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Characteristics, Treatment Patterns and Outcomes of Patients Presenting with Venous Thromboembolic Events After Knee Arthroscopy in the RIETE Registry

--Manuscript Draft--

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Dear Dr. Becker,

We thank you for the opportunity to resubmit our manuscript. Please find below the Reviewer's comments from our submission to *Journal of Thrombosis and Thrombolysis*. We have included point-by-point responses to each comment and the corresponding changes made to the main text. In addition, changes to the main text can be found tracked in the manuscript. We have made substantial revisions in response to the Reviewer's critiques and feel that the revised manuscript is greatly improved.

Reviewer 1

1. **Recurrent VTE was only studied for first 3 months duration and follow up data was only available for 56 of the 101 post arthroscopy so conclusions cannot be made accurately about recurrence. It would be helpful to know how many arthroscopies were performed as part of the registry and out of that 101 patients had VTE- this would give the problem perspective It would be helpful if absolute numbers were available and not detailed as "per 100 patient years"**

   We thank the reviewer for the opportunity to clarify. All patients in RIETE must have at least 90 days follow-up. Thus, 3 months of follow-up was available for all patients (101 post arthroscopy VTE and 19,218 unprovoked VTE). In fact, median follow up was 201-311 days in the various groups. Perhaps the reviewer is referring to follow-up *after anticoagulation was stopped* when they are referring to 56 patients? These patients were compared with 61 post bone-fracture patients and with 6,410 patients with unprovoked VTE for whom this long-term follow-up was available (table 5). However, indeed, regarding what happens after anticoagulation was stopped, we agree with the reviewer that conclusions cannot be made accurately. We have tried to address this matter in the **discussion, paragraph 1**:

   "While recurrent VTE did occur once anticoagulation was stopped, we could not identify differences in event rates in comparison to patients with a clearly provoked or

unprovoked VTE. However, **drawing firm conclusions may not be possible given our small sample size.**"

And, **discussion, paragraph 2**:
"**While firm conclusions cannot be drawn**, some patients did have recurrent VTE once anticoagulation was stopped."

Regarding the reviewer's second comment - Unfortunately, we do not have the data regarding the overall number of patients who underwent arthroscopy, because entry into the RIETE registry occurs at the time of the venous thromboembolic event. Thus, the denominator is unknown to us.

Regarding the reviewer's comment about data presentation – we provided data per 100 patient years in order to standardize across different follow-up periods in the different groups. Thus, respectfully, absolute number may actually present a wrong impression.

Reviewer 2

1. **The rationale for including a third group (post fracture) needs to be explained; seems to be more useful for a separate analysis (Manuscript), provided that additional and detailed data are available. A comparison with total knee replacement would have been more promising.**

We thank the reviewer for the opportunity to clarify. We have chosen to include two comparisons: one to patients who developed an unprovoked VTE and another to patients who developed VTE post bone-fracture. Patients post bone-fracture were chosen as they represent a group who have a provoked event. In the **discussion, paragraph 2** we attempt to clarify:

"In order to provide context, we compared post-arthroscopy VTE to two separate cohorts: those with clearly unprovoked VTE and those with provoked VTE after bone-fracture".

We agree with the reviewer that there is much more to report regarding these patients.

Regarding the reviewer's second comment - While the RIETE registry does include patients with VTE post total knee replacement, we opted to choose a different representation for provoked VTE in order to avoid confusion, as knee replacement is very different than knee arthroscopy.

2. **As there are substantial differences in baseline patient characteristics, and in view of the very large number of unprovoked VTE in RIETE, attempts could have been undertaken (or at least discussed) to match patients or to use propensity scores, or similar.**

Thank you for this comment. We agree that, in general, adjusted, or matched, analyses in comparative observational studies can sometimes provide important insights. However, there are several specific flaws to performing adjusted or propensity matched analyses with the current study.

Because of the modest sample size and low event rates, traditional methods of adjustment are unfortunately invalid (traditional rule of thumb is to include one covariate for adjustment for every 10 events in the study population). Regarding propensity matching, despite reporting on the largest group of patients with post-arthroscopy VTE in the literature, the overall sample size is still modest and the confidence intervals surrounding our observed event rates are very wide. Thus, unfortunately, only minimal additional information is likely to be provided apart from simply selecting and shrinking the comparator population.

Given all of the above issues, we aimed to compare our post-arthroscopy patients to a "naturally occurring" similar population. As noted above, this is why we also included the analysis of post bone-fracture patients. While not a true adjusted analysis, this does

provide additional context to the reader regarding the findings in our post-arthroscopy population.

3. **In the discussion section the authors state that they could not identify differences in the event rates between provoked and unprovoked VTE. This could be explained by the small number of patients undergoing knee arthroscopy.**

   Thank you. We agree with the reviewer. We made the following changes to the **discussion, paragraph 1** to add clarity:

   "While recurrent VTE did occur once anticoagulation was stopped, we could not identify differences in event rates in comparison to patients with a clearly provoked or unprovoked VTE. However, **drawing firm conclusions may not be possible given our small sample size.**"

4. **The percentage of DOAC use was twice as high in the arthroscopy group compared to unprovoked patients. Here, a discussion on the enrollment time periods of the two groups (and availability of DOACs) is missing**

   Thank you for this comment. Direct oral anticoagulants (DOAC) were introduced to the European market in 2013. Patients included in the current study were recruited between 2009 and 2017. Patients across the various groups were recruited over a similar period. Thus, the difference in DOAC prescription reflects more of a practice difference than a difference in the period of recruitment.

   We added a clarification in the **discussion, paragraph 2**:

"While more patients in the post-arthroscopy group received a DOAC, it should be noted that this did not reflect differences in availability as most patients were recruited over similar timeframes."

5. **The written English has to be reviewed and corrected (spelling errors and wording)**

   Thank you for the opportunity to improve our manuscript. We have scrutinized our re-submission and did our best to minimize such errors. We wholeheartedly welcome any further suggestions.

6. **Table 1 should show the odds ratio (last column) compared with unprovoked VTE**

   We apologize if there was any issue with the format that reached the reviewer or if we are misunderstanding the reviewer's request. Table 1 indeed has two comparisons: Arthroscopy vs. Provoked (the column before last) and Arthroscopy vs. Unprovoked (last column).

7. **Table 2: high rate of syncope in PE patients should be mentioned**

   Thank you for pointing this out. We have now highlighted the high rate of syncope in the **discussion, paragraph 1**:

   "Nonetheless, in absolute terms the incidence of syncope was still high."

8. **P9: However, this practice may over-estimate the incidence of DVT and *may* result in treatment-related complications.**

   Thank you again for the opportunity to avoid mistakes. We have revised according to the reviewer's recommendation.

Characteristics, Treatment Patterns and Outcomes of Patients Presenting with Venous Thromboembolic Events After Knee Arthroscopy in the RIETE Registry

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

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Abstract:

Background

Knee arthroscopy is the most common orthopedic procedure worldwide. While incidence of post-arthroscopy venous thromboembolic events (VTE) is low, treatment patterns and patient outcomes have not been described.

