From the Southern Association for Vascular Surgery

Analysis of noncatheter-associated upper extremity deep venous thrombosis from the RIETE registry

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ABSTRACT

Objective: We sought to determine the risk factors for subsequent bleeding and recurrent venous thromboembolism (VTE) events following isolated noncatheter-associated upper extremity deep venous thrombosis (non-CA-UEDVT) to better inform future treatment decisions for this group of patients.

Methods: The RIETE registry (Registro Informatizado de Enfermedad TromboEmbólica [Computerized Registry of Patients with Venous Thromboembolism]) is a prospective international registry of patients with objectively confirmed symptomatic VTE. Patients with a symptomatic, isolated, proximal UEDVT from March 2001 through March 2015 were analyzed. Any patient with an indwelling catheter or pacemaker lead at the DVT site and at the time of thrombosis was considered to have a CA-UEDVT and was excluded. Patient and treatment characteristics such as age, gender, comorbidities, VTE risk factors, treatment drug, and duration were collected. Outcomes examined included recurrent DVT, subsequent pulmonary embolism (PE), and hemorrhage. Multivariate analysis was performed using stepwise logistic regression.

Results: Of the 1100 patients who met the study criteria, 580 (53%) were male. The mean age of the patients was 50 ± 20 years, and overall patient survival at 1 year was 85%. Recurrent VTE occurred in 59 patients (5.4%). Of these, 46 patients (4%) had recurrent DVT, 10 (0.9%) had a PE following UEDVT diagnosis, and 3 (0.3%) had both. PE was fatal in three patients (0.3%). Bleeding occurred in 50 patients (4.5%), major bleeding in 19 patients (1.7%), and fatal bleeding in 6 patients (0.5%). On multivariate analysis, malignant disease was associated with VTE recurrence (odds ratio [OR], 2.00; 95% confidence interval [CI], 1.04-3.45; $P < .04$), whereas hemorrhage was associated with age (OR, 1.03; 95% CI, 1.01-1.05; $P = .002$) and malignant disease (OR, 2.53; 95% CI, 1.34-4.76; $P < .005$). Hemorrhage and recurrent VTE were also significantly associated (OR, 2.79; 95% CI, 1.16-6.76; $P < .03$).

Conclusions: PE following non-CA-UEDVT is rare. Malignant disease was associated with VTE recurrence. Age and malignant disease were associated with hemorrhage, and VTE recurrence was associated with hemorrhage. Further prospective studies should be undertaken to best determine length of anticoagulation treatment for the varied populations of patients with UEDVT. (J Vasc Surg: Venous and Lym Dis 2016;■:1-7.)

Studies of upper extremity deep venous thrombosis (UEDVT) have reported variable incidence of associated pulmonary embolism (PE), from as high as 15% to as low as 2%.[1,2] There are two possible explanations for this wide variation. The first is that patient entry criteria and data reporting have varied among investigators. Some studies have reported concomitant PE and subsequent PE together as an outcome, potentially exaggerating the risk of PE in patients presenting with only UEDVT.[1,3-6] The second reason the rates of PE may vary is that these studies used undifferentiated populations of patients with UEDVT, including a variety of underlying causes and risk factors. Catheter-associated UEDVT (CA-UEDVT), for example, can result from repeated injury to the endothelium, leading to platelet activation, smooth muscle proliferation, and atherosclerotic-like lesions.[7] In contrast, effort-induced thrombosis, or Paget-Schroetter syndrome, is caused by chronic venous injury from external compression leading to external scar formation, although intimal injury may also contribute.[8] Finally, there are patients with one or more hypercoagulable states that originate from extrinsic or intrinsic factors (eg, cancer, postoperative status, trauma). With such a variety of underlying causes leading to a common clinical presentation of UEDVT, it is not surprising that

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outcomes in the existing literature are highly variable. Nonetheless, the American College of Chest Physicians guidelines from 2012 and 2016 view patients with UEDVT as a homogeneous group and recommend anticoagulation for all patients with UEDVT for 3 months or longer.[9,10]

Subgroup analysis of larger established databases may lead to more tailored treatments, reducing complications and increasing effectiveness. The RIETE registry (Registro Informatizado de Enfermedad TromboEmbólica) is a multicenter, international observational registry of consecutive patients with symptomatic, objectively confirmed, acute venous thromboembolism (VTE). Data are reported from 176 sites, mostly in Spain (78% of patients) as well as in 18 other countries worldwide (22% of patients). The large number of reporting centers makes it one of few databases with sufficiently robust recruitment to thoroughly examine the clinically important outcomes in more select subgroups.

