Timing and characteristics of venous thromboembolism after noncancer surgery

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ABSTRACT

Background: Venous thromboembolism (VTE) is a major cause of morbidity and mortality postoperatively. The use of pharmacologic prophylaxis is effective in reducing the incidence of VTE. However, the prophylaxis is often discontinued at hospital discharge, especially for those with benign disease. The implications of this practice are not known. We assessed the data from a large, ongoing registry regarding the time course of VTE and outcomes after noncancer surgery.

Methods: We analyzed the RIETE (Computerized Registry on Venous Thromboembolism) registry, which includes data from consecutive patients with symptomatic confirmed VTE. In the present study, we focused on general surgical patients who had developed symptomatic postoperative VTE in the first 8 weeks after noncancer surgery. The main objective was to assess the interval between surgery and the occurrence of VTE. Additional variables included the clinical presentation associated with the event, the use of thrombosis prophylaxis, and unfavorable outcomes.

Results: The data from 3296 patients were analyzed. The median time from surgery to the detection of VTE was 16 days (interquartile range, 8-30 days). Of the VTE events, 77% were detected after the first postoperative week and 27% after 4 weeks. Overall, 43.9% of the patients with VTE had received pharmacologic prophylaxis after surgery for a median of 8 days (interquartile range, 5-14 days), and three quarters of the VTE events were detected after pharmacologic prophylaxis had been discontinued. Overall, 54% of the patients with VTE had presented with pulmonary embolism. For 15% of the patients, the clinical outcome was unfavorable, including 4% who had died within 90 days.

Conclusions: The risk of VTE after noncancer general surgery remains high for ≤2 months. More than one half of the patients had presented with symptomatic PE as the VTE event, and 15% had had unfavorable outcomes. Only 44% of these patients had received pharmacologic prophylaxis for around 1 week. (J Vasc Surg Venous Lymphat Disord 2021;9:859-67.)

Keywords: Deep vein thrombosis; Duration of risk; Pulmonary embolism; Surgery; Thromboprophylaxis

Venous thromboembolism (VTE) is a common and potentially serious postoperative complication, especially after major orthopedic or oncologic surgery. The incidence of symptomatic VTE in the first postoperative month has been ~2% for patients treated for abdominal or pelvic cancer or after bariatric surgery but has not been adequately documented for patients without cancer.[1,2] The risk of postoperative VTE depends on intrinsic factors related to patient characteristics and extrinsic factors related to the surgical procedure and its duration, perioperative immobilization, and the appearance of postoperative complications.[3,4]

For many years, the risk of VTE was assumed to be limited to the period of hospitalization or until the patient had resumed full ambulation. However, recent studies have shown that the thrombotic risk remains high for ≥3 months during the postoperative period.[3-5] One study reported that for patients who had presented with symptomatic VTE after surgery for abdominal

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*A full list of the RIETE (Computerized Registry on Venous Thromboembolism) Investigators is provided in the Appendix (online only).

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cancer, the mean interval between surgery and the detection of VTE was 24 days.[6]

In the past 30 years, numerous clinical trials have shown that prophylactic methods, especially those based on low-dose anticoagulant agents administered during hospital admission, decrease the incidence of postoperative VTE.[7,8] Later, several studies reported that prolonging pharmacologic prophylaxis for 4 weeks was more effective and as safe as the currently recommended period of 7 to 10 days after abdominal cancer surgery.[9-11] Therefore, recent VTE prevention guidelines have recommended extending pharmacologic prophylaxis to 4 weeks in patients undergoing abdominal and pelvic oncologic surgery and for those at "especially high risk," although no general agreement has been reached regarding the definition of the latter term.[12-14]

Regarding surgery for benign diseases, few studies have analyzed the time course of postoperative VTE, and the optimal duration of prophylaxis for these patients has not been adequately addressed in most recent guidelines. Thus, thromboprophylaxis has been restricted to hospitalization or, at most, 7 to 10 days.[15] Increasingly, patients have been discharged within the first postoperative week. In addition, multimodal action protocols have also been associated with progressively reduced hospital stays (ie, 3-5 days after major surgery).[16,17] Thus, if prophylaxis is limited to hospital admission and discontinued at discharge, many patients at high risk of VTE will not be sufficiently protected.

The RIETE (Computerized Registry of Thromboembolic Disease) records the clinical data for consecutive patients with confirmed symptomatic VTE. Analysis of the RIETE data enables researchers to determine the natural history and clinical presentation of VTE.

The main aim of the present study was to determine the duration of the risk of symptomatic postoperative VTE for noncancer general surgery patients. We also considered the form of presentation and evolution of this condition during the 3 months after its detection and treatment.

METHODS

An analysis was performed of the data from consecutive patients with symptomatic deep vein thrombosis (DVT) or pulmonary embolism (PE) detected within the first 2 months after noncancer general surgery. DVT included distal and proximal thrombi confirmed by objective diagnosis (contrast venography or ultrasonography for DVT; pulmonary angiography, ventilation/perfusion lung scintigraphy, or computed tomography angiography for PE). The present study included patients enrolled in the RIETE registry, a prospective international registry that was started in 2001 and remains active currently with participation of 245 hospitals in 18 countries. The RIETE database includes consecutive patients who experienced a symptomatic episode of VTE (ClinicalTrials.gov identifier, NCT02832245).