Methods

Patients from the "Registro Informatizado Enfermedad TromboEmbolica" (RIETE) who had confirmed post-arthroscopy VTE were compared to patients with provoked, post bone-fracture, and to patients with unprovoked VTE. Baseline characteristics, presenting signs and symptoms, treatment and outcomes including recurrent VTE, bleeds or death were compared.

Results

A total of 101 patients with post-arthroscopy VTE and 19,218 patients with unprovoked VTE were identified. Post-arthroscopy patients were younger (49.5 vs. 66 years, P<0.0001) and had less history of VTE [5.9% vs. 20%, OR 0.26 (0.11-0.59)]. Among patients with isolated DVT, there were fewer proximal DVT in the post-arthroscopy group [40% vs. 86%, OR 0.11 (0.06-0.19)]. Treatment duration was shorter in the post-arthroscopy group (174±140 vs. 311±340 days, P<0.0001) and more often with DOAC [OR 3.67 (1.95-6.89)]. Recurrent VTE occurred in 6.18 (1.96-14.9) and 11.9 (11.0-12.8) per 100 patient years [HR 0.52 (0.16-1.26)] after treatment in the post-arthroscopy and unprovoked groups, respectively. Recurrent VTE occurred in 5.17 (1.31-14.1) per 100 patient years in a separate post bone-fracture group (n = 147), also not statistically different than the post-arthroscopy recurrence rate.

Conclusions

After anticoagulation ~~is stopped~~cessation, some patients post-knee arthroscopy develop VTE. While our small sample size precludes drawing firm conclusions, this signal should warrant further research into the optimal treatment duration for these patients, as some patients may be at increased risk for long-term recurrence.

Key Points:

- Treatment patterns for patients with post-arthroscopy VTE ~~defer than~~differ from those for patients with unprovoked VTE
- Bleeding or thrombotic complications were uncommon during anticoagulation
- Once anticoagulation is stopped, recurrent VTE occurs in some patients with post-arthroscopy VTE
- Future research should be aimed at identifying which patients with post-arthroscopy VTE should be treated with long-term anticoagulation

Introduction:

Knee arthroscopy is usually an elective procedure, performed in relatively young patients, often without thromboprophylaxis[1]. Importantly, these procedures are common; 4 million knee arthroscopies are performed annually, typically in the outpatient setting[2, 3]. After the procedure is done, patients often ambulate on their other leg and are fully ambulatory within a few weeks. However, despite short procedural duration and early ambulation, proximal deep vein thrombosis (DVT)[4, 5] and pulmonary embolism (PE) may occur [6-13] with fatal PE cases reported[14-16]. Risk factors for developing venous thromboembolic events (VTE) after these procedures and analysis of prevention methods have been published [1, 5, 17-23]. However, treatment patterns have not been systematically reported and data regarding patient outcomes are variable[3, 18, 19]. We therefore sought to describe patient characteristics, treatment patterns and outcomes in patients who developed VTE after knee arthroscopy in the "Registro Informatizado Enfermedad TromboEmbolica" (RIETE) [24]. Furthermore, we compared these to patients who developed either provoked, post bone fracture, or unprovoked VTE within the registry.

Methods:

RIETE is a multi-center, multi-national, ongoing prospective registry of confirmed acute VTE that has been populated since March 2001 [24]. RIETE is registered at Clinicaltrials.gov (NCT: 02832245). As of June 2017, over 72,000 patients have been enrolled to the registry, from 179 centers around the world. Importantly, to study the outcomes of patients in real-world practice, RIETE does not mandate specific treatment protocols and treatment is at the discretion of attending physicians at the participating sites. Only patients with at least 3 months of follow-up are included. Data quality is constantly monitored by a contract research organization (CRO). All patients provide oral consent to their participation in the registry, according to the requirements of the Ethics Committee within each participating hospital.

As noted, only objectively confirmed VTE (ultrasonography or venography for DVT, pulmonary angiography or helical computed tomography scan for PE) are included in~~to~~ the registry.

Participating centers have local Institutional Review Board approval with patients providing informed consent for registry enrollment.

VTE Groups

Patients who developed VTE between February 2009 and December 2017 within 60 days of knee arthroscopy were compared to: 1) patients with unprovoked VTE; and 2) patients with provoked VTE post bone fracture. Unprovoked VTE were defined as lacking transient risk factors including recent immobilization >4 days, recent surgery, estrogen use, pregnancy or puerperium, and recent travel. Post bone fracture VTE was defined as occurring within 60 days of a fracture.

Variables

For each patient, the following information was obtained: demographics, past medical history, history of prior thrombosis and known thrombophilia; signs, symptoms and laboratory data at presentation; treatment including anticoagulation use and type and whether thrombolysis or an inferior vena cava filter were offered; and outcomes during the first 3 months including VTE recurrence, bleeding and mortality.

Outcomes

Major bleeding was defined as occurring in a critical site (retroperitoneal, spinal, or intracranial), bleeding requiring transfusion of 2 or more units of packed red blood cells, or fatal bleeding [25]. Fatal PE was defined as any death occurring within 10 days of confirmed PE without an alternative explanation.

Recurrent DVT was defined as a new episode of symptomatic and objectively confirmed ipsilateral or contralateral DVT. Proximal DVT was defined as occurring in the popliteal vein or in a more proximal vein.

Statistical analysis

Mann-Whitney test and Student t-test were used to compare continuous variables, and categorical variables were compared by the Fisher exact test. Odds ratios (ORs) with 95%

confidence intervals (CIs) were calculated, and a two tailed P value of .05 was considered statistically significant. All reported analyses were unadjusted due to the lack of clinical granularity necessary for true adjustment for confounders in the examined clinical scenarios. SPSS software (version 15; SPSS Inc, Chicago, IL) was used for statistical management of the data.

Results:

A total of 101 patients with post-arthroscopy VTE and 19,218 patients with unprovoked VTE were identified.

Post-arthroscopy patients were younger (49.5 vs. 66 years, P<0.0001), more often male [68% vs. 55%, OR 1.77 (1.16-2.69)] and had less history of DVT or PE [5.9% vs. 20%, OR 0.26 (0.11-0.59)] compared to patients with unprovoked VTE, respectively (Table 1). Also, post-arthroscopy patients had a lower incidence of chronic diseases such as diabetes [OR 0.06 (0.01-0.45)], hypertension [OR 0.32 (0.20-0.50)] and chronic lung disease [OR 0.23 (0.07-0.72)] compared to patients with unprovoked VTE. One average VTE occurred within 22.3±17.1 days of surgery; 71% of patients with VTE after arthroscopy had received pharmacologic prophylaxis, for an average of 12.1±7.9 days. There was no difference in the rate of known thrombophilia between groups (2.0% vs. 3.4%).

About half of the patients in both groups presented with PE (49% and 57%, for the post-arthroscopy and unprovoked groups, respectively). Among patients with isolated PE, a minority of patients in both groups presented with ~~syncope (18% and 15%) or~~ hypotension (4.1% and 2.4%) or syncope (18% and 15%). Among patients with isolated DVT, there were fewer proximal DVT in the post-arthroscopy group [40% vs. 86%, OR 0.11 (0.06-0.19)]. Otherwise, presentation was similar between groups (Table 2).