Previous analysis of this registry by Munoz et al in 2008 found that patients with UEDVT less frequently presented with clinically overt PE but had similar, low rates of recurrent PE and DVT compared with those with lower extremity DVT.[11] Following this, Baumann Kreuziger et al in 2015 focused on patients with CA-UEDVT, noting that recurrent PE and DVT were decreased for patients in this subset with a duration of anticoagulation >90 days and increased in CA-UEDVT patients with renal insufficiency.[12] This current study intended to use the power of the RIETE registry to evaluate factors that may influence the outcomes of non-CA-UEDVT.

METHODS

The RIETE registry enrolls patients with a UEDVT in the subclavian vein, axillary vein, or both. Patients with a DVT in one of these proximal upper extremity veins from March 2001 through March 2015 were abstracted from the registry. Any patient with an indwelling catheter or pacemaker lead at the site and time of thrombosis was considered to have a CA-UEDVT and was excluded. Patients who presented with a synchronous symptomatic PE (n = 207) or lower extremity DVT (n = 101) were also excluded. All patients provided informed consent, and all participating sites obtained local Institutional Review Board approval.

Patient and treatment characteristics, such as age, gender, comorbidities, VTE risk factors, treatment drug, and duration, were collected and analyzed. Outcomes included recurrent DVT, subsequent PE (grouped together as recurrent VTE), and hemorrhage. Because the registry is observational, with no protocol for surveillance imaging, patients were evaluated for recurrent DVT and PE when symptoms arose and completed by local practice pattern. Hemorrhage was defined as any documented bleeding episode in the medical record; major hemorrhage was defined as bleeding in the retroperitoneum, bleeding in the intrathecal space, bleeding in the intracranial space, fatal bleeding, or bleeding requiring transfusion of at least 2 units of packed red blood cells.

The Wilcoxon rank test was used to compare group medians for continuous patient data, and the Fisher exact test was used to analyze categorical data. Stepwise multivariate logistical regression was performed using gender, history of malignant disease, recent surgery, immobility, history of DVT/PE, VTE recurrence/bleeding, acute phase drug, long-term drug, and estrogen therapy as variables. The log-rank test was used to compare Kaplan-Meier survival between groups.

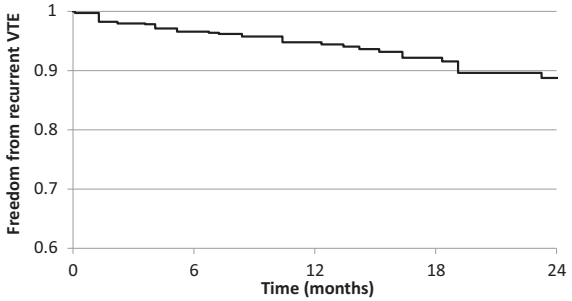
RESULTS

At the time of data abstraction, there were exactly 1100 patients who met the study criteria. The median age of the patients was 50 years (range, 15-96), and 580 patients (53%) were male. There were 314 inpatients (29%) and 761 outpatients (71%). Of these outpatients, 449 (60%) were admitted following their diagnosis. At least 90 days of follow-up was available in all but 23 patients alive at that time point. All of the remaining 23 patients had between 80 and 90 days of follow-up.

The most common risk factor for initial UEDVT was a history of cancer, noted in 319 patients (29%), and 182 of these had metastatic disease. Surgery in the past 2 months (n = 65; 6%) and immobility (n = 99; 9%) were also common risk factors. Immobility related to trauma was relatively rare, seen in 66 patients (2.8%). During the 2 months preceding diagnosis, 110 patients (10%) were taking estrogens, progesterones, or estrogen receptor modulators. Height data were available on only 776 patients. Among those with available height data, obesity was relatively rare, with 113 patients (14.6%) having a body mass index of ≥30 and only 28 patients (3.61%) with body mass index of ≥35. At the time of UEDVT presentation, 38 patients (4%) carried a diagnosis of thrombophilia, and 124 patients (11%) had a history of VTE. Of the 364 patients tested for thrombophilia after presentation, 124 patients (34%) were positively diagnosed with hypercoagulable disorders. Last, there were 35 patients (3.2%) who had effort-induced thrombosis.