ARTICLE HIGHLIGHTS

- **Type of Research:** An analysis of data from RIETE (Computerized Registry on Venous Thromboembolism), an ongoing, international, multicenter, and prospective registry of consecutive venous thromboembolism (VTE) cases
- **Key Findings:** After nononcologic general surgery, the median time to the development of VTE was 16 days, with 77% of events presenting after 1 week and 25% after 30 days. Less than one half of the patients had received prophylaxis for a median of 8 days, and two thirds of VTE events had occurred after its discontinuation.
- **Take Home Message:** The risk of VTE persisted for longer than expected after nononcologic surgery. One half of these patients with VTE had presented with symptomatic pulmonary embolism, and 15% had had unfavorable outcomes.

Because it is an observational registry, the patients are treated according to the usual clinical practice at each hospital. The data recorded include the patient characteristics, initial presentation of VTE and its diagnosis, and the use of pharmacologic prophylaxis, including the dosage and duration. A prospective follow-up protocol for ≥3 months is performed. A description of RIETE and its methods have been previously reported.[18]

The present study included only general surgery patients who had experienced symptomatic VTE within the first 8 weeks after noncancer surgery. Patients participating in a clinical trial when VTE had first presented, those for whom the follow-up period of ≥3 months was not completed, those who had undergone orthopedic or trauma fracture surgery, and those with active cancer or ongoing oncologic treatment were excluded. All the patients included in the study had provided written and oral consent to participate. The Clinical Research Ethics Committee of the Germans Trias i Pujol University Hospital in Badalona and the Catalan Institute of Health approved the present project (approval no. 05122006).

Study variables. The main study variable was the time elapsed in days from the intervention until the diagnosis of VTE. Clinical events that had presented after 7 and 28 days of surgery were also considered.

For each patient, the data recorded included the clinical and epidemiologic characteristics, including age, sex, weight, height, and body mass index (BMI), the presence of major bleeding in the previous month, a history of heart disease, smoking, diabetes, high blood pressure, and statin treatment. Also considered were variables related to the intervention, such as the type of surgery, form of presentation (DVT or PE, or both), surgical approach (conventional vs minimally invasive, including

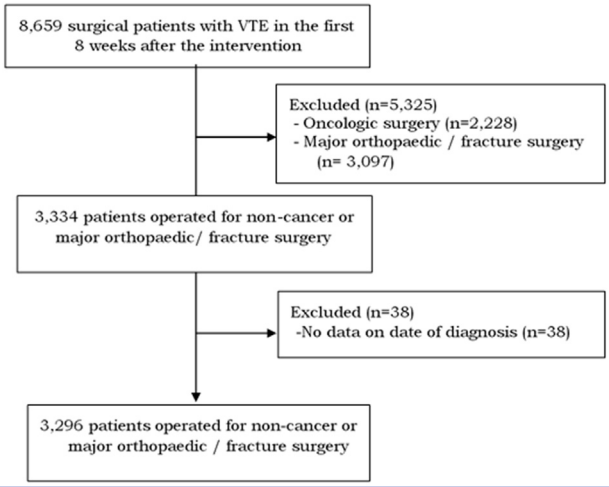


Fig 1. Flow diagram of patient selection. *VTE,* Venous thromboembolism.

endoscopic, laparoscopic, and endovascular procedures). The use of pharmacologic thromboprophylaxis, duration, and doses were recorded for all patients. The risk factors for VTE, including immobilization for ≥4 days for nonoperative reasons during the 2 months before the detection of VTE (before or after surgery), a history of VTE, a family history of VTE, hormonal treatment, varicose veins, childbirth in the previous 2 months before the detection of VTE or thrombophilia. We also tracked major bleeding, recurrent thrombosis after treatment (any type of confirmed VTE, including DVT in the lower or upper extremities, PE, superficial vein thrombosis, or other locations), and death during the first 3 postoperative months.

Statistical analysis. The numerical variables are presented as the mean ± standard deviation or median and interquartile range (IQR) for nonparametric data. The absolute and relative frequencies were calculated for the categorical variables. The normality of the distribution of the numeric variables was confirmed using the Kolmogorov-Smirnov test. The relationship between the numeric variables and the presentation time (dichotomized as before and after 7 or 28 days) was subjected to bivariate analysis, using the Student *t* test or Mann-Whitney *U* test for nonparametric data. The Pearson χ^2 test or the Fisher exact test was used for the qualitative variables. A multivariate multinomial logistic regression model was performed. The dependent variable considered was the time elapsed from surgery until the presentation of VTE, categorized as <7 days, 7 to 28 days, and >28 days. A univariate multinomial logistic regression analysis was performed for every predictor at a time. Those that were statistically significant were included in the multivariate model, and a backward stepwise selection method was used, with the maximum likelihood ratio test as the elimination method at each step. The odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were calculated for the final model. SPSS Statistics for Windows, version 19, software (IBM Corp, Armonk, NY) was used for all statistical analyses.

RESULTS

Study characteristics. From January 2001 to January 2019, the RIETE had recorded data for 8659 patients who had undergone surgery in the 2 months before the diagnosis of VTE. After excluding those with cancer and those who had undergone major orthopedic and fracture surgery, 3296 patients were included in the present study (Fig 1). The surgical interventions included 1084 gastrointestinal tract procedures (32.9%), 469 genitourinary procedures (14.2%), 423 neurosurgery procedures (12.8%), 251 venous surgery procedures (7.6%), 219 arterial procedures (6.6%), and 850 chest, neck, abdominal wall, or breast surgery procedures (25.8%). The median age was 60 years (IQR, 44-72 years), 52.9% were women, and 49.4% were overweight or obese (Table I). Of the 1376 patients for whom information was available, open surgical procedures were documented for 1089 patients (79%) and minimally invasive procedures for 276 patients (31%).