Nearly all patients in each group were treated with anticoagulation initially. Treatment duration was shorter in the post-arthroscopy group (173.8±140 days vs. 311.1±340.3 days,

P<0.0001) and more often with direct oral anticoagulants (DOAC) initially [OR 3.67 (1.95-6.89)], and at 3 months [OR 2.67 (1.71-4.18)] (Table 3).

During treatment with anticoagulation, recurrent VTE occurred in 1.97 (0.10-9.73) and 2.33 (2.11-2.58) per 100 patient years in the post-arthroscopy and unprovoked groups, respectively (Table 4). There were no major bleeds in the post-arthroscopy group and there were 2.31 (2.09-2.56) per 100 patient years in the unprovoked group.

Follow-up was available for 56 and 6,410 patients, in the post-arthroscopy and unprovoked groups, respectively (Table 5). After treatment was stopped, recurrent VTE occurred in 6.18 (1.96-14.9) and 11.9 (11.0-12.8) per 100 patient years in the post-arthroscopy and in the unprovoked groups, respectively HR 0.52 (0.16-1.26).

Comparison to Patients with Post-Bone Fracture VTE

There were 147 patients with post bone-fracture VTE. These patients were older (55.4 vs. 49.5 years, P<0.01), and more were diabetic (6.8% vs. 1%, P<0.05) compared to patients with post-arthroscopy VTE. O~~, but o~~therwise baseline characteristics and presentation were ~~quite~~ similar. Treatment patterns were also similar, though fewer patients in the post bone-fracture group received DOAC (15% vs. 26%, P<0.05). The mean duration of therapy post bone-fracture was 215.3±258.5 days. During treatment with anticoagulation mortality occurred in 7.3 (2.96-15.2) per 100 patient years in the post bone-fracture group, while none of the patient in the post-arthroscopy group had died (P<0.05). Otherwise, outcomes during treatment with anticoagulation and after anticoagulation was stopped were similar between patients ~~with post-fracture and post-arthroscopy VTE~~in both groups.

Discussion:

In this first systematic analysis of post knee-arthroscopy VTE, most patients had a benign presentation including distal DVT or low-risk PE. Nonetheless, in absolute terms the incidence of syncope was still high. Treatment typically included anticoagulation and adverse events ~~while still being treated~~ during treatment were uncommon. While recurrent VTE did occur once anticoagulation was stopped, we could not identify differences in event rates ~~when~~

~~comparing~~in comparison to patients with a clearly provoked or unprovoked VTE. However, drawing firm conclusions may not be possible given our small sample size.

Descriptions of post-arthroscopy VTE treatment and outcomes are lacking in the literature. Several case-reports have reported fatal PE post knee-arthroscopy[15, 16]. In a retrospective series of 102 patients undergoing knee arthroscopy, 8 developed calf-DVT and at a median of 118 days 50% had auto-lysed, while 1 had propagated to the popliteal vein[1]. In the Efficacy of Rivaroxaban for thromboprophylaxis after Knee Arthroscopy (ERIKA) study 120 patients undergoing knee-arthroscopy received prophylaxis with rivaroxaban and were compared to 119 patients who received placebo [19]. While the study reported outcomes for all patients, 7 patients in the placebo arm developed proximal (n=1) or distal (n=6) DVT while 1 patient in the study arm developed distal DVT (P=0.03). Treatment was not reported, however none of the patients developed PE or died. Similarly, in the largest study to-date where 1327 patients undergoing knee-arthroscopy were randomized to receive low molecular weight heparin or placebo for thromboprophylaxis, at 3 months the incidence of VTE was 0.6% in the treatment arm and 0.4% in the control arm and while treatment was not detailed, no deaths were noted [3]. In contrast, the current study included only patients who have already sustained a VTE. We report management and outcomes. In order to provide context, we compared post-arthroscopy VTE ~~twice~~to two separate cohorts: ~~once to~~ those with clearly unprovoked VTE and ~~once to clearly~~ those with provoked VTE after bone-fracture. On average, treatment was longer than 6 months; more than the typical duration of therapy for provoked events[26]. While more patients in the post-arthroscopy group received a DOAC, it should be noted that this did not reflect differences in availability as most patients were recruited over similar timeframes. During the course of anticoagulation, there were no differences in the rate of patients ~~developing~~ who developed VTE recurrences between patients with post-arthroscopy and either comparison group. While firm conclusions cannot be drawn, ~~Strikingly,~~ some patients did have recurrent VTE once anticoagulation was stopped. In absolute terms the recurrence rate was lower than in the unprovoked group, however not in a statistically significant manner. But, recurrent events were also noted in patients with post-fracture VTE. This is in contrast to published recurrence rates for provoked VTE[27].

Strengths of the current study include the detailed description of treatment and outcomes during and after anticoagulation. However, our study has limitations. As there were very few outcomes in the post-arthroscopy group, we cannot comment about the association of baseline characteristics and outcomes. We could not report on specific procedural data; however increased procedural risk was demonstrated across all indications of knee arthroscopy[10]. Finally, we only reported symptomatic events. Proactive surveillance may detect patients with asymptomatic DVT[1, 4, 19]. However, this practice may over-estimate the incidence of DVT[3, 5] and may result in treatment-related complications[14]. Furthermore, by reporting only symptomatic events our results reflect clinical practice[3, 21, 28].

Conclusions:

In this largest study to date examining post-knee arthroscopy VTE treatment and outcomes, there were few thrombotic complications during anticoagulation. Recurrent VTE did occur in some patients after~~once~~ anticoagulation ~~was stopped~~cessation. Our small sample size and low event rate preclude drawing strong conclusions, however this signal should warrant further investigation into the optimal treatment duration for these patients as long-term prevention may be warranted for some.

Table 1: Baseline Patient Characteristics of Patients Presenting with Post-Knee Arthroscopy and Unprovoked Venous Thromboembolism

Characteristics	Arthroscopy	Fracture lower extremities	Unprovoked	P Value / Odds ratio (95% CI) Arthroscopy vs. fracture	P Value / Odds ratio (95% CI) Arthroscopy vs. unprovoked
Patients, N	***101***	***147***	***19,218***		
Age	49.5±13.1	55.4±18.8†	66±16.8‡	0.004	0.000
Male sex	69 (68%)	79 (54%)*	10,563 (55%)†	1.86 (1.09-3.15)	1.77 (1.16-2.69)
Body weight(Kg/m^2±SD)	27.6±4.8	27.9±4.3	28.7±5.5	0.627	0.083
BMI	27.6±4.8	27.9±4.3	28.7±5.5	0.627	0.083
Chronic lung disease	3 (3.0%)	5 (3.4%)	2,270 (12%)†	0.87 (0.20-3.72)	0.23 (0.07-0.72)
Congestive heart failure	3 (3.0%)	13 (8.8%)	1,258 (6.5%)	0.32 (0.09-1.14)	0.44 (0.14-1.38)
Diabetes	1 (0.99%)	10 (6.8%)*	2,654 (14%)‡	0.14 (0.02-1.09)	0.06 (0.01-0.45)
Hypertension	23 (23%)	40 (27%)	9,268 (48%)‡	0.79 (0.44-1.42)	0.32 (0.20-0.50)
Prior myocardial infarction	4 (4.0%)	8 (5.4%)	1,262 (6.6%)	0.72 (0.21-2.45)	0.59 (0.22-1.60)
Prior ischemic stroke	2 (2.0%)	1 (0.68%)	1,069 (5.6%)	2.95 (0.26-32.97)	0.34 (0.08-1.39)
Recent major bleeding	0	4 (2.7%)	183 (0.95%)	-	-
Active cancer	1 (0.99%)	6 (4.1%)	0	0.24 (0.03-1.98)	-
History of DVT or PE	6 (5.9%)	6 (4.1%)	3,756 (20%)‡	1.48 (0.46-4.74)	0.26 (0.11-0.59)
Pregnancy	0	0	0	-	-
Hormone use	6 (5.9%)	7 (4.8%)	0	1.26 (0.41-3.88)	-
Antiphospholipid syndrome	1 (0.99%)	2 (1.4%)	433 (2.3%)	0.73 (0.06-8.10)	0.43 (0.06-3.12)
Known thrombophilia	2 (2.0%)	1 (0.68%)	645 (3.4%)	2.95 (0.26-32.97)	0.58 (0.14-2.36)
Thromboprophylaxis	72 (71%)	123 (84%)*	0	0.48 (0.26-0.90)	-
LMWH	70 (69%)	114 (78%)	0	0.65 (0.37-1.16)	-
UFH	0	0	0	-	0
DOAC	0	0	0	-	0
Others	1 (0.99%)	0	0	-	
Unspecified	1 (0.99%)	0	0	-	
Duration (mean days ±SD)	12.1±7.9	23±14.8‡	-	0.000	-

