patients had distal DVT in this setting (8,13). Furthermore, only 40% patients with fatal PE in the group of patients with non-surgical trauma had received thromboprophylaxis. Those with contusions (without bone fracture) or ankle sprain were amongst those who were less likely to receive prophylaxis, and three of them died of PE. In the remaining groups with fatal PE, almost 100% of patients had received prophylaxis. Our data therefore suggest that the use of adequate VTE prophylaxis should be implemented in a broader population of trauma patients **like suggest some European guidelines in ambulatory patients with lower limb immobilisation and any of the following temporary risk factors: rigid immobilization, non-weight-bearing status, and acute severe injury (dislocation, fracture o tendon rupture)(10,11,25).**

Patients with more comorbidities were those with hip fracture, as they were the oldest patients and therefore had the worst prognosis,**with the highest major bleeding, and the highest recurrent PE and the highest mortality rate for PE. Chronic heart failure and cancer are common risk factor for major bleeding and overall death and the hip fracture surgery is an independent risk factor of mortality (Table V). These results are similar to those found in other studies, where patients having hip fracture surgery have the highest rates of DVT (46-50%) and fatal PE (2.5-7.5%) and the 90 day risk of overall death is 13 % (25,27).**

In the absence of randomized trials performed in this setting, the advantages of VTE prophylaxis in patients with minor orthopaedic surgery or non-surgical trauma remain controversial. A recent meta-analysis (23) on prevention of VTE events with LMWH in the non major orthopaedic setting (patients with leg immobilization for fracture or soft-tissue injury of the lower limb or in patients undergoing knee arthroscopy), suggested some efficacy of LMWH in preventing VTE in patients with reduced mobility in the non-major orthopaedic setting compared with placebo or no treatment.

A recent randomized trial evaluated the use of VTE prophylaxis after knee arthroscopy (POT-KAST) or lower limb casting (POT-CAST), and concluded that 8 days of prophylaxis with LMWH was not effective in preventing symptomatic VTE events in the POT-KAST group (16). However, mean duration of the arthroscopies was less than 30 minutes (there was no ligament surgery), and

thus could be considered minor surgery with a low VTE risk, according to Caprini's risk stratification (24). Moreover, some European guidelines and the American College of Chest Physicians guideline of 2004 did recommend LMWH for patients undergoing arthroscopic knee surgery following a prolonged or complicated procedure (11,25,26). These European guidelines also recommended prophylaxis with LMWH for patients with lower limb immobilization or complete non-weight bearing.

On the other hand, in the POT-CAST trial patients were at low risk for VTE, the doses of LMWH were low (2850 IU of nadroparin or 2500 IU of dalteparin) and up to 50% of patients developed VTE after the cast had been removed. In our study, we can't know the timing of VTE in the group of patients with no surgical trauma, but could be necessary to prolong the prophylaxis in selected patients, when the cast is removed.

The present descriptive study has certain limitations with heterogenous subgroups of patients, where physicians freely prescribed prophylaxis and treatment. This may understandably limit the interpretation of the results. The major shortcoming of this epidemiological study is the lack of total number for each different orthopaedic surgery condition. This denominator is lacking hence a true prevalence can not be calculated and the different incidences cannot be compared. **Our study has not shown that patients receiving thromboprophylaxis in the no major orthopaedic surgery group and in patients with nonsurgical trauma group are significantly associated with a reduction in mortality.**

Conclusions:

Given the unexpected high rate of VTE in patients with non-major orthopaedic surgery or non-surgical trauma and the similar 3-month outcome in terms of PE, recurrent PE or major bleeding with the other subgroup (elective arthroplasty) and of the potential efficacy of pharmacological VTE prophylaxis in this population, further research is needed to determine more precisely which patients should be eligible to receive prophylaxis. **Patients undergoing hip fracture surgery have the worst prognosis.**

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Disclosure of Interests

The authors declare that they have no potential conflicts of interest relevant to this article.

Ethical Standard

(i)“All patients gave their informed consent prior to being included in the study.