Interval to postoperative VTE detection. The median time elapsed from surgery to the detection of VTE was 16 days (IQR, 8-30 days). This interval was longer for patients who had undergone neurosurgery or

Table I. Patient characteristics (N = 3296)

Characteristic	Patients
Male sex	1551 (47.1)
Age, years	
Median	60
IQR	44-72
BMI, kg/m^2	
Median	27.14
IQR	24.3-30.7
Overweight/obesity (BMI ≥25 kg/m^2)	1628 (49.4)
Obesity (BMI ≥30 kg/m^2)	689 (20.9)
Major bleeding in previous month	252 (7.6)
Smoker	310 (9.4)
Diabetes	317 (9.6)
Hypertension	856 (26)
Immobilization	391 (11.9)
Personal history of DVT/PE	310 (9.4)
Family history of DVT	14 (0.4)
Childbirth in 2 months before VTE detection	201 (6.1)
Thrombophilia	92 (2.8)

BMI, Body mass index; *DVT,* deep vein thrombosis; *IQR,* interquartile range; *PE,* pulmonary embolism.
Data presented as number (%), unless noted otherwise.

cholecystectomy, for whom the median value was 20 days (IQR, 9-34 days) and 19 days (IQR, 6-39 days), and similar for those who had undergone surgery for intestinal perforation, arterial procedures, or liposuction. The operations associated with the earliest appearance of VTE were intestinal occlusion (median interval to VTE presentation, 12 days; IQR, 7.7-25.5 days), cesarean section (median interval to VTE presentation, 13 days; IQR, 6-21 days), and appendectomy (median interval to VTE presentation, 14 days; IQR, 7-24 days; Table II).

The interval from surgery to VTE was longer for the patients who had developed DVT (median, 19 days; IQR, 9-31 days) compared with those who had developed PE (median, 15 days; IQR, 7-28.25 days; $P < .001$). Most of the VTE events (77%) had been detected after the first postoperative week, followed by 55.5% after 2 weeks and 26.9% after 4 weeks (Fig 2).

Factors associated with extended VTE risk. The following factors were associated with the presentation of VTE at ≥7 days after surgery: male sex, older age, form of presentation (DVT or PE), type of surgery, presence of thrombophilia, and the use of VTE prophylaxis. The duration of prophylaxis was a median of 10 days for those whose VTE had appeared after the first week. The median time for prophylaxis was 5 days for those whose VTE had occurred during the first week (Table III).

The patients who had presented with VTE >4 weeks after surgery were mostly men, older, had received concomitant treatments, without recent major bleeding in the month before VTE, and were more likely to have diabetes or hypertension. In patients who had presented with VTE >28 days after surgery, 47.9% had received thromboprophylaxis compared with 42.5% of those who presented earlier ($P = .006$). The proportion of patients who had presented with VTE after 28 postoperative days was significantly greater for those with previous immobilization (Table III).

The multivariate analysis of factors associated with VTE developing 7 to 28 days after surgery identified male sex (OR, 1.28; 95% CI, 1.01-1.61) and type of surgery vs other forms of intervention: abdominal or genitourinary surgery (OR, 1.57; 95% CI, 1.20-2.05), neurosurgical intervention (OR, 1.90; 95% CI, 1.27-2.84), and vascular surgery (OR, 2.03; 95% CI, 1.38-2.99).

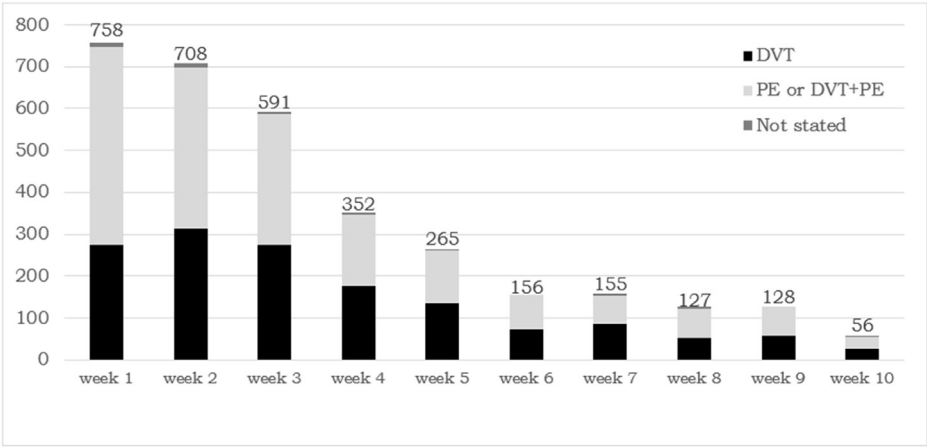
The factors associated with late postoperative VTE (>28 days) were male sex (OR, 1.64; 95% CI, 1.26-2.12), older age (OR, 1.02; 95% CI, 1.01-1.02]), immobilization for ≥4 days during the 2 months before the detection of VTE (OR, 1.534; 95% CI, 1.04-2.27), and the type of surgery performed, with greater risk for patients who had undergone neurosurgery, vascular surgery, or abdominal/genitourinary surgery. The presence of major bleeding during the previous month was associated with an earlier presentation of VTE (OR, 0.31; 95% CI, 0.17-0.55; Table IV).