Duration (median days, IQR)	10 (7-14)	21 (10-30)	-	-	-

BMI – Body mass index, CI – Confidence interval, DVT – Deep vein thrombosis, PE – Pulmonary embolism. *p <0.05; †p <0.01; ‡p <0.001.

Table 2: Presenting Signs, Symptoms in Patients Presenting with Post-Knee Arthroscopy and Unprovoked Venous Thromboembolism					
Signs / Symptoms	**Arthroscopy**	**Fracture lower extremities**	**Unprovoked**	**P Value / Odds ratio (95% CI)**	**P Value / Odds ratio (95% CI)**
All patients, N	***101***	***147***	***19,218***		
Initial VTE presentation,					
Pulmonary embolism	49 (49%)	83 (56%)	10,959 (57%)	0.73 (0.44-1.21)	0.71 (0.48-1.05)
In patients with PE	*49*	*83*	*10,959*		
Cough	8 (16%)	14 (17%)	2,422 (22%)	0.96 (0.37-2.49)	0.69 (0.32-1.47)
Dyspnea	34 (69%)	65 (78%)	8,791 (80%)	0.63 (0.28-1.40)	0.56 (0.30-1.03)
Chest pain	34 (69%)	60 (72%)	5,168 (47%)†	0.87 (0.40-1.89)	2.54 (1.38-4.67)
Syncope	9 (18%)	6 (7.2%)	1,606 (15%)	2.89 (0.96-8.69)	1.31 (0.63-2.71)
Heart rate >110 mm Hg	7 (15%)	27 (34%)*	1,835 (17%)	0.35 (0.14-0.88)	0.86 (0.38-1.92)
SBP levels <90 mm Hg	2 (4.1%)	0	266 (2.4%)	-	1.71 (0.41-7.08)
Sat O2 levels <90% (N=5,928)	5 (21%)	10 (21%)	1,600 (27%)	0.97 (0.29-3.26)	0.71 (0.26-1.90)
In patients with only DVT	*52*	*64*	*8,259*		
Swollen limb	47 (90%)	55 (86%)	7,445 (90%)	1.54 (0.48-4.91)	1.03 (0.41-2.59)
Upper limb	1 (2.5%)	2 (4.9%)	656 (11%)	0.50 (0.04-5.74)	0.20 (0.03-1.44)
secondary to catheter	1 (100%)	0	109 (17%)	0.333	0.167
Lower limb	51 (98%)	62 (97%)	7,679 (95%)	1.65 (0.14-18.67)	2.54 (0.35-18.46)
Proximal	20 (40%)	41 (66%)†	6,490 (86%)‡	0.34 (0.16-0.74)	0.11 (0.06-0.19)
CI – Confidence interval, DVT – Deep vein thrombosis, PE – Pulmonary embolism, VTE – Venous thromboembolic event. *p <0.05; †p <0.01; ‡p <0.001.					

Table 3: Treatment Patterns in Patients Presenting with Post-Knee Arthroscopy and Unprovoked Venous Thromboembolism

Treatment	Arthroscopy	Fracture lower extremities	Unprovoked	P Value / Odds ratio (95% CI)	P Value / Odds ratio (95% CI)
All patients, N	***101***	***147***	***19,218***		
Mean days (±SD)	200.9±222.1	204.3±200.4	310.8±335.9‡	0.902	0.000
Median days (IQR)	115 (98-244)	146 (95-229)	199 (114-370)	-	-
Initial therapy,					
Unfractionated heparin	5 (5.0%)	9 (6.1%)	983 (5.1%)	0.80 (0.26-2.46)	0.97 (0.39-2.38)
Low-molecular-weight heparin	79 (78%)	117 (80%)	16,430 (85%)*	0.92 (0.50-1.71)	0.61 (0.38-0.98)
Mean LMWH dose (IU/kg/day)	173.1±34.1	176.8±46.8	174.8±41.5	0.546	0.713
DOACs	11 (11%)	12 (8.2%)	620 (3.2%)‡	1.38 (0.58-3.25)	3.67 (1.95-6.89)
Thrombolysis	2 (2.0%)	4 (2.7%)	341 (1.8%)	0.72 (0.13-4.02)	1.12 (0.27-4.55)
No anticoagulation	0	0	16 (0.08%)	-	1.000
Vena cava filter	1 (0.99%)	4 (2.7%)	284 (1.5%)	0.36 (0.04-3.25)	0.67 (0.09-4.80)
Duration: mean days (SD)	11.8±12.5	11.6±22.7	13.5±43.4	0.934	0.693
Duration: median days (IQR)	7 (5-15)	7 (4-14)	8 (5-11)	-	-
Long-term therapy*,					
VKAs	65 (64%)	96 (65%)	13,721 (71%)	0.96 (0.56-1.63)	0.72 (0.48-1.09)
LMWH	9 (8.9%)	22 (15%)	2,792 (15%)	0.56 (0.24-1.26)	0.58 (0.29-1.14)
DOACs	26 (26%)	22 (15%)*	2,208 (11%)‡	1.97 (1.04-3.72)	2.67 (1.71-4.18)
Duration: mean days (SD)	173.8±140	215.3±258.5	311.1±340.3‡	0.105	0.000
Duration: median days (IQR)	107 (89-233)	139 (92-221)	195 (111-367)	-	-

DOAC – Direct oral anticoagulant, LMWH – Low molecular weight heparin, VKA – Vitamin K antagonist

* Long-term therapy was defined as the later of the following: 1) After 10 days of the VTE; 2) After bridging between UFH or LMWH; 3) For DOAC, once loading was complete (e.g. 21 days for rivaroxaban). *p <0.05; ‡p <0.001.