Most patients presented with both a painful and edematous limb (n = 814; 74%); 49 patients (4.5%) presented with only limb pain and 166 patients (15.1%) with only limb edema. Diagnosis of DVT was made with duplex ultrasonography in 995 patients (90%) and venography in 58 patients (5%). Computed tomography was used for 43 patients (4%), and magnetic resonance imaging was diagnostic for 4 patients (0.4%).

The most common initial anticoagulant was low-molecular-weight heparin (LMWH, n = 975; 88.6%). Long term, vitamin K antagonists were the most common UEDVT treatment (n = 649; 59.0%), followed by LMWH (n = 394; 35.8%) and new oral anticoagulants



Months	3	6	12	24
Recurrent VTE	22	33	41	52
Patients at risk	1021	674	336	103

Fig 1. Kaplan-Meier freedom from pulmonary embolism (PE) or recurrent deep venous thrombosis (DVT) following diagnosis of noncatheter-associated upper extremity deep venous thrombosis (non-CA-UEDVT). Overall, recurrence is not rare, and venous thromboembolism (*VTE*) occurs at a steady rate of about 5% per year.

(NOACs), such as thrombin or factor Xa inhibitors (n = 18; 1.7%). Only four patients did not receive long-term anticoagulation. LMWH as a long-term anticoagulant was most commonly used in patients with cancer, making up 77% of its use ($P < .0001$). The median duration of anticoagulation was 145 days, with a range of 2 to 2384 days. Excluding early deaths, there were 11 patients with <30 days of treatment. Two of these patients stopped anticoagulation because of hemorrhage, and there was no clearly documented reason for short anticoagulation duration in the other nine patients. There was not a consistent treatment protocol among patients with effort-induced thrombosis. Thrombolysis alone was undertaken in five of these patients and combined with decompressive surgery for four patients, whereas another three patients underwent decompressive surgery without thrombolysis. All were treated with long-term anticoagulation including vitamin K antagonists (n = 20), followed by LMWH (n = 12) and NOACs (n = 3).

Recurrent VTE was confirmed in 59 patients (5.4%). Of these, 46 patients (4.2%) had recurrent extremity DVT, 10 (0.9%) had PE, and 3 (0.3%) had both. Results of Kaplan-Meier analysis of recurrent VTE are presented in Fig 1. About one-third (n = 13) of extremity DVT recurrences presented during anticoagulation. Univariate analysis of risk factors for VTE recurrence are listed in Table I. Patients with multiple risk factors including cancer, obesity, postoperative status, immobility, prior VTE, thrombophilia, and age older than 65 years had a higher rate of recurrent VTE (7.6%) compared with those with only one risk factor (4.5%), although this difference did not reach statistical significance ($P > .06$). On multivariate analysis (Table II), recurrent VTE was predicted by malignant disease (odds ratio, 2.00; 95% confidence interval, 1.04-3.45) and a hemorrhagic event (odds ratio, 2.67; 95% confidence interval, 1.10-6.45).

Hemorrhage occurred in 50 patients (4.5%) and major hemorrhage in 19 patients (1.7%). Results of Kaplan-Meier analysis of freedom from hemorrhage are presented in Fig 2. Only 4 of the 50 patients who experienced hemorrhage had completed their anticoagulation. Univariate analysis of risk factors for hemorrhage are listed in Table III. Patients with hemorrhage also had a shorter duration of treatment (91 days [range,

Table I. Risk of pulmonary embolism (PE) or recurrent deep venous thrombosis (*DVT*) based on patient or treatment characteristics (N = 1100)