Presentation of postoperative VTE as DVT or PE. In the study population, 1465 patients (44.1%) had presented with isolated DVT, 1355 (41.1%) with isolated PE, and 439

Table II. VTE type, time of presentation, and thromboprophylaxis stratified by surgery type

Surgery type	All VTE	Isolated DVT	PE with or without DVT	Time to VTE, days	Postoperative thromboprophylaxis	Thromboprophylaxis duration, days
Appendectomy	71 (2.2)	28 (40.6)	41 (59.4)	14 (7-24)	37 (52.1)	7 (4-11)
Cesarean section	150 (4.6)	78 (52)	72 (48)	13 (6-21)	33 (22)	6.5 (2.75-9.25)
Bariatric surgery	66 (2)	23 (35.4)	42 (64.6)	15 (8-31)	49 (75.4)	9.5 (5.25-13.75)
Cholecystectomy	136 (4.1)	54 (40)	81 (60)	19 (6-39)	86 (63.2)	9 (5-15)
Abdominal wall	205 (6.2)	98 (48.5)	104 (51.5)	17 (9-31.2)	86 (42)	7 (3-10)
Liposuction	21 (0.6)	9 (42.9)	12 (57.1)	19 (10.5-30.5)	6 (28.6)	7 (5.75-13.5)
Intestinal occlusion	50 (1.5)	20 (40)	30 (60)	12 (7.7-25.5)	41 (82)	12.5 (7-19.25)
Intestinal perforation	49 (1.5)	18 (37.5)	30 (62.5)	19.5 (8.7-33.5)	39 (79.6)	12 (7-20)
Gastroduodenal ulcer	14 (0.4)	5 (35.7)	9 (64.3)	16 (11.5-29.5)	7 (50)	10 (9.25-18.75)
Other abdominal	322 (9.8)	133 (41.7)	186 (58.3)	17 (8-31)	195 (60.6)	9 (5-16)
Genitourinary	469 (14.2)	204 (43.9)	261 (56.1)	15 (8-26)	215 (45.8)	6 (4-10)
Neurosurgery	423 (12.8)	212 (50.4)	209 (49.6)	20 (9-34)	160 (37.8)	10 (5-15.5)
Arterial	219 (6.6)	99 (45.4)	119 (54.6)	19 (11-31)	129 (58.9)	10 (6.25-15)
Venous	251 (7.6)	103 (42.6)	139 (57.4)	17 (11-30)	105 (41.8)	8 (5-10)
Other	850 (25.8)	381 (45.4)	459 (54.6)	15 (7-31)	259 (30.5)	9 (5-15.5)
Total	3296 (100)	1465 (44.45)	1794 (54.43)	16 (8-30)	1447 (43.9)	8 (5-14)

DVT, Deep vein thrombosis; *PE*, pulmonary embolism; *VTE*, venous thromboembolism.
Data presented as number (%) or median (interquartile range).



	week 1	week 2	week 3	week 4	week 5	week 6	week 7	week 8	week 9	week 10	Total
n	758	708	591	352	265	156	155	127	128	56	3296
%	23.00%	21.50%	17.90%	10.70%	8.00%	4.70%	4.70%	3.90%	3.90%	1.70%	100.00%
Cumulative %	23.00%	44.50%	62.40%	73.10%	81.10%	85.90%	90.60%	94.40%	98.30%	100.00%	100.00%

Fig 2. Time-course and type of postoperative venous thromboembolism (VTE). *DVT,* Deep vein thrombosis; *PE,* pulmonary embolism.

(13.3%) with both DVT and PE. Therefore, more than one half of the patients with VTE after noncancer surgery had presented with PE after most types of surgical intervention: 64.6% after bariatric surgery, 60% after cholecystectomy, and 62.5% after surgery for intestinal perforation. A presentation as isolated DVT was more frequent after cesarean section (52%) and neurosurgery (50.4%; Table II).

Thromboprophylaxis. Among the patients with postoperative VTE, 1447 (43.9%) had received postoperative pharmacologic thromboprophylaxis. Most (86.2%) had received low-molecular-weight heparin. The median duration of pharmacologic thromboprophylaxis was 8 days (IQR, 5-14 days). The surgical procedures with the lowest rate of prophylaxis were cesarean section (22%) and liposuction (28.6%). Thromboprophylaxis was used most frequently for bariatric surgery patients (75.4%) and procedures performed for intestinal perforation or occlusion (79.6% and 82%, respectively). These operations were associated with a longer prophylaxis duration (median, 12 days). After genitourinary surgery or cesarean section, the median duration of prophylaxis was <1 week (Table II).

For the patients who had received prophylaxis, the median interval after surgery to the detection of VTE was 19 days (IQR, 9-32 days). For those not receiving prophylaxis, the interval was 15 days (IQR, 8-29 days). Of the patients receiving prophylaxis, 72.3% had developed VTE once prophylaxis had been discontinued.

Clinical events during follow-up. During the first 3 months of follow-up after the detection of VTE and initiation of treatment, 210 patients (6.4%) had experienced major bleeding, 167 (5.1%) had experienced recurrence, and 132 (4%) had died. Thus, ~15% of the patients who had developed symptomatic VTE after noncancer surgery had had an adverse outcome (Supplementary Table, online only).