Table 4: Outcomes in Patients Presenting with Post-Knee Arthroscopy and Unprovoked Venous Thromboembolism During Anticoagulation

	Arthroscopy		Fracture lower extremities		Unprovoked	
	N	Events per 100 patient-years	N	Events per 100 patient-years	N	Events per 100 patient-years
Patients, N	***101***		***147***		***19,218***	
Duration of follow-up						
Mean days (±SD)	201±222		204±200		311±336‡	
Median days (IQR)	115 (98-244)		146 (95-229)		199 (114-370)‡	
Recurrent DVT	1	1.97 (0.10-9.73)	2	2.46 (0.41-8.11)	218	1.35 (1.18-1.54)
Recurrent PE	0	-	2	2.47 (0.41-8.15)	160	0.99 (0.84-1.15)
Recurrent VTE	1	1.97 (0.10-9.73)	4	4.98 (1.58-12.0)	373	2.33 (2.11-2.58)
Major bleeding	0	-	3	3.65 (0.93-9.94)	374	2.31 (2.09-2.56)
Non-major bleeding	4	7.50 (2.38-18.1)	1	1.23 (0.06-6.06)	660	4.14 (3.84-4.47)
Death	0	-	6	7.30 (2.96-15.2)*	632	3.87 (3.57-4.18)
Fatal PE	0	-	0	-	49	0.30 (0.22-0.39)
Fatal bleeding	0	-	0	-	42	0.26 (0.19-0.34)

*p <0.05; ‡p <0.001.

Table 5: Outcomes in Patients Presenting with Post-Knee Arthroscopy and Unprovoked Venous Thromboembolism After Anticoagulation Discontinuation

	Arthroscopy		Fracture lower extremities		Unprovoked	
	N	Events per 100 patient-years	N	Events per 100 patient-years	N	Events per 100 patient-years
Patients, N	***56***		***61***		***6,410***	
Duration of follow-up,						
Mean days (±SD)	451±508		348±463		321±383	
Median days (IQR)	231 (95-694)		136 (59-359)		178 (57-438)	

Recurrent DVT	2	2.89 (0.49-9.56)	3	5.17 (1.31-14.1)	330	5.91 (5.29-6.57)
Recurrent PE	2	3.09 (0.52-10.2)	0	-	327	5.87 (5.26-6.53)
Recurrent VTE	4	6.18 (1.96-14.9)	3	5.17 (1.31-14.1)	657	11.9 (11.0-12.8)
Major bleeding	0	-	0	-	37	0.66 (0.47-0.90)
Non-major bleeding	0	-	0	-	44	0.79 (0.58-1.04)
Death	0	-	2	3.44 (0.58-11.4)	256	4.55 (4.02-5.13)
Fatal PE	0	-	0	-	4	0.07 (0.02-0.17)
Fatal bleeding	0	-	0	-	17	0.30 (0.18-0.47)

Compliance with Ethical Standards:

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Conflict of interest:

IW serves on the Scientific Advisory Board, Novate Medical. JG serves on the Board of Directors for PERT Consortium, a 501c3 not-for-profit organization. RK serves on the Board of Directors for VIVA Physicians Inc, a 501c3 not-for-profit organization. He is a paid consultant or serves on the Advisory Board for Medtronic, Philips/ Volcano, BTG, Janssen, Vesper Medical, Innovein, Spectranetics, Inari, Boston Scientific. He has received research support from BTG. JIA declares no conflicts of interests. CF declares no conflicts of interests. SS declares no conflicts of interests. AB declares no conflicts of interests. JB declares no conflicts of interests. JGG declares no conflicts of interests. MM declares no conflicts of interests.

Participating centers have local Institutional Review Board approval with patients providing informed consent for registry enrollment.

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Characteristics, Treatment Patterns and Outcomes of Patients Presenting with Venous Thromboembolic Events After Knee Arthroscopy in the RIETE Registry

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Abstract:

Background

Knee arthroscopy is the most common orthopedic procedure worldwide. While incidence of post-arthroscopy venous thromboembolic events (VTE) is low, treatment patterns and patient outcomes have not been described.

Methods

Patients from the "Registro Informatizado Enfermedad TromboEmbolica" (RIETE) who had confirmed post-arthroscopy VTE were compared to patients with provoked, post bone-fracture, and to patients with unprovoked VTE. Baseline characteristics, presenting signs and symptoms, treatment and outcomes including recurrent VTE, bleeds or death were compared.

Results

A total of 101 patients with post-arthroscopy VTE and 19,218 patients with unprovoked VTE were identified. Post-arthroscopy patients were younger (49.5 vs. 66 years, P<0.0001) and had less history of VTE [5.9% vs. 20%, OR 0.26 (0.11-0.59)]. Among patients with isolated DVT, there were fewer proximal DVT in the post-arthroscopy group [40% vs. 86%, OR 0.11 (0.06-0.19)]. Treatment duration was shorter in the post-arthroscopy group (174±140 vs. 311±340 days, P<0.0001) and more often with DOAC [OR 3.67 (1.95-6.89)]. Recurrent VTE occurred in 6.18 (1.96-14.9) and 11.9 (11.0-12.8) per 100 patient years [HR 0.52 (0.16-1.26)] after treatment in the post-arthroscopy and unprovoked groups, respectively. Recurrent VTE occurred in 5.17 (1.31-14.1) per 100 patient years in a separate post bone-fracture group (n = 147), also not statistically different than the post-arthroscopy recurrence rate.

Conclusions

After anticoagulation cessation, some patients post-knee arthroscopy develop VTE. While our small sample size precludes drawing firm conclusions, this signal should warrant further research into the optimal treatment duration for these patients, as some patients may be at increased risk for long-term recurrence.

Key Points:

- Treatment patterns for patients with post-arthroscopy VTE differ from those for patients with unprovoked VTE
- Bleeding or thrombotic complications were uncommon during anticoagulation
- Once anticoagulation is stopped, recurrent VTE occurs in some patients with post-arthroscopy VTE
- Future research should be aimed at identifying which patients with post-arthroscopy VTE should be treated with long-term anticoagulation

Introduction:

Knee arthroscopy is usually an elective procedure, performed in relatively young patients, often without thromboprophylaxis[1]. Importantly, these procedures are common; 4 million knee arthroscopies are performed annually, typically in the outpatient setting[2, 3]. After the procedure is done, patients often ambulate on their other leg and are fully ambulatory within a few weeks. However, despite short procedural duration and early ambulation, proximal deep vein thrombosis (DVT)[4, 5] and pulmonary embolism (PE) may occur [6-13] with fatal PE cases reported[14-16]. Risk factors for developing venous thromboembolic events (VTE) after these procedures and analysis of prevention methods have been published [1, 5, 17-23]. However, treatment patterns have not been systematically reported and data regarding patient outcomes are variable[3, 18, 19]. We therefore sought to describe patient characteristics, treatment patterns and outcomes in patients who developed VTE after knee arthroscopy in the "Registro Informatizado Enfermedad TromboEmbolica" (RIETE) [24]. Furthermore, we compared these to patients who developed either provoked, post bone-fracture, or unprovoked VTE within the registry.

