EPIDEMIOLOGY OF VENOUS THROMBOEMBOLISM AFTER LOWER LIMB ARTHROPLASTY : THE FOTO STUDY

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Abbreviated title : Venous thromboembolism in orthopedic surgery

Summary statement : The epidemiological FOTO study confirms that incidence of symptomatic venous thromboembolism after lower limb arthroplasty is low.

[1]Committees and Investigators participating in the FOTO (Enquête Française Observationelle sur l'incidence à 3 mois des événements ThrombO-emboliques veineux symptomatiques chez des patients opérés d'une prothèse totale de hanche ou de genou) Study participants are listed in the Appendix.

ABSTRACT

Background: In view of recent substantial changes in the management of orthopedic surgery patients, a study was performed to update data on epidemiology of venous thromboembolism in patients undergoing lower limb arthroplasty according to contemporary practice.

Methods: We performed a prospective observational study of a cohort of consecutive patients hospitalized for total hip or knee replacement in June 2003. The primary study outcome was the incidence of symptomatic venous thromboembolism at three months. All events were adjudicated by an independent critical event committee.

Results: The data of 1080 patients (mean age: 68.0 years) were available, 63.2% undergoing total hip replacement and 36.8% total knee replacement. Pharmacological thromboprophylaxis was administered for a mean of 36 days and used injectable antithrombotics in more than 99% of patients, irrespective of the type of surgery. The incidence of the primary study outcome was 1.8% (20 events; 95% confidence interval: 1.0 to 2.6%). The incidences were 1.3% and 2.8% in hip and knee surgery patients, respectively. There were two pulmonary embolisms, both in knee surgery patients, none fatal. Thirty-five percent of venous thromboembolism occurred after hospital discharge. Age of at least 75 years and absence of ambulation before hospital discharge were the only significant ($p<0.05$) predictors of venous thromboembolism. The rate of clinically significant bleeding was 1.0% and that of death was 0.9%.

Conclusions: The incidence of symptomatic venous thromboembolism after lower limb arthroplasty is low, even if there is still a need to improve thromboprophylaxis, notably in patients undergoing knee arthroplasty. (247 words)

INTRODUCTION

Life-threatening in the short term and leading to a high level of morbidity in the long term, venous thromboembolism is the most feared complication following lower limb arthroplasty.[1] It was also the most common cause of emergency readmission after these surgical procedures.[2] Within the last decade, the management of orthopedic patients has undergone substantial changes aimed at preventing the occurrence of venous thromboembolism.[3] For example, following the results of a number of clinical trials showing that extending thromboprophylaxis from one week to four to six weeks after surgery reduced the incidence of late episodes of symptomatic venous thromboembolism,[4-8] extended-duration prophylaxis is increasingly given to patients operated on for lower limb arthroplasty.[9] However, these data, obtained in randomized clinical trials in selected patients, may not reflect routine practice. Furthermore, available epidemiological studies on the incidence of symptomatic venous thromboembolism after lower limb arthroplasty were performed before the routine use of extended-duration thromboprophylaxis.[9-18] In the most recently published large epidemiological study in this setting, only 50% patients undergoing total hip or knee arthroplasty received extended-duration thromboprophylaxis.[9] Recent advances in surgical and anesthetic techniques such as more frequent use of regional anesthesia techniques,[9] may also explain changes in the epidemiology of venous thromboembolism after lower limb arthroplasty. The observational prospective FOTO study was performed to update the epidemiological data on venous thromboembolism complications following elective primary total hip or knee arthroplasty in patients managed according to contemporary practice.

MATERIALS AND METHODS

The FOTO study was a national, multicenter, observational, prospective study of a cohort of consecutive patients undergoing surgery for total hip or knee replacement.

Patients

Consecutive patients aged at least 18 years, hospitalized in public or private hospitals for total hip or knee replacement, and giving their informed consent were recruited. Patients operated on for revision hip or knee arthroplasty as well as patients operated on for hip arthroplasty following hip fracture were excluded. All medical or surgical procedures were performed by each centre according to its usual practice. As this prospective survey did not impact on the daily clinical practice, no ethical review board approval was requested. However, the study was conducted in accordance with the ethical principles stated in the Declaration of Helsinki.