Of those patients with a diagnosis of VTE >7 days after surgery, the incidence of major bleeding was lower than that in those who had developed VTE within 7 days. The patients who had developed VTE >28 days after surgery had had a greater incidence of recurrence (6.3% vs 4.6%; $P = .048$) and death (5.2% vs 3.6%; $P = .036$) compared with the patients who had presented with VTE within the first postoperative month. No significant differences were found between these groups regarding the incidence of major bleeding (Supplementary Table, online only).

DISCUSSION

Previous research has shown that more than one half of the thrombotic events experienced by general surgery patients occurs after their discharge from the hospital.[4] Some studies have report a lower incidence. One study reported that 25% of VTE events developing after hepatectomy had occurred after hospital discharge.[19] For patients who had undergone colorectal resection, the proportion was 33%.[20] Most studies of the natural history of VTE have focused on its appearance after hospital discharge, a less precise measure than the number of days. However, hospitalization times have been decreasing, and, very often, patients will be discharged within the first week after surgery.[16]

Table III. Variables related to timing of VTE appearance on bivariate analysis

Variable	Early VTE			Late VTE		
	≤7 Days (n = 758; 23%)	>7 Days (n = 2538; 77%)	*P* value	≤28 Days (n = 2409; 73.1%)	>28 Days (n = 887; 26.9%)	*P* value
Male sex	316 (41.7)	1235 (48.7)	.001	1076 (44.7)	475 (53.6)	<.001
Age, years	58.5 (41-70)	60 (44-73)	.005	58 (41-71)	64 (50-75)	<.001
BMI, kg/m^2	27.43 (24.7-31.1)	27.04 (24.2-30.5)	.053	27.15 (24.3-30.8)	27.11 (24.2-30.4)	.944
Overweight/obesity (BMI ≥25 kg/m^2)	388 (71.7)	1240 (68.4)	.137	1181 (69)	447 (69.5)	.803
Obesity (BMI ≥30 kg/m^2)	170 (31.4)	519 (28.6)	.207	514 (30)	175 (27.2)	.182
Concomitant treatment	437 (60.7)	1498 (62.9)	.293	1387 (60.6)	548 (67.4)	.001
Major bleeding in previous month	66 (8.7)	186 (7.3)	.210	216 (9)	36 (4.1)	<.001
Personal history of AMI/UA	48 (9.1)	149 (9.4)	.816	144 (9.3)	53 (9.4)	.961
Smoker	82 (16)	228 (14.8)	.504	233 (15.5)	77 (13.9)	.356
Diabetes	71 (13.5)	246 (15.6)	.237	215 (14)	102 (18)	.024
Hypertension	200 (37.7)	656 (41.5)	.130	583 (37.8)	273 (47.9)	<.001
Statin use	120 (23.4)	340 (21.7)	.418	334 (22)	126 (22.5)	.835
Symptoms			<.001			.006
Isolated DVT	274 (36.6)	1191 (47.4)		1036 (43.5)	429 (48.9)	
PE or DVT + PE	474 (63.4)	1320 (52.6)		1346 (56.5)	448 (51.1)	
Surgery			<.001			.072
Abdominal/genital	355 (46.8)	1198 (47.2)		1164 (48.3)	389 (43.9)	
Neurosurgery	83 (10.9)	340 (13.4)		292 (12.1)	131 (14.8)	
Vascular	77 (10.2)	393 (15.5)		336 (13.9)	134 (15.1)	
Other	243 (32.1)	607 (23.9)		617 (25.6)	233 (26.3)	
Open surgery	247 (75.5)	842 (81.1)	.028	776 (71.3)	313 (28.7)	.110
Thromboprophylaxis	304 (40.2)	1143 (45.1)	.017	1023 (42.5)	424 (47.9)	.006
Active principle: LMWH	275 (93.2)	972 (93.2)	.987	884 (92.3)	363 (95.5)	.033
Duration, days	5 (3-7)	10 (6-15)	<.001	7 (4-11)	11 (7-24)	<.001
Immobilization	77 (10.2)	314 (12.4)	.098	250 (10.4)	141 (15.9)	<.001
History of VTE	65 (8.6)	245 (9.7)	.372	226 (9.4)	84 (9.5)	.938
Hormonal treatment	117 (4.8)	32 (4.4)	.654	1112 (4.8)	37 (4.3)	.603
Varicose veins	474 (20.3)	129 (19.4)	.617	430 (19.6)	173 (21.6)	.221
Childbirth in 2 months before VTE detection	48 (6.4)	153 (6.1)	.757	176 (7.4)	25 (2.8)	<.001
Thrombophilia	29 (4.3)	63 (2.7)	.036	69 (3.2)	23 (2.9)	.699

AMI, Acute myocardial infarction; *BMI*, body mass index; *DVT*, deep vein thrombosis; *LMWH*, low-molecular-weight heparin; *PE*, pulmonary embolism; *UA*, unstable angina; *VTE*, venous thromboembolism.
Data presented as number (%) or median (interquartile range).

Our study found that the risk of developing VTE remains elevated for ≥2 months in the RIETE population. More than one half of these patients had presented with PE. Overall, 15% of the patients had had poor outcomes. Less than one half of the patients with postoperative VTE had received thromboprophylaxis after surgery (median, 8 days), and nearly three quarters had experienced VTE after prophylaxis discontinuation.