Methods:

RIETE is a multi-center, multi-national, ongoing prospective registry of confirmed acute VTE that has been populated since March 2001 [24]. RIETE is registered at Clinicaltrials.gov (NCT: 02832245). As of June 2017, over 72,000 patients have been enrolled to the registry, from 179 centers around the world. Importantly, to study the outcomes of patients in real-world practice, RIETE does not mandate specific treatment protocols and treatment is at the discretion of attending physicians at the participating sites. Only patients with at least 3 months of follow-up are included. Data quality is constantly monitored by a contract research organization (CRO). All patients provide oral consent to their participation in the registry, according to the requirements of the Ethics Committee within each participating hospital.

As noted, only objectively confirmed VTE (ultrasonography or venography for DVT, pulmonary angiography or helical computed tomography scan for PE) are included in the registry.

Participating centers have local Institutional Review Board approval with patients providing informed consent for registry enrollment.

VTE Groups

Patients who developed VTE between February 2009 and December 2017 within 60 days of knee arthroscopy were compared to: 1) patients with unprovoked VTE; and 2) patients with provoked VTE post bone-fracture. Unprovoked VTE were defined as lacking transient risk factors including recent immobilization >4 days, recent surgery, estrogen use, pregnancy or puerperium, and recent travel. Post bone fracture VTE was defined as occurring within 60 days of a fracture.

Variables

For each patient, the following information was obtained: demographics, past medical history, history of prior thrombosis and known thrombophilia; signs, symptoms and laboratory data at presentation; treatment including anticoagulation use and type and whether thrombolysis or an inferior vena cava filter were offered; and outcomes during the first 3 months including VTE recurrence, bleeding and mortality.

Outcomes

Major bleeding was defined as occurring in a critical site (retroperitoneal, spinal, or intracranial), bleeding requiring transfusion of 2 or more units of packed red blood cells, or fatal bleeding [25]. Fatal PE was defined as any death occurring within 10 days of confirmed PE without an alternative explanation.

Recurrent DVT was defined as a new episode of symptomatic and objectively confirmed ipsilateral or contralateral DVT. Proximal DVT was defined as occurring in the popliteal vein or in a more proximal vein.

Statistical analysis

Mann-Whitney test and Student t-test were used to compare continuous variables, and categorical variables were compared by the Fisher exact test. Odds ratios (ORs) with 95%

confidence intervals (CIs) were calculated, and a two tailed P value of .05 was considered statistically significant. All reported analyses were unadjusted due to the lack of clinical granularity necessary for true adjustment for confounders in the examined clinical scenarios. SPSS software (version 15; SPSS Inc, Chicago, IL) was used for statistical management of the data.

Results:

A total of 101 patients with post-arthroscopy VTE and 19,218 patients with unprovoked VTE were identified.

Post-arthroscopy patients were younger (49.5 vs. 66 years, P<0.0001), more often male [68% vs. 55%, OR 1.77 (1.16-2.69)] and had less history of DVT or PE [5.9% vs. 20%, OR 0.26 (0.11-0.59)] compared to patients with unprovoked VTE, respectively (Table 1). Also, post-arthroscopy patients had a lower incidence of chronic diseases such as diabetes [OR 0.06 (0.01-0.45)], hypertension [OR 0.32 (0.20-0.50)] and chronic lung disease [OR 0.23 (0.07-0.72)] compared to patients with unprovoked VTE. One average VTE occurred within 22.3±17.1 days of surgery; 71% of patients with VTE after arthroscopy had received pharmacologic prophylaxis, for an average of 12.1±7.9 days. There was no difference in the rate of known thrombophilia between groups (2.0% vs. 3.4%).

About half of the patients in both groups presented with PE (49% and 57%, for the post-arthroscopy and unprovoked groups, respectively). Among patients with isolated PE, a minority of patients in both groups presented with hypotension (4.1% and 2.4%) or syncope (18% and 15%). Among patients with isolated DVT, there were fewer proximal DVT in the post-arthroscopy group [40% vs. 86%, OR 0.11 (0.06-0.19)]. Otherwise, presentation was similar between groups (Table 2).

Nearly all patients in each group were treated with anticoagulation initially. Treatment duration was shorter in the post-arthroscopy group (173.8±140 days vs. 311.1±340.3 days,

P<0.0001) and more often with direct oral anticoagulants (DOAC) initially [OR 3.67 (1.95-6.89)], and at 3 months [OR 2.67 (1.71-4.18)] (Table 3).

During treatment with anticoagulation, recurrent VTE occurred in 1.97 (0.10-9.73) and 2.33 (2.11-2.58) per 100 patient years in the post-arthroscopy and unprovoked groups, respectively (Table 4). There were no major bleeds in the post-arthroscopy group and there were 2.31 (2.09-2.56) per 100 patient years in the unprovoked group.

Follow-up was available for 56 and 6,410 patients, in the post-arthroscopy and unprovoked groups, respectively (Table 5). After treatment was stopped, recurrent VTE occurred in 6.18 (1.96-14.9) and 11.9 (11.0-12.8) per 100 patient years in the post-arthroscopy and in the unprovoked groups, respectively HR 0.52 (0.16-1.26).

Comparison to Patients with Post-Bone Fracture VTE

There were 147 patients with post bone-fracture VTE. These patients were older (55.4 vs. 49.5 years, P<0.01), and more were diabetic (6.8% vs. 1%, P<0.05) compared to patients with post-arthroscopy VTE. Otherwise baseline characteristics and presentation were similar. Treatment patterns were also similar, though fewer patients in the post bone-fracture group received DOAC (15% vs. 26%, P<0.05). The mean duration of therapy post bone-fracture was 215.3±258.5 days. During treatment with anticoagulation mortality occurred in 7.3 (2.96-15.2) per 100 patient years in the post bone-fracture group, while none of the patient in the post-arthroscopy group had died (P<0.05). Otherwise, outcomes during treatment with anticoagulation and after anticoagulation was stopped were similar between patients in both groups.

Discussion:

In this first systematic analysis of post knee-arthroscopy VTE, most patients had a benign presentation including distal DVT or low-risk PE. Nonetheless, in absolute terms the incidence of syncope was still high. Treatment typically included anticoagulation and adverse events during treatment were uncommon. While recurrent VTE did occur once anticoagulation was stopped, we could not identify differences in event rates in comparison to patients with a

clearly provoked or unprovoked VTE. However, drawing firm conclusions may not be possible given our small sample size.