Study Design

The main demographic, medical and surgery data of the patients were recorded during hospitalization. All centers reporting critical events were monitored by a clinical research assistant who reviewed the data entry in the study book and collected source documents. In addition, monitoring visits were performed in 10% of the centers which did not report critical events. At three months, patients were asked to complete and return the standardized datasheet on their health status. When this was not done, the investigator attempted to contact, by telephone, either the

practitioners who had managed the patient or the patient directly; if this was unsuccessful, the final point of contact was the Death Registry of the town hall.

Before entering the study, all participating patients were informed of its aim and modalities, and requested to refer immediately to the local investigator in the case of onset of any symptoms or sign suggestive of VTE or bleeding.

Study Outcomes

The primary study outcome was the incidence of confirmed symptomatic venous thromboembolism (VTE) defined as deep-vein thrombosis, fatal or non-fatal pulmonary embolism, or both at three months. Other study outcomes were overall mortality at three months, and the occurrence of any clinically significant bleeding or rehospitalization within the three months after surgical procedure.

Deep-vein thrombosis was confirmed by ultrasonography,[19] or venography. Pulmonary embolism was confirmed by high-probability lung scanning,[20] pulmonary angiography, or helical computerized tomography.[21] All VTE episodes were further reviewed by an independent Critical Event Committee to check the quality of the data and therefore to confirm the true incidence of VTE. Clinically significant bleeding was defined as fatal bleeding, bleeding in a critical organ (intraocular, intracranial, pericardial, retroperitoneal, intraspinal or in adrenal glands), bleeding at the surgical site leading to reoperation, or bleeding leading to blood transfusion. All these events were also adjudicated by the Critical Event Committee.

Statistical Analysis

Assuming a 2.5% incidence of symptomatic venous thromboembolism,[4,8,18,22] it was calculated that 1911 patients were needed to achieve the limits of a 95% two-

sided confidence interval at ± 0.7%. Taking into account that a number of patients would not be evaluable, the recruitment target was 2000 patients.

In France, according to the French Program of Medicalisation of Information Systems (Programme de Médicalisation des Systèmes d'Information, PMSI), the number of orthopedic centers performing hip or knee arthroplasty is approximately 1000. In order to have a short recruitment period, only centers performing at least 10 total hip or knee replacements per month were contacted, i.e. 400 centers. On the basis of previous comparable studies, it was assumed that 200 of these centers would agree to participate to the protocol. To recruit 2000 patients, it was therefore calculated that the recruitment period would be three weeks. The recruitment was competitive between centers. Overall, 151 centers volunteered to take part in the study.

We calculated the incidence and associated 95% confidence interval for the various outcomes. We analyzed risk factors for symptomatic venous thromboembolism by univariate analysis, with determination of odds ratios and corresponding 95% confidence intervals.

P value <0.05 was considered as statistically significant. Data were processed and analyzed by the SAS-Windows™ software (version 8.2).

RESULTS

Patients

Overall, 1810 patients were enrolled in 151 centers within 17 days in June 2003. The data were incomplete in 13 patients and inclusion/exclusion criteria were not met in 27 patients. In addition, systematic screening for venous thrombosis at hospital discharge was performed by ultrasonography in 664 patients; data on this practice were missing in 26 patients. As this procedure may lead to an overestimation of the frequency of symptomatic venous thromboembolism,[7] these patients were excluded from the analysis, leaving 1080 (61.0%) patients recruited in 105 centers (68 private hospitals and 37 public hospitals, Appendix). No one of these 1080 patients belonged to centers in which a systematic ultrasound assessment was performed before hospital discharge. Seven of these patients were lost to follow-up at three months.