(ii)“All procedures involving human participants were in accordance with the 1964 Helsinki declaration and its subsequent amendments”.

(iii) "The study was approved by the Research Ethics Committee (or Institutional Review Board)".

Abbreviations list

CrCl: creatinine clearance;
DVT: deep vein thrombosis;
LMWH: low-molecular-weight heparin;
PE: pulmonary embolism;
VTE: venous thromboembolism;

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Table I. Type of surgery or trauma according to initial VTE presentation and use of VTE prophylaxis.

	N	DVT alone	Non fatal PE	Fatal PE	VTE prophylaxis
All patients,	***4,569***	***2,285 (50%)***	***2,254 (49%)***	***30 (0.66%)***	***2,729 (60%)***
Elective arthroplasty	**943**	**446 (47%)**	**492 (52%)**	**5 (0.53%)**	**883 (94%)**
Hip arthroplasty	460	220 (48%)	238 (52%)	3 (0.65%)	433 (94%)
Knee arthroplasty	483	226 (47%)	256 (53%)	2 (0.41%)	451 (93%)
Hip fracture	**445**	**188 (42%)**	**248 (56%)**	**9 (2.02%)**	**412 (93%)**
Non-major orthopaedic surgery,	**1,045**	**485 (46%)**	**555 (53%)**	**5 (0.48%)**	**745 (71%)**
Lower-extremity fracture	203	88 (43%)	114 (56%)	1 (0.49%)	178 (88%)
Meniscus surgery	151	78 (52%)	73 (48%)	0	115 (76%)
Upper-extremity fracture	80	24 (31%)	54 (69%)	2 (2.5%)	45 (56%)
Tendinous surgery	57	25 (44%)	32 (56%)	0	44 (77%)
Ligaments surgery	55	29 (53%)	26 (47%)	0	43 (78%)
Hallux valgus	48	32 (67%)	16 (33%)	0	30 (63%)
Limb amputation	33	9 (27%)	23 (70%)	1 (3.0%)	28 (85%)
Politrauma	15	6 (40%)	9 (60%)	0	10 (67%)
Other/unknown	403	194 (48%)	208 (52%)	1 (0.25%)	252 (63%)
Non-surgical trauma,	**2,136**	**1,166 (55%)**	**958 (45%)**	**11 (0.51%)**	**689 (32%)**
Lower-extremity fracture	436	222 (51%)	211 (48%)	3 (0.69%)	281 (64%)
Lower extremity contusions	386	242 (63%)	141 (37%)	2 (0.52%)	53 (14%)
Ankle sprain	265	181 (68%)	84 (32%)	1 (0.38%)	70 (26%)
Other fractures	189	75 (40%)	112 (59%)	2 (1.1%)	66 (35%)
Fibrilar rupture	178	112 (63%)	66 (37%)	0	36 (20%)
Vertebral fracture	89	39 (44%)	49 (55%)	1 (1.1%)	26 (29%)
Pelvis fracture	84	35 (42%)	48 (57%)	1 (1.2%)	58 (69%)
Lower extremity tendinitis	70	40 (57%)	30 (43%)	0	12 (17%)
Traumatic brain injury	68	30 (44%)	38 (56%)	0	19 (28%)
Upper extremity injury	67	29 (43%)	37 (55%)	0	7 (10%)
Other/unknown	304	161 (53%)	142 (47%)	1 (0.33%)	61 (20%)

Comparisons were made using patients with elective arthroplasty as reference: $^{*}p < 0.05$; $^{\dagger}p < 0.01$; $^{\ddagger}p < 0.001$

Abbreviations: VTE, venous thromboembolism; DVT, deep vein thrombosis; PE, pulmonary embolism.

Table II. Baseline characteristics in 4,569 patients who developed acute venous thromboembolism after orthopaedic surgery or trauma.