Descriptions of post-arthroscopy VTE treatment and outcomes are lacking in the literature. Several case-reports have reported fatal PE post knee-arthroscopy[15, 16]. In a retrospective series of 102 patients undergoing knee arthroscopy, 8 developed calf-DVT and at a median of 118 days 50% had auto-lysed, while 1 had propagated to the popliteal vein[1]. In the Efficacy of Rivaroxaban for thromboprophylaxis after Knee Arthroscopy (ERIKA) study 120 patients undergoing knee-arthroscopy received prophylaxis with rivaroxaban and were compared to 119 patients who received placebo [19]. While the study reported outcomes for all patients, 7 patients in the placebo arm developed proximal (n=1) or distal (n=6) DVT while 1 patient in the study arm developed distal DVT (P=0.03). Treatment was not reported, however none of the patients developed PE or died. Similarly, in the largest study to-date where 1327 patients undergoing knee-arthroscopy were randomized to receive low molecular weight heparin or placebo for thromboprophylaxis, at 3 months the incidence of VTE was 0.6% in the treatment arm and 0.4% in the control arm and while treatment was not detailed, no deaths were noted [3]. In contrast, the current study included only patients who have already sustained a VTE. We report management and outcomes. In order to provide context, we compared post-arthroscopy VTE to two separate cohorts: those with clearly unprovoked VTE and those with provoked VTE after bone-fracture. On average, treatment was longer than 6 months; more than the typical duration of therapy for provoked events[26]. While more patients in the post-arthroscopy group received a DOAC, it should be noted that this did not reflect differences in availability as most patients were recruited over similar timeframes. During the course of anticoagulation, there were no differences in the rate of patients who developed VTE recurrences between patients with post-arthroscopy and either comparison group. While firm conclusions cannot be drawn, some patients did have recurrent VTE once anticoagulation was stopped. In absolute terms the recurrence rate was lower than in the unprovoked group, however not in a statistically significant manner. But, recurrent events were also noted in patients with post-fracture VTE. This is in contrast to published recurrence rates for provoked VTE[27].

Strengths of the current study include the detailed description of treatment and outcomes during and after anticoagulation. However, our study has limitations. As there were very few outcomes in the post-arthroscopy group, we cannot comment about the association of baseline characteristics and outcomes. We could not report on specific procedural data; however increased procedural risk was demonstrated across all indications of knee arthroscopy[10]. Finally, we only reported symptomatic events. Proactive surveillance may detect patients with asymptomatic DVT[1, 4, 19]. However, this practice may over-estimate the incidence of DVT[3, 5] and may result in treatment-related complications[14]. Furthermore, by reporting only symptomatic events our results reflect clinical practice[3, 21, 28].

Conclusions:

In this largest study to date examining post-knee arthroscopy VTE treatment and outcomes, there were few thrombotic complications during anticoagulation. Recurrent VTE did occur in some patients after anticoagulation cessation. Our small sample size and low event rate preclude drawing strong conclusions, however this signal should warrant further investigation into the optimal treatment duration for these patients as long-term prevention may be warranted for some.

Table 1: Baseline Patient Characteristics of Patients Presenting with Post-Knee Arthroscopy and Unprovoked Venous Thromboembolism

Characteristics	Arthroscopy	Fracture lower extremities	Unprovoked	P Value / Odds ratio (95% CI) Arthroscopy vs. fracture	P Value / Odds ratio (95% CI) Arthroscopy vs. unprovoked
Patients, N	***101***	***147***	***19,218***		
Age	49.5±13.1	55.4±18.8†	66±16.8‡	0.004	0.000
Male sex	69 (68%)	79 (54%)*	10,563 (55%)†	1.86 (1.09-3.15)	1.77 (1.16-2.69)
Body weight(Kg/m^2±SD)	27.6±4.8	27.9±4.3	28.7±5.5	0.627	0.083
BMI	27.6±4.8	27.9±4.3	28.7±5.5	0.627	0.083
Chronic lung disease	3 (3.0%)	5 (3.4%)	2,270 (12%)†	0.87 (0.20-3.72)	0.23 (0.07-0.72)
Congestive heart failure	3 (3.0%)	13 (8.8%)	1,258 (6.5%)	0.32 (0.09-1.14)	0.44 (0.14-1.38)
Diabetes	1 (0.99%)	10 (6.8%)*	2,654 (14%)‡	0.14 (0.02-1.09)	0.06 (0.01-0.45)
Hypertension	23 (23%)	40 (27%)	9,268 (48%)‡	0.79 (0.44-1.42)	0.32 (0.20-0.50)
Prior myocardial infarction	4 (4.0%)	8 (5.4%)	1,262 (6.6%)	0.72 (0.21-2.45)	0.59 (0.22-1.60)
Prior ischemic stroke	2 (2.0%)	1 (0.68%)	1,069 (5.6%)	2.95 (0.26-32.97)	0.34 (0.08-1.39)
Recent major bleeding	0	4 (2.7%)	183 (0.95%)	-	-
Active cancer	1 (0.99%)	6 (4.1%)	0	0.24 (0.03-1.98)	-
History of DVT or PE	6 (5.9%)	6 (4.1%)	3,756 (20%)‡	1.48 (0.46-4.74)	0.26 (0.11-0.59)
Pregnancy	0	0	0	-	-
Hormone use	6 (5.9%)	7 (4.8%)	0	1.26 (0.41-3.88)	-
Antiphospholipid syndrome	1 (0.99%)	2 (1.4%)	433 (2.3%)	0.73 (0.06-8.10)	0.43 (0.06-3.12)
Known thrombophilia	2 (2.0%)	1 (0.68%)	645 (3.4%)	2.95 (0.26-32.97)	0.58 (0.14-2.36)
Thromboprophylaxis	72 (71%)	123 (84%)*	0	0.48 (0.26-0.90)	-
LMWH	70 (69%)	114 (78%)	0	0.65 (0.37-1.16)	-
UFH	0	0	0	-	0
DOAC	0	0	0	-	0
Others	1 (0.99%)	0	0	-	
Unspecified	1 (0.99%)	0	0	-	
Duration (mean days ±SD)	12.1±7.9	23±14.8‡	-	0.000	-

Duration (median days, IQR)	10 (7-14)	21 (10-30)	-	-	-

BMI – Body mass index, CI – Confidence interval, DVT – Deep vein thrombosis, PE – Pulmonary embolism. *p <0.05; †p <0.01; ‡p <0.001.

Table 2: Presenting Signs, Symptoms in Patients Presenting with Post-Knee Arthroscopy and Unprovoked Venous Thromboembolism

Signs / Symptoms	Arthroscopy	Fracture lower extremities	Unprovoked	P Value / Odds ratio (95% CI)	P Value / Odds ratio (95% CI)
All patients, N	***101***	***147***	***19,218***		
Initial VTE presentation,					
Pulmonary embolism	49 (49%)	83 (56%)	10,959 (57%)	0.73 (0.44-1.21)	0.71 (0.48-1.05)
In patients with PE	*49*	*83*	*10,959*		
Cough	8 (16%)	14 (17%)	2,422 (22%)	0.96 (0.37-2.49)	0.69 (0.32-1.47)
Dyspnea	34 (69%)	65 (78%)	8,791 (80%)	0.63 (0.28-1.40)	0.56 (0.30-1.03)
Chest pain	34 (69%)	60 (72%)	5,168 (47%)†	0.87 (0.40-1.89)	2.54 (1.38-4.67)
Syncope	9 (18%)	6 (7.2%)	1,606 (15%)	2.89 (0.96-8.69)	1.31 (0.63-2.71)
Heart rate >110 mm Hg	7 (15%)	27 (34%)*	1,835 (17%)	0.35 (0.14-0.88)	0.86 (0.38-1.92)
SBP levels <90 mm Hg	2 (4.1%)	0	266 (2.4%)	-	1.71 (0.41-7.08)
Sat O2 levels <90% (N=5,928)	5 (21%)	10 (21%)	1,600 (27%)	0.97 (0.29-3.26)	0.71 (0.26-1.90)
In patients with only DVT	*52*	*64*	*8,259*		
Swollen limb	47 (90%)	55 (86%)	7,445 (90%)	1.54 (0.48-4.91)	1.03 (0.41-2.59)
Upper limb	1 (2.5%)	2 (4.9%)	656 (11%)	0.50 (0.04-5.74)	0.20 (0.03-1.44)
secondary to catheter	1 (100%)	0	109 (17%)	0.333	0.167
Lower limb	51 (98%)	62 (97%)	7,679 (95%)	1.65 (0.14-18.67)	2.54 (0.35-18.46)
Proximal	20 (40%)	41 (66%)†	6,490 (86%)‡	0.34 (0.16-0.74)	0.11 (0.06-0.19)

CI – Confidence interval, DVT – Deep vein thrombosis, PE – Pulmonary embolism, VTE – Venous thromboembolic event. *p <0.05; †p <0.01; ‡p <0.001.