The mean age of the population was 68.0 years, with 33.3% (358/1074) being at least 75 years (Table 1). There were more women (56.3%) than men. The most frequent risk factors for venous thromboembolism were varicose veins in 34.4% of patients and obesity in 28.6% of patients. Moderate or severe renal impairment was found in 6.8% of patients.

The majority (63.2%) of patients underwent surgery for total hip replacement. Surgery was performed for osteoarthritis in 94.7% (1013/1070) of patients. Knee surgery patients were on average five years older than hip surgery patients; the women/men ratio and the percentage of obese patients were also higher in knee surgery patients.

Surgery

Operations were conducted under ‘regional anesthesia only’ in 31.0% (327/1056) of patients; this rate was higher in knee surgery than in hip surgery patients (Table 2). Surgery was less than two hours in 85.5% (887/1038) of patients. Eighty-one percent of patients began weight bearing within 48 hours after surgery, and 97.4% began walking during hospitalization. Mean time (±SD) to start of ambulation after surgery was 2.9±1.6 days. Patients were discharged after a mean period of 10.6 days.

Thromboprophylaxis and concomitant treatments

Pharmacological thromboprophylaxis was almost exclusively performed using injectable antithrombotics (Table 3). They were initiated pre-operatively in 25.7% of patients. The dose was administered according to labeling in 90.8% (973/1071) of patients; the administered dose was above the approved dosage regimen in 5.7% (61/1071) of patients. The mean duration of administration of thromboprophylactic drugs was 36.1 ± 9.8 days, with 95.3 % receiving the treatment for more than 21 days. Graduated compression stockings were worn by 59.1%. The above data did not differ substantially by type of surgery.

Clinical events

The rate of the composite of adjudicated confirmed symptomatic venous thromboembolism during the three month study period was 1.8% (20 events, 95% confidence interval: 1.0 to 2.6; Table 4). Figure 1 shows the time to occurrence of each venous thromboembolic event according to the type of surgery. Thirty-five percent (7/20) of these events occurred after hospital discharge. The overall rate was

1.3% in patients undergoing total hip replacement and 2.8% in patients undergoing total knee replacement.

Among 74 suspected venous thromboses, 20 (27.0%) were validated by the adjudication committee. There were 18 (1.7%) deep-vein thromboses, four of which were proximal: 2 (0.3%) occurred in patients undergoing total hip replacement and 2 (0.5%) in patients undergoing total knee replacement. Seven (38.9%) deep-vein thromboses occurred after hospital discharge with three events after hip surgery and four events after knee surgery.

Two of nine (22.2%) suspected pulmonary embolisms were validated by the adjudication committee, giving an incidence of 0.2%. Both pulmonary embolisms occurred in patients undergoing total knee replacement, two and three days after surgery, respectively. Neither was fatal.

In patients suspected of having venous thromboembolism, a curative treatment for venous thromboembolism was given by local investigators to 26 patients, giving an overall rate of 2.4%. The rate was 2.1% (14/679) in patients operated on for total hip replacement and 3.0% (12/396) in patients operated on for total knee replacement.

A total of 11 (1.0%) clinically significant bleedings were reported, including one fatal bleeding after total hip replacement and five bleedings leading to re-intervention. No bleeding was in a critical organ. Sixty-four percent (7/11) of these episodes were observed before hospital discharge. None of these clinically significant bleedings occurred in patients with moderate or severe renal impairment. Rehospitalization concerned 60 (5.6%) patients. Two re-hospitalizations were for suspicion of venous thromboembolism and two for wound hematoma. The rates of clinically significant bleeding and of rehospitalization were similar regardless of the type of surgery.

Death was reported in 10 (0.9%) patients, five after total hip replacement and five after total knee replacement. Death was sudden in three patients but none of the seven documented deaths were related to venous thromboembolism events. Three (30%) deaths occurred after hospital discharge, one in hip surgery and two in knee surgery patients.