The median interval from surgical intervention to the detection of VTE in our series was 16 days. The VTE events for three quarters of the patients were detected >1 week postoperatively and one of four after 1 month. The factors associated with the late presentation of VTE were male sex, older age, previous immobilization, and type of surgery. This risk was significantly greater for patients who had undergone neurosurgery, vascular surgery, abdominal surgery, or genitourinary surgery.

Other studies, such as those using the National Surgical Quality Improvement Program, have reported intervals from surgery to VTE diagnosis similar to ours (eg, 14 days for patients who had undergone hepatectomy[19]). Likewise, in patients who had undergone colorectal resection (with or without cancer), the median interval was 17.9 days,[20] similar to the findings from another study, with 17 and 16 days for DVT and PE, respectively.[21] A study of patients who had undergone plastic and

Table IV. Variables related to timing of VTE on multinomial logistic regression analysis

Variable	VTE timing		
	≤7 Days	7-28 Days	VTE >28 days
Male sex	1 (Ref)	1.277 (1.015-1.607)[a]	1.638 (1.264-2.122)[a]
Age	1 (Ref)	1.003 (0.997-1.010)	1.018 (1.010-1.025)[a]
Immobilization	1 (Ref)	1.007 (0.701-1.447)	1.539 (1.043-2.272)[a]
Major bleeding	1 (Ref)	1.027 (0.686-1.534)	0.310 (0.173-0.554)[a]
Type of surgery (other)	1 (Ref)	1 (Ref)	1 (Ref)
Abdominal/genitourinary		1.569 (1.203-2.048)[a]	1.453 (1.072-1.971)[a]
Neurosurgery		1.897 (1.269-2.836)[a]	2.095 (1.338-3.281)[a]
Vascular		2.032 (1.381-2.990)[a]	1.789 (1.161-2.756)[a]

Ref, Reference (presentation <7 days taken as reference category); *VTE*, venous thromboembolism.
[a] $P < .05$.

reconstructive surgery showed results similar to ours, with >50% of VTE events in high-risk patients diagnosed 15 to 60 days after surgery.[22] Other investigators have reported substantially shorter times, with an average of 8 days after benign general surgery,[23] probably owing to the inclusion of ambulatory surgery or a shorter follow-up period.

Regarding the type of VTE at presentation, our results showed that of the patients who had undergone benign major surgery, more than one half of those who had developed VTE had presented with PE, either isolated or associated with DVT. The proportions reported by other studies were slightly lower, with 44% presenting with PE[24] after abdominopelvic surgery, one third after major noncardiac surgery,[25] and 42.6% after bariatric surgery. Our results were also in line with those reported for patients treated for abdominopelvic cancer[26] and after colon surgery[27] or bariatric surgery,[2] confirming that the most serious form of VTE presents earlier. A possible explanation for this finding is that the symptoms from PE are more evident than those from DVT.

In relation to the poor outcomes during the follow-up period, the incidence of recurrence and death was greater for those in whom VTE was observed >28 days after surgery. For patients undergoing colorectal surgery, one study found similar results but greater in-hospital mortality,[19] probably because of the inclusion of cancer patients.

As reported by other studies,[28,29] despite thromboprophylaxis, some patients will develop postoperative VTE. This might result from its incorrect use, either with inappropriate doses or an insufficient duration, especially for obese and overweight patients. According to our data, no significant differences were observed in the doses administered to obese or overweight patients and the doses administered to those with normal weight. According to the 2019 guidelines from the American Society of Hematology, pharmacologic prophylaxis should be continued for 19 to 42 days for patients who have undergone major surgery, without specifying whether such surgery refers to oncologic surgery.[30] The results from another RIETE study of patients with abdominopelvic cancer showed a longer duration of prophylaxis (average, 13 days), although still shorter than recommended.[26]

Some investigators have identified age as a predictive factor for late postoperative VTE,[4,31] just as in our study. Regarding the type of surgery, our results agree with those from other studies, reporting a greater risk of late VTE presentation after abdominopelvic surgery.[32,33] Several studies, mostly of bariatric surgery, have reported that a higher BMI is associated with the late presentation of VTE.[4,20,21,27,31] For these patients, the latest European guidelines have recommended ≥14 days of pharmacologic prophylaxis.[34] However, in the present study of general surgical patients, no statistically significant relationship was observed between the duration of VTE risk and BMI.

Study limitations. Our study had limitations that must be acknowledged. First, because the study data were obtained from a registry of symptomatic VTE cases, we did not have information on surgical patients who had not presented with VTE that would have enabled us to calculate the incidence in each case and compare the characteristics of the two groups. Thus, we could not establish a direct relationship between the use of prophylaxis and the prevention of VTE, because all the patients in the database had had VTE. However, our data showed that a high percentage of patients had developed VTE after prophylaxis had been discontinued, suggesting that a rebound effect could occur. Second, the hospitals' participation in the RIETE registry is voluntary, which raises the possibility of sample selection bias, because RIETE hospitals might be more interested in VTE. Third, the registry does not collect information on the duration of the surgical procedure, occurrence of other surgical complications, length of hospital stay, urgency of the procedure,

or use of mechanical prophylaxis. Also, no information is available from the RIETE on the type of anesthesia, comorbidity index, or any other factors that might indicate the disease severity of the patient.