Table 3: Treatment Patterns in Patients Presenting with Post-Knee Arthroscopy and Unprovoked Venous Thromboembolism

Treatment	Arthroscopy	Fracture lower extremities	Unprovoked	P Value / Odds ratio (95% CI)	P Value / Odds ratio (95% CI)
All patients, N	***101***	***147***	***19,218***		
Mean days (±SD)	200.9±222.1	204.3±200.4	310.8±335.9‡	0.902	0.000
Median days (IQR)	115 (98-244)	146 (95-229)	199 (114-370)	-	-
Initial therapy,					
Unfractionated heparin	5 (5.0%)	9 (6.1%)	983 (5.1%)	0.80 (0.26-2.46)	0.97 (0.39-2.38)
Low-molecular-weight heparin	79 (78%)	117 (80%)	16,430 (85%)*	0.92 (0.50-1.71)	0.61 (0.38-0.98)
Mean LMWH dose (IU/kg/day)	173.1±34.1	176.8±46.8	174.8±41.5	0.546	0.713
DOACs	11 (11%)	12 (8.2%)	620 (3.2%)‡	1.38 (0.58-3.25)	3.67 (1.95-6.89)
Thrombolysis	2 (2.0%)	4 (2.7%)	341 (1.8%)	0.72 (0.13-4.02)	1.12 (0.27-4.55)
No anticoagulation	0	0	16 (0.08%)	-	1.000
Vena cava filter	1 (0.99%)	4 (2.7%)	284 (1.5%)	0.36 (0.04-3.25)	0.67 (0.09-4.80)
Duration: mean days (SD)	11.8±12.5	11.6±22.7	13.5±43.4	0.934	0.693
Duration: median days (IQR)	7 (5-15)	7 (4-14)	8 (5-11)	-	-
Long-term therapy*,					
VKAs	65 (64%)	96 (65%)	13,721 (71%)	0.96 (0.56-1.63)	0.72 (0.48-1.09)
LMWH	9 (8.9%)	22 (15%)	2,792 (15%)	0.56 (0.24-1.26)	0.58 (0.29-1.14)
DOACs	26 (26%)	22 (15%)*	2,208 (11%)‡	1.97 (1.04-3.72)	2.67 (1.71-4.18)
Duration: mean days (SD)	173.8±140	215.3±258.5	311.1±340.3‡	0.105	0.000
Duration: median days (IQR)	107 (89-233)	139 (92-221)	195 (111-367)	-	-

DOAC – Direct oral anticoagulant, LMWH – Low molecular weight heparin, VKA – Vitamin K antagonist

* Long-term therapy was defined as the later of the following: 1) After 10 days of the VTE; 2) After bridging between UFH or LMWH; 3) For DOAC, once loading was complete (e.g. 21 days for rivaroxaban). *p <0.05; ‡p <0.001.

Table 4: Outcomes in Patients Presenting with Post-Knee Arthroscopy and Unprovoked Venous Thromboembolism During Anticoagulation

	Arthroscopy		Fracture lower extremities		Unprovoked	
	N	Events per 100 patient-years	N	Events per 100 patient-years	N	Events per 100 patient-years
Patients, N	***101***		***147***		***19,218***	
Duration of follow-up						
Mean days (±SD)	201±222		204±200		311±336‡	
Median days (IQR)	115 (98-244)		146 (95-229)		199 (114-370)‡	
Recurrent DVT	1	1.97 (0.10-9.73)	2	2.46 (0.41-8.11)	218	1.35 (1.18-1.54)
Recurrent PE	0	-	2	2.47 (0.41-8.15)	160	0.99 (0.84-1.15)
Recurrent VTE	1	1.97 (0.10-9.73)	4	4.98 (1.58-12.0)	373	2.33 (2.11-2.58)
Major bleeding	0	-	3	3.65 (0.93-9.94)	374	2.31 (2.09-2.56)
Non-major bleeding	4	7.50 (2.38-18.1)	1	1.23 (0.06-6.06)	660	4.14 (3.84-4.47)
Death	0	-	6	7.30 (2.96-15.2)*	632	3.87 (3.57-4.18)
Fatal PE	0	-	0	-	49	0.30 (0.22-0.39)
Fatal bleeding	0	-	0	-	42	0.26 (0.19-0.34)

*p <0.05; ‡p <0.001.

Table 5: Outcomes in Patients Presenting with Post-Knee Arthroscopy and Unprovoked Venous Thromboembolism After Anticoagulation Discontinuation

	Arthroscopy		Fracture lower extremities		Unprovoked	
	N	Events per 100 patient-years	N	Events per 100 patient-years	N	Events per 100 patient-years
Patients, N	***56***		***61***		***6,410***	
Duration of follow-up,						
Mean days (±SD)	451±508		348±463		321±383	
Median days (IQR)	231 (95-694)		136 (59-359)		178 (57-438)	

Recurrent DVT	2	2.89 (0.49-9.56)	3	5.17 (1.31-14.1)	330	5.91 (5.29-6.57)
Recurrent PE	2	3.09 (0.52-10.2)	0	-	327	5.87 (5.26-6.53)
Recurrent VTE	4	6.18 (1.96-14.9)	3	5.17 (1.31-14.1)	657	11.9 (11.0-12.8)
Major bleeding	0	-	0	-	37	0.66 (0.47-0.90)
Non-major bleeding	0	-	0	-	44	0.79 (0.58-1.04)
Death	0	-	2	3.44 (0.58-11.4)	256	4.55 (4.02-5.13)
Fatal PE	0	-	0	-	4	0.07 (0.02-0.17)
Fatal bleeding	0	-	0	-	17	0.30 (0.18-0.47)

Compliance with Ethical Standards:

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Conflict of interest:

IW serves on the Scientific Advisory Board, Novate Medical. JG serves on the Board of Directors for PERT Consortium, a 501c3 not-for-profit organization. RK serves on the Board of Directors for VIVA Physicians Inc, a 501c3 not-for-profit organization. He is a paid consultant or serves on the Advisory Board for Medtronic, Philips/ Volcano, BTG, Janssen, Vesper Medical, Innovein, Spectranetics, Inari, Boston Scientific. He has received research support from BTG. JIA declares no conflicts of interests. CF declares no conflicts of interests. SS declares no conflicts of interests. AB declares no conflicts of interests. JB declares no conflicts of interests. JGG declares no conflicts of interests. MM declares no conflicts of interests.

Participating centers have local Institutional Review Board approval with patients providing informed consent for registry enrollment.

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