The results, with regard to VTE, major bleeding and death, of the 664 patients who were excluded from the study main analysis because they underwent a systematic ultrasonography screening for venous thrombosis at hospital discharge are presented in table 5. Mainly distal and muscular asymptomatic DVTs were recorded. A major bias could be suggested: most of the asymptomatic patients turned into symptomatic patients as soon as the diagnosis of DVT was performed. The same type of argument accounts for the non-fatal PE rate. These results have prompted the editorial board of the study to only focus on the results of the 1080 remaining non-screened patients.

Risk factors for symptomatic venous thromboembolism

On univariate analysis, age of at least 75 years and absence of ambulation before hospital discharge were the only significant ($p<0.05$) predictors of symptomatic venous thromboembolism at three months (Table 6). Multivariate analysis was not performed because there were only 11 events and 2 significant variables by univariate analysis.

DISCUSSION

The FOTO study was a large, multicenter, observational, prospective study on the incidence of venous thromboembolic complications in patients undergoing lower limb arthroplasty according to contemporary practice. Compared with rates of symptomatic venous thromboembolism after total hip or knee replacement in previous epidemiologic studies, 1.1% to 10.6%,[9,11,13,15-18] the 1.8% (95% confidence interval: 1.0-2.6) rate observed in FOTO is one of the lowest. Likewise, the rates of symptomatic pulmonary embolism ranged between 0.4% to 1.5% in earlier studies,[9,11,12,15,16,23] compared with 0.2% (95% confidence interval: 0-0.5) in the present study. Moreover, none of the pulmonary embolisms observed in FOTO was fatal.

There are several possible explanations for the lower incidence of venous thromboembolism observed in FOTO. First, an important difference between the present study and earlier epidemiological studies is that pharmacological thromboprophylaxis was administered for a mean duration of 36 days with 95.3 % of patients receiving the treatment for more than 21 days. This is in agreement with a recent epidemiological study which, following results from a number of clinical trials,[4-8] showed that the percentage of patients benefiting from extended-duration thromboprophylaxis was increasing.[9] In the United States, fewer than one third of patients undergoing total hip or knee arthroplasty received extended prophylaxis between 1991 and 1993;[16] this rate was around 50% between 1996 and 2002.[9] In view of the fact that the value of extended-duration thromboprophylaxis, unequivocal in hip arthroplasty, is less certain in knee arthroplasty[4], it is interesting that the duration of thromboprophylaxis was similar in both types of surgery. A similar practice was also found among US surgeons.[9]

Pharmacological thromboprophylaxis was almost exclusively performed using injectable antithrombotics. The protocol did not seek more specific information concerning the therapy used, though it may be assumed, on the basis of French practice, that it was mostly low-molecular-weight heparins. In contrast, in the United States, vitamin K antagonists are still the main anticoagulant prescribed in this setting.[9] However, in a recent meta-analysis of thromboprophylaxis trials in patients undergoing major orthopedic surgery, low-molecular-weight heparins were more effective than vitamin K antagonists.[24]

Another reason that may account for the lower incidence of venous thromboembolism in FOTO compared with previous studies concern the overall management of patients. For instance, a high percentage of patients had early ambulation, a factor we showed, as others[25], to protect against venous thromboembolism.

Comparisons with previous epidemiological studies indicate that advances in the reduction in venous thromboembolism concerned more hip than knee replacement patients. While, in earlier comparative studies, the rate of venous thromboembolism was higher after total hip replacement (2.4-2.8%) than after total knee replacement (1.7-2.1%),[16,18] in FOTO, the incidence of these events was lower after total hip replacement (1.3%) than after total knee replacement (2.8%). Also, all pulmonary embolisms were observed in knee surgery patients. These differences cannot be due to a difference in thromboprophylaxis regimens, similar in type and duration of administration in the two surgical procedures. We believe that the positive data obtained in hip replacement patients result from the widespread use of extended-duration thromboprophylaxis, since the percentage of post-discharge venous thromboembolism was markedly reduced in FOTO patients as compared with