Our study has shown that the risk of VTE persists for ≥2 months postoperatively in noncancer patients. In addition, we have provided an analysis of a large series of consecutive patients with VTE who were treated according to real-world clinical practice without the restrictive selection criteria used in most clinical trials. This is especially true for patients with multiple comorbidities, including elderly patients, pregnant women, and those with chronic disease. This is relevant, because the findings from our study can be applied to patients who will qualify for clinical trials. Moreover, we obtained information about the initial clinical presentation of VTE, the number of days elapsed from the intervention to the diagnosis of VTE, the use and duration of pharmacologic prophylaxis, and 3-month follow-up results. These data are of major importance and are lacking from most previous observational studies. Finally, the RIETE registry includes cases of VTE occurring ≤2 months after the surgical intervention. In contrast, other registries, such as the National Surgical Quality Improvement Program, restricts the follow-up data to the first postoperative month, which has been shown to be insufficient to assess the real burden of postoperative VTE.

CONCLUSIONS

The results from our study have shown that the risk of VTE after surgery for benign processes is not limited to the first postoperative week but remains elevated for a longer period. In our study, 25% of patients with VTE had developed this complication after the fourth postoperative week. The use of thromboprophylaxis is suboptimal, including the proportion of patients receiving it and its duration. For some procedures, the 7-day thromboprophylaxis recommended as the minimum in most clinical practice guidelines will not be achieved because of earlier discharge. Furthermore, 15% of the patients who developed this potentially avoidable complication had a poor outcome. Studies involving the RIETE database bridge the gap between academic guidelines and clinical practice realities.

Our results highlight the need to improve the implementation and quality of postoperative prophylaxis, even for patients without cancer, who have a high VTE risk, and to increase the follow-up to ≥2 months after the intervention to better assess the incidence of postoperative VTE. Prospective studies are needed to establish the optimal duration of postoperative antithrombotic prophylaxis after nononcologic surgery according to the patient's risk factors and type of surgery.

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REFERENCES

1. Serrano PE, Parpia S, Valencia M, Simunovic M, Bhandari M, Levine M. Incidence of delayed venous thromboembolic events in patients undergoing abdominal and pelvic surgery for cancer: a systematic review and meta-analysis. ANZ J Surg 2019;89:1217-23.
2. Aminian A, Andalib A, Khorgami Z, Cetin D, Burguera B, Bartholomew J, et al. Who should get extended thromboprophylaxis after bariatric surgery? A risk assessment tool to guide indications for post-discharge pharmacoprophylaxis. Ann Surg 2017;265:143-50.
3. Alsubaie H, Leggett C, Lambert P, Park J, Hochman D, Wirtzfeld D, et al. Diagnosis of VTE postdischarge for major abdominal and pelvic oncologic surgery: implications for a change in practice. Can J Surg 2015;58:305-11.
4. Bouras G, Burns EM, Howell AM, Bottle A, Athanasiou T, Darzi A. Risk of post-discharge venous thromboembolism and associated mortality in general surgery: a population-based cohort study using linked hospital and primary care data in England. PLoS One 2015;10:1-16.
5. Sweetland S, Green J, Liu B, De González AB, Canonico M, Reeves G, et al. Duration and magnitude of the postoperative risk of venous thromboembolism in middle aged women: prospective cohort study. BMJ 2009;339:32.
6. Arcelus JI, Monreal M, Caprini JA, Guisado JG, Soto MJ, Nunez MJ, et al. Clinical presentation and time-course of postoperative venous thromboembolism: results from the RIETE registry. Thromb Haemost 2008;99:546-51.
7. Huo MH, Muntz J. Extended thromboprophylaxis with low-molecular-weight heparins after hospital discharge in high-risk surgical and medical patients: a review. Clin Ther 2009;31:1129-41.
8. Bottaro FJ, Elizondo MC, Doti C, Bruetman JE, Perez Moreno PD, Bullorsky EO, et al. Efficacy of extended thrombo-prophylaxis in major abdominal surgery: what does the evidence show? A meta-analysis. Thromb Haemost 2008;99:1104-11.
9. Fagarasanu A, Alotaibi GS, Hrimiuc R, Lee AYY, Wu C. Role of extended thromboprophylaxis after abdominal and pelvic surgery in cancer patients: a systematic review and meta-analysis. Ann Surg Oncol 2016;23:1422-30.
10. Li M, Guo Q, Hu W. Incidence, risk factors, and outcomes of venous thromboembolism after oncologic surgery: a systematic review and meta-analysis. Thromb Res 2019;173:48-56.
11. Felder S, Rasmussen MS, King R, Sklow B, Kwaan M, Madoff R, et al. Prolonged thromboprophylaxis with low molecular weight heparin for abdominal or pelvic surgery. Cochrane Database Syst Rev 2018;2018:CD004318.