	Elective arthroplasty	Hip fracture	Non-major orthopaedic surgery	Non-surgical trauma
Patients, N	***943***	***445***	***1,045***	***2,136***
Clinical characteristics,				
Male gender	331 (35%)	146 (33%)	547 (52%)‡	1,011 (47%)‡
Age <50 years	37 (3.9%)	58 (13%)‡	409 (39%)‡	872 (41%)‡
Age >80 years	176 (19%)	224 (50%)‡	97 (9.3%)‡	423 (20%)
Body weight (kg±SD)	77±14	70±15‡	79±16*	77±16
Underlying conditions,				
Chronic lung disease	73 (7.7%)	48 (11%)	51 (4.9%)†	161 (7.5%)
Chronic heart failure	51 (5.4%)	38 (8.5%)*	33 (3.2%)*	101 (4.7%)
CrCl levels <60 mL/min	385 (41%)	256 (58%)‡	178 (17%)‡	567 (27%)‡
Anaemia	678 (72%)	309 (69%)	358 (34%)‡	541 (25%)‡
Additional risk factors for VTE,				
Cancer	44 (4.7%)	58 (13%)‡	52 (5.0%)	127 (5.9%)
Hormonal therapy	10 (1.1%)	4 (0.9%)	69 (6.8%)‡	175 (8.4%)‡
Prior VTE	82 (8.7%)	36 (8.1%)	84 (8.0%)	173 (8.1%)
Initial VTE presentation,				
Pulmonary embolism	495 (53%)	257 (58%)	559 (54%)	969 (45%)‡
For patients with PE,				
SBP levels <100 mm Hg	41 (8.3%)	25 (9.7%)	40 (7.2%)	85 (8.8%)
Heart rate >100 bpm	167 (34%)	97 (38%)	206 (37%)	356 (37%)
Sat O_2 <90%	69 (14%)	56 (22%)‡	65 (12%)	157 (16%)
VTE prophylaxis,				
Yes	886 (94%)	412 (93%)	745 (71%)‡	689 (32%)‡
With low-molecular-weight heparin	789 (84%)	388 (87%)	685 (66%)‡	628 (29%)‡
Mean LMWH dose (IU/kg/day)	6,053±3,406	4,490±1,194	6,527±9,027	4,662±4,253
Duration (days±SD)	17±12	21±14	18±14	24±44‡
Time to VTE (days±SD)	21±38	26±20	26±18†	22±73

Comparisons were made using patients with elective arthroplasty as reference: *p <0.05; †p <0.01; ‡p <0.001

Abbreviations: SD, standard deviation; CrCl, creatinine clearance; VTE, venous thromboembolism; PE, pulmonary embolism; SBP, systolic blood pressure; bpm, beats per minute; LMWH, low-molecular-weight heparin; IU, international units.

Table III. Therapeutic strategies.

	Elective arthroplasty	Hip fracture	Non-major orthopaedic surgery	Non-surgical trauma
Patients, N	***943***	***445***	***1,045***	***2,136***
Initial therapy,				
Low-molecular-weight heparin	826 (88%)	387 (87%)	875 (84%)*	1,850 (87%)
Mean LMWH dose (IU/kg/day)	176±40	180±41	178±39	177±43
Unfractionated heparin	66 (7.0%)	40 (9.0%)	80 (7.7%)	105 (4.9%)*
Fondaparinux	21 (2.2%)	11 (2.5%)	28 (2.7%)†	67 (3.1%)
Rivaroxaban	11 (1.2%)	0*	30 (2.9%)	49 (2.3%)*
Thrombolytics	6 (0.64%)	3 (0.67%)	18 (1.7%)*	38 (1.8%)*
Inferior vena cava filter	6 (0.64%)	9 (2.0%)*	18 (1.7%)*	39 (1.8%)*
Long-term treatment,				
Vitamin K antagonists	635 (68%)	251 (60%)†	675 (65%)	1,355 (65%)
Low-molecular-weight heparin	180 (19%)	115 (28%)‡	173 (17%)	409 (20%)
Mean LMWH dose (IU/kg/day)	138±44	147±46	139±49	140±51
Duration of therapy,				
Mean days (±SD)	117±238	103±225	104±201	121±245
Meadian days (range, IQR)	27 (132)	31 (131)	18 (112)	34 (142)

Comparisons were made with patients with elective arthroplasty as reference: *p <0.05; †p <0.01; ‡p <0.001

Abbreviations: LMWH, low-molecular-weight heparin; IU, international units; SD, standard deviation; IQR, interquartile range.