previous studies in which extended-duration thromboprophylaxis was not routinely performed; specifically, the percentage, which varied between 64 and 76% in earlier studies,[11,16] was 33% in FOTO. In contrast, in knee surgery patients, in whom the value of extended-duration thromboprophylaxis has not yet been clearly demonstrated,[4] the rate of out-of-hospital thromboembolic events has not changed over time, being 47% in an earlier study [16] and 44% in the present study. This difference between hip and knee surgery might be explained by specific characteristics of knee surgery with use of tourniquet and extensive disruption of soft tissue and bone leading to extensive local release of prothrombotic tissue factor.[4] More effective but at least as safe antithrombotic therapies are therefore needed for preventing in-hospital venous thromboembolism episodes, especially in knee joint replacement surgery.

The 1.0% bleeding rate in FOTO appears to be low, confirming data of clinical trials showing that extended-duration thromboprophylaxis did not result in an excess of major bleeding[8]. However, the risk of bleeding cannot be considered to be negligible, since bleeding resulted in the death of one patient and led to surgical reintervention in five patients. This highlights a key issue in orthopedic surgery: improvements in efficacy of new antithrombotic drugs in terms of thrombosis prevention must not be at the cost of a greater bleeding risk.

We believe that our findings are valid and reflect clinical practice in 2003. All data were collected prospectively from patients enrolled over a short period, limiting the risk of recruitment bias. Unlike clinical trials, there were no exclusion criteria. However, the study was limited to orthopedic centers performing ten or more lower limb arthroplasties per month, so the applicability of the results to centers with lower volume is unknown. Yet, FOTO did not concern only large teaching University

hospitals, but also private institutions, which eventually made up 64.8 % of the participating centers. The number of recruited patients was approximately half the number predefined in the statistical analysis, but was nevertheless large. This was due to the fact that we did not analyze patients having a screening test for deep-vein thrombosis at hospital discharge. Indeed, due to the frequency of non-specific lower extremity symptoms after lower limb orthopedic surgery, the local investigator could have been led to label a number of venous thromboembolic events *a posteriori* as symptomatic, resulting in an overestimation of the actual rate of symptomatic venous thromboembolism.[7] The 90-day duration of follow-up was chosen to include all events likely to be related to the operation. Importantly, the follow-up of analyzed patients was almost 100%. Clinically relevant symptomatic events were objectively documented and adjudicated by a central committee, as always performed in large phase 3 and 4 clinical studies.

In conclusion, extended-duration thromboprophylaxis with injectable antithrombotics was routinely performed in patients undergoing hip or knee arthroplasty in France in 2003. This therapeutic approach was responsible for a relatively low incidence of symptomatic venous thromboembolism, especially in patients undergoing total hip replacement, even if there is still a need for improving the prevention of symptomatic venous thromboembolism events in patients undergoing total knee surgery, without compromising bleeding safety.

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Table 1. Patient characteristics

Characteristics	Any arthroplasty N=1080	Total hip replacement N=679	Total knee replacement N=396
Male/Female, n/N (%)	469/604	318/356	149/245
Age (yr), mean ± SD	68.0 ± 11.6	66.1 ± 12.6	71.3 ± 8.7
Body weight (kg), mean ± SD	76.1 ± 15.8	74.2 ± 15.7	79.3 ± 15.4
Body mass index (kg/m^2), mean ± SD	27.7 ± 5.1	26.8 ± 4.6	29.3 ± 5.4
Body mass index >30 kg/m^2, n/N (%)	295/1032 (28.6)	150/664 (22.6)	143/387 (37.0)
Thromboembolic risk factors			
History of deep-vein thrombosis, n/N (%)	98/1075 (9.1)	49/679 (7.2)	49/396 (12.4)
History of pulmonary embolism, n/N (%)	32/1072 (3.0)	21/679 (3.1)	11/396 (2.8)
Post-thrombotic syndrome, n/N (%)	20/1070 (1.9)	11/679 (1.6)	9/396 (2.3)
Varicose veins, n/N (%)	368/1069 (34.4)	210/679 (30.9)	157/396 (39.6)
Currently active cancer, n/N (%)	20/1072 (1.9)	14/679 (2.1)	6/396 (1.5)
Myeloproliferative disorder, n/N (%)	4/1071 (0.4)	1/679 (0.2)	3/396 (0.8)
Paralysis of lower limbs, n/N (%)	1/1071 (0.1)	0/679 (0)	1/396 (0.3)
Hormonal therapy, n/N (%)	44/1068 (4.1)	32/679 (4.7)	12/396 (3.0)
Cardiac disease at risk of thromboembolism, n/N (%)	113/1077 (10.5)	69/678 (10.2)	44/394 (11.2)
Coronary or peripheral artery disease, n/N (%)	150/1075 (14.0)	82/677 (12.1)	67/393 (17.0)
Creatinine clearance [30-50] mL/min, n/N (%)*	54/935 (5.8)	37/596 (6.2)	17/335 (5.1)
Creatinine clearance <30 mL/min, n/N (%)*	10/935 (1.1)	6/596 (1.0)	4/335 (1.2)