Patient or treatment characteristic	Present		Not present		*P* value[a]
	VTE recurrence, No. (%)	Total No.	VTE recurrence, No. (%)	Total No.	
Male	33 (5.7)	580	26 (5.0)	520	.69
Malignant disease	28 (8.8)	319	31 (4.0)	781	.0028
Metastatic cancer	16 (8.8)	182	10 (9.3)	108	1.00
Hemorrhage <30 days before UEDVT diagnosis	2 (15)	13	57 (5.2)	1030	.15
Secondary to effort	0 (0)	35	59 (5.5)	1065	.25
Immobility	4 (4.0)	99	55 (5.5)	1001	.81
Recent surgery (<60 days)	4 (6.2)	65	55 (5.3)	1035	.77
Hormonal therapy	1 (0.91)	110	58 (6.0)	968	.076
Abnormal renal function (Cr > 1)	5 (5.3)	89	52 (5.4)	959	1.00
Thrombophilia at time of diagnosis	3 (8)	38	49 (5.2)	903	.45
Thrombophilia diagnosed later	5 (4.0)	124	16 (6.7)	240	.35
Anticoagulant	LMWH 27 (6.9)	394	Anti-vitamin K 25 (3.9)	649	.039
History of DVT	11 (8.9)	124	48 (4.4)	976	.086

Cr, Creatinine; *LMWH*, low-molecular-weight heparin; *UEDVT*, upper extremity deep venous thrombosis; *VTE*, venous thromboembolism.
[a]Fisher exact test.

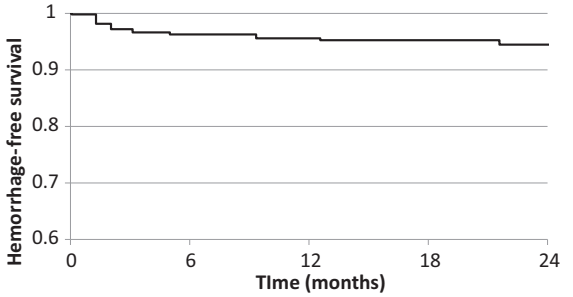
Table II. Risk of hemorrhage following upper extremity deep venous thrombosis (*UEDVT*) diagnosis based on patient or treatment characteristics (N = 1100)

Patient or treatment characteristic	Present		Not present		*P* value[a]
	Bleeding complication, No. (%)	Total, No.	Bleeding complication, No. (%)	Total, No.	
Male	32 (5.5)	580	18 (3.5)	520	.11
Malignant disease	31 (9.7)	319	19 (2.4)	781	<.0001
Hemorrhage in month before UEDVT diagnosis	1 (7.7)	13	49 (4.5)	1087	.46
Secondary to effort	0 (0)	35	50 (4.7)	1065	.40
Immobility	8 (8.1)	99	42 (4.2)	1001	.12
Recent surgery	5 (7.7)	65	45 (4.4)	1035	.21
Hormonal therapy	1 (0.9)	110	49 (4.9)	990	.053
Abnormal renal function	5 (5.3)	94	44 (4.6)	915	.80
Thrombophilia at time of diagnosis	1 (2.6)	38	49 (4.6)	1062	1.00
Thrombophilia diagnosed later	38 (0.8)	124	7 (2.9)	240	.27
Long-term anticoagulant	LMWH 26 (6.6)	394	Anti-vitamin K 17 (2.6)	649	.0022
History of DVT	6 (4.8)	124	44 (4.5)	976	.82
Recurrent VTE	7 (11.9)	59	43 (4.1)	1041	.014

DVT, Deep venous thrombosis; *LMWH*, Low-molecular-weight heparin; *VTE*, venous thromboembolism.
[a]Fisher exact test.

0-2384] vs 149 days [range, 0-2363]) compared with those without hemorrhage ($P < .0001$). Results for multivariate analysis of factors associated with bleeding are also listed in Table II. Multivariate analysis revealed correlation between hemorrhage and recurrent VTE; however, closer inspection of patients with both of these events did not reveal any particular timing pattern to suggest causality.