Table IV. Ninety-day outcome.

	Elective arthroplasty	Hip fracture	Non-major orthopaedic surgery	Non-surgical trauma
Patients, N	***943***	***445***	***1,045***	***2,136***
Events				
Recurrent PE	3 (0.32%)	6 (1.35%)*	4 (0.38%)	10 (0.47%)
Recurrent DVT	5 (0.53%)	2 (0.45%)	6 (0.57%)	13 (0.61%)
Recurrent VTE	8 (0.85%)	8 (1.8%)	10 (1.0%)	23 (1.1%)
Major bleeding	15 (1.6%)	18 (4.0%)†	16 (1.5%)	29 (1.4%)
Sites of bleeding,				
Gastrointestinal	2 (0.21%)	6 (1.3%)†	3 (0.29%)	7 (0.33%)
Haematoma	2 (0.21%)	0	8 (0.77%)*	9 (0.42%)
Retroperitoneal	1 (0.11%)	1 (0.22%)	0	3 (0.14%)
Intra-articular	3 (0.32%)	0	0	1 (0.05%)
Cerebral	2 (0.21%)	0	0	3 (0.14%)
Overall death	30 (3.2%)	65 (15%)‡	20 (1.9%)	86 (4.0%)
Causes of death,				
Pulmonary embolism	5 (0.53%)	9 (2.0%)†	5 (0.48%)	11 (0.51%)
Initial PE	3 (0.32%)	8 (1.8%)†	4 (0.38%)	10 (0.47%)
Recurrent PE	2 (0.21%)	1 (0.22%)	1 (0.10%)	1 (0.05%)
Bleeding	2 (0.21%)	2 (0.45%)	0	2 (0.09%)
Disseminated cancer	1 (0.11%)	6 (1.3%)†	3 (0.29%)	8 (0.37%)
Heart failure	0	4 (0.90%)†	1 (0.10%)	2 (0.09%)
Respiratory insufficiency	2 (0.21%)	4 (0.90%)	0	9 (0.42%)

Comparisons were made with patients with elective hip or knee arthroplasty as reference: *p <0.05; †p <0.01; ‡p <0.001

Abbreviations: PE, pulmonary embolism; DVT, deep vein thrombosis; VTE, venous thromboembolism.

Table V. Adjusted odds ratios for each 90-day outcome.

	Odds ratio (95% CI)	p
VTE recurrent,		
Type of surgery or trauma,		
Elective arthroplasty	-	0.44
Hip fracture		
Non-major orthopaedic surgery		
Non-surgical trauma		
Major bleeding,		
Type of surgery or trauma,		
Elective arthroplasty	-	0.18
Hip fracture		
Non-major orthopaedic surgery		
Non-surgical trauma		
PE (vs. DVT)	3.53 (2.02-6.15)	<0.001
Chronic heart failure	2.29 (1.19-4.40)	0.01
CrCl levels <60 mL/min	2.63 (1.64-4.21)	<0.001
Cancer	2.26 (1.19-4.29)	0.01
Overall death,		
Type of surgery or trauma,		
Elective arthroplasty	1 (ref.)	<0.001
Hip fracture	3.13 (1.93-5.09)	<0.001
Non-major orthopaedic surgery	0.79 (0.43-1.44)	0.44
Non-surgical trauma	1.37 (0.87-2.15)	0.18
SBP levels <100 mm Hg	2.82 (1.78-4.45)	<0.001
Heart rate >100 bpm	1.88 (1.35-2.61)	<0.001
Sat O_2 <90%	1.72 (1.16-2.54)	0.007
Age <50 years	0.35 (0.18-0.68)	0.002
Age >80 years	3.07 (2.19-4.29)	<0.001
Chronic heart disease	3.54 (2.37-5.31)	<0.001
Cancer	4.98 (3.43-7.23)	<0.001