*Creatinine clearance was calculated using the Cockcroft formula

Table 2. Surgery characteristics

Characteristics	Any arthroplasty	Total hip replacement	Total knee replacement
	N=1080	N=679	N=396
Type of anesthesia			
- General anesthesia only, n/N (%)	511/1056 (48.4)	399/665 (60.0)	111/390 (28.5)
- General + regional anesthesia, n/N (%)	218/1056 (20.6)	98/665 (14.7)	120/390 (30.8)
- Neuraxial anesthesia only, n/N (%)	265/1056 (25.0)	155/665 (23.3)	110/390 (28.2)
- Peripheral nerve block only, n/N (%)	3/1056 (0.3)	0/665	3/390 (0.8)
- Neuraxial anesthesia+ peripheral nerve block, n/N (%)	59/1056 (5.6)	13/665 (2.0)	46/390 (11.8)
Weight bearing ≤48 hours following surgery, n/N (%)	860/1062 (81.0)	545/669 (81.5)	314/392 (80.1)
Ambulation before hospital discharge, n/N (%)	1025/1052 (97.4)	642/661 (97.1)	382/390 (97.9)
Duration of hospital stay (days), mean ± SD	10.6 ± 6.5	10.2 ± 4.4	11.4 ± 9.0

Table 3. Characteristics of treatment

Treatment	Any arthroplasty N=1080	Total hip replacement N=679	Total knee replacement N=396
Pre-operative initiation of thromboprophylaxis, n/N (%)	277/1076 (25.7)	182/679 (26.8)	95/396 (24.0)
Type of pharmacological thromboprophylaxis*			
- Injectable antithrombotic, n/N (%)	1075/1076 (99.9)	679/679 (100)	395/396 (99.7)
- Vitamin K antagonist, n/N (%)	24/831 (2.9)	19/534 (3.6)	5/289 (1.7)
- Aspirin or other antiplatelet agent, n/N (%)	12/810 (1.5)	7/521 (1.3)	5/289 (1.7)
Duration of pharmacological thromboprophylaxis (days), mean ± SD	36.1 ± 9.8	36.4 ± 9.6	35.6 ± 9.9
Duration of pharmacological thromboprophylaxis			
- < 8 days, n/N (%)	6/1017 (0.6)	2/639 (0.3)	4/377 (1.1)
- 8 – 21 days, n/N (%)	42/1017 (4.1)	20/639 (3.1)	21/377 (5.6)
- >21 days, n/N (%)	969/1017 (95.3)	617/639 (96.6)	352/377 (93.4)
Graduated compression stockings, n/N (%)	635/1074 (59.1)	388/675 (57.5)	243/394 (61.7)
Nonsteroidal anti-inflammatory agents after surgery, n/N (%)	609/1061 (57.4)	375/669 (56.1)	229/387 (59.2)

*The total number of patients is higher than 1080 because some patients were receiving different types of thromboprophylactic agent concurrently