12. Gould MK, Garcia DA, Wren SM, Karanicolas PJ, Arcelus JI, Heit JA, et al. Prevention of VTE in nonorthopedic patients: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2012;141(Suppl):e227S.
13. Key NS, Khorana AA, Kuderer NM, Bohlke K, Lee AYY, Arcelus JI, et al. Venous thromboembolism prophylaxis and treatment in patients with cancer: ASCO clinical practice guideline update. J Clin Oncol 2020;38:496-520.
14. Farge D, Bounameaux H, Brenner B, Cajfinger F, Debourdeau P, Khorana AA, et al. International clinical practice guidelines including guidance for direct oral anticoagulants in the treatment and prophylaxis of venous thromboembolism in patients with cancer. Lancet Oncol 2016;17:e452-66.
15. Mismetti P, Laporte S, Darmon JY, Buchmuller A, Decousus H. Meta-analysis of low molecular weight heparin in the prevention of venous thromboembolism in general surgery. Br J Surg 2001;88:913-30.
16. Kehlet H. Fast-track surgery—an update on physiological care principles to enhance recovery. Langenbecks Arch Surg 2011;396:585-90.
17. Abraham N. Enhanced recovery after surgery programs hasten recovery after colorectal resections. World J Gastrointest Surg 2011;3:1.
18. Bikdeli B, Jimenez D, Hawkins M, Ortiz S, Prandoni P, Brenner B, et al. Rationale, design and methodology of the Computerized Registry of Patients with Venous Thromboembolism (RIETE). Thromb Haemost 2018;118:214-24.
19. Tzeng CWD, Curley SA, Vauthey JN, Aloia TA. Distinct predictors of pre- versus post-discharge venous thromboembolism after hepatectomy: analysis of 7621 NSQIP patients. HPB (Oxford) 2013;15:773-80.
20. Alhassan N, Sabapathy MTC, Liberman PCAS, Charlebois P, Stein BL. Risk factors for post-discharge venous thromboembolism in patients undergoing colorectal resection: a NSQIP analysis. Tech Coloproctol 2018;22:955-64.
21. Fleming FJ, Kim MJ, Salloum RM, Young KC, Monson JR. How much do we need to worry about venous thromboembolism after hospital discharge? A study of colorectal surgery patients using the National Surgical Quality Improvement Program database. Dis Colon Rectum 2010;53:1355-60.
22. Pannucci CJ, Bailey SH, Dreszer G, Fisher Wachtman C, Zumsteg JW, Jaber RM, et al. Validation of the Caprini risk assessment model in plastic and reconstructive surgery patients. J Am Coll Surg 2011;212:105-12.
23. Pannucci CJ, Shanks A, Moote MJ, Bahl V, Cederna PS, Naughton NN, et al. Identifying patients at high risk for venous thromboembolism requiring treatment after outpatient surgery. Ann Surg 2012;255:1093-9.
24. Nelson RE, Grosse SD, Waitzman NJ, Lin J, Duvall SL, Patterson O, et al. Using multiple sources of data for surveillance of postoperative venous thromboembolism among surgical patients treated in Department of Veterans Affairs hospitals, 2005–2010. Thromb Res 2019;135:636-42.
25. Smilowitz NR, Gupta N, Guo Y, Maldonado TS, Eikelboom JW, Goldhaber SZ, et al. Trends in perioperative venous thromboembolism associated with major noncardiac surgery. TH Open 2017;1:e82-91.
26. Bustos Merlo AB, Arcelus Martinez JI, Turino Luque JD, Valero B, Villalobos A, Aibar MA, et al. Form of presentation, natural history and course of postoperative venous thromboembolism in patients operated on for pelvic and abdominal cancer: analysis of the RIETE registry. Cir Esp 2017;95:328-34.
27. Beal EW, Tumin D, Chakedis J, Porter E, Moris D, Zhang X-F, et al. Which patients require extended thromboprophylaxis after colectomy? Modeling risk and assessing indications for post-discharge pharmacoprophylaxis. World J Surg 2018;42:2242-51.
28. Hirsch DR, Ingenito EP, Goldhaber SZ. Prevalence of deep venous thrombosis among patients in medical intensive care. JAMA 1995;274:335-7.
29. Wang TF, Wong CA, Milligan PE, Thoelke MS, Woeltje KF, Gage BF. Risk factors for inpatient venous thromboembolism despite thromboprophylaxis. Thromb Res 2014;133:25-9.
30. Anderson DR, Morgano GP, Bennett C, Dentali F, Francis CW, Garcia DA, et al. American Society of Hematology 2019 guidelines for management of venous thromboembolism: prevention of venous thromboembolism in surgical hospitalized patients. Blood Adv 2019;3:3898-944.
31. Iannuzzi JC, Young KC, Kim MJ, Gillespie DL, Monson JRT, Fleming FJ. Prediction of postdischarge venous thromboembolism using a risk assessment model. J Vasc Surg 2013;58:1014-20.e1.
32. Benlice C, Holubar SD, Gorgun E, Stocchi L, Lipman JM, Kalady MF, et al. Extended venous thromboembolism prophylaxis after elective surgery for IBD patients. Dis Colon Rectum 2018;61:1170-9.
33. Cassidy MR, Rosenkranz P, McAneny D. Reducing postoperative venous thromboembolism complications with a standardized risk-stratified prophylaxis protocol and mobilization program. J Am Coll Surg 2014;218:1095-104.
34. Venclauskas L, Maleckas A, Arcelus JI. European guidelines on perioperative venous thromboembolism prophylaxis: surgery in the obese patient. Eur J Anaesthesiol 2018;35:147-53.

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APPENDIX (online only).

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Supplementary Table (online only). Clinical events during follow-up

		Early VTE			Late VTE		
Variable	Total	≤7 Days (n = 758)	>7 Days (n = 2538)	*P* value	≤ 28 Days (n = 2408)	>28 Days (n = 887)	*P* value
Recurrence	167 (5.1)	33 (4.4)	134 (5.3)	.308	111 (4.6)	56 (6.3)	.048
Major bleeding	210 (6.4)	60 (7.9)	150 (5.9)	.047	163 (6.8)	47 (5.3)	.126
Death	132 (4)	22 (2.9)	110 (4.3)	.078	86 (3.6)	46 (5.2)	.036

VTE, Venous thromboembolism.
Data presented as number (%).