Table 4. Adjudicated rate of events

Events	Any arthroplasty N=1080			Total hip replacement surgery N=679	Total knee replacement surgery N=396
	Whole study period, n (%) [95% confidence interval]	Before hospital discharge, n	After hospital discharge, n	Whole study period, n (%)	Whole study period, n (%)
Symptomatic venous thromboembolism (primary outcome)	20 (1.8) [1.0-2.6]	13	7	9 (1.3)	11 (2.8)
Symptomatic deep-vein thrombosis	18 (1.7) [0.9-2.5]	11	7	9 (1.3)	9 (2.3)
Proximal*	4	2	2	2	2
Distal*	6	5	1	3	3
Muscular*	11	6	5	5	6
Symptomatic pulmonary embolism**	2 (0.2) [0.0-0.5]	2	0	0	2 (0.5)
Clinically significant bleeding	11 (1.0) [0.4-1.6]	7	4	7 (1.0)	4 (1.0)
Death	10 (0.9) [0.4-1.5]	7	3	5 (0.7)	5 (1.3)
Re-hospitalization	60 (5.6) [4.2-6.9]	-	-	36 (5.3)	24 (6.1)

*One patient may have more than one site
**None of the pulmonary embolisms was fatal

Table 5. Adjudicated rate of events in patients with systematic ultrasonography screening for venous thrombosis at hospital discharge

Events	Any arthroplasty		
	N=664		
	Whole study period, n (%) [95% confidence interval]	Before hospital discharge, n	After hospital discharge, n
Symptomatic venous thromboembolism	35 (5.3%) [3.6-7.0]	28	7
Asymptomatic deep-vein thrombosis	32 (4.8%) [3.3-6.4]	28	4
Proximal*	2	2	0
Distal*	18	17	1
Muscular*	16	14	2
Symptomatic pulmonary embolism**	7 (1.1%) [0.3-1.9]	5	2
Clinically significant bleeding	11 (1.7%) [0.7-2.7]	1	10
Death	0 (0%) [0.0-0.0]	0	0
Re-hospitalization	25 (3.8%) [2.3-5.3]	-	25

*One patient may have more than one site
**None of the pulmonary embolisms was fatal

Table 6. Univariate analyses of significant risk factors for symptomatic venous thromboembolism (primary outcome)

Potential predictive factors for symptomatic venous thromboembolism	Odds Ratio	95% Confidence Interval	p
Sex: female *versus* male	3.5	0.8 – 16.4	0.13
Age: ≥75 years *versus* <75 years	3.6	1.0 – 12.2	**0.049**
Body mass index: [25-30] kg/m^2 *versus* <25 kg/m^2	1.2	0.2 – 7.1	1.00
Body mass index: >30 kg/m^2 *versus* <25 kg/m^2	3.5	0.7 – 16.7	0.16
History of deep-vein thrombosis: yes *versus* no	2.2	0.5 – 10.5	0.27
Varicose veins: yes *versus* no	0.7	0.2 – 2.7	0.76
Type of surgery: TKR *versus* THR	2.1	0.6 – 6.8	0.23
General anesthesia: yes *versus* no	0.8	0.2 – 2.7	0.75
Weight bearing after surgery: ≤48 hours *versus* >48 hours	0.4	0.1 – 1.4	0.24
Ambulation before hospital discharge: yes *versus* no	0.1	0.0 – 0.5	**0.03**
Pre-operative initiation of pharmacological thromboprophylaxis: yes *versus* no	1.4	0.4 – 5.8	0.70

APPENDIX

The members of the FOTO (Enquête Française Observationelle sur l'incidence à 3 mois des événements ThrombO-emboliques veineux symptomatiques chez des patients opérés d'une prothèse totale de hanche ou de genou) Study Group were: **Steering Committee:** J. Barré, P.Mismetti, P. Ravaud, C. M. Samama. **Critical Event Committee:** J. Barré, P. Mertl, F. Parent. **Data Monitoring and Statistical Analysis:** Sanofi-Synthelabo (France). **Participating centers:**

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