Kaplan-Meier analysis of overall survival is depicted in Fig 3. Overall, 1-year patient mortality was 15.2%. The most common cause of death listed was neoplasia (n = 68; 46.6% of deaths), followed by respiratory failure (n = 15; 10.3% of deaths), infection (n = 11; 7.5%), multiorgan failure (n = 10; 6.8%), and "unknown" (n = 21; 14.4%). Bleeding was the cause of death in six patients (0.6% overall, 4.1% of deaths), whereas PE was confirmed to be the cause of death in three patients (0.3% overall, 2.1% of deaths).



Months	3	6	12	24
Hemorrhage	36	39	44	45
Patients at risk	934	701	279	122

Fig 2. Kaplan-Meier freedom from hemorrhagic complications. These complications occur at a higher rate during the first 3 months after diagnosis, when most patients are anticoagulated.

DISCUSSION

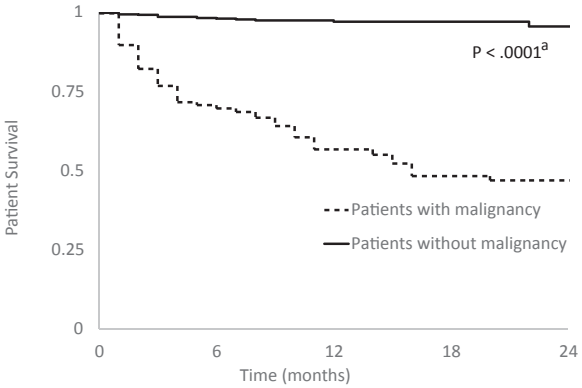
Although it has been difficult to prove the effectiveness of anticoagulation therapy for UEDVT in preventing the relatively rare subsequent PE and recurrent DVT, the risk of hemorrhagic complications from anticoagulation is well documented.[2,7] Ideally, prospective trials would determine which patients benefit from anticoagulation and demonstrate the most effective length of treatment. Until then, the only way to render evidence-based treatment decisions is to further define the varied UEDVT subgroups and retrospectively examine their outcomes. This allows more nuanced decision-making, especially for patients at high risk of complications from their anticoagulation. This analysis uses the numerical power of the large RIETE registry to examine the outcomes of patients with symptomatic, proximal non-CA-UEDVT. From our analysis, malignant disease and age were significant risk factors for VTE recurrence for patients with non-CA-UEDVT. These conclusions are precisely opposite to a previous RIETE analysis of CA-UEDVT patients that found a lower rate of recurrent VTE among older patients and those with malignant disease.[12] Although there is no clear reason for this discrepancy, it does highlight the danger of drawing general conclusions for all patients with a UEDVT and supports more careful parsing of the patient subgroups on the basis of precipitating factors.

Table III. Multivariate analysis of the factors associated with venous thromboembolism (*VTE*) recurrence (recurrent deep venous thrombosis [DVT] or subsequent pulmonary embolism [PE]) and bleeding

Patient or treatment characteristic	OR[a] (95% CI)	*P* value[a]
VTE recurrence		
Malignant disease	2.00 (1.04-3.45)	.039
LMWH vs warfarin	1.24 (0.63-2.45)	.25
Hemorrhage	2.67 (1.10-6.45)	.030
Hemorrhage		
Age	1.03 (1.01-1.05)	.0020
Malignant disease	2.53 (1.34-4.76)	.0042
Recurrent VTE	2.79 (1.16-6.76)	.023

CI, Confidence interval; *LMWH,* low-molecular-weight heparin; *OR,* odds ratio.
[a]Stepwise logistic regression.

Based on this finding, one might conclude that patients with non-CA-UEDVT and cancer would benefit from more aggressive anticoagulation. However, the risks of anticoagulation in these patients should also be considered as malignant disease was strongly predictive of hemorrhage by multivariate analysis, along with advanced age. The elderly cancer patient with non-CA-UEDVT presents a clinical dilemma to the treating physician, who must balance the risk of recurrent VTE with iatrogenic hemorrhage. Some resolution may be provided by analysis of Kaplan-Meier survival curves for freedom from VTE recurrence and hemorrhage (Figs 1 and 2). Hemorrhage occurred primarily in the first few months after UEDVT diagnosis, the time during which most patients are anticoagulated. Following this period, there was a flattening of the hemorrhage-free survival curve reflecting a decrease in the subsequent observed rate of bleeding. In contrast to this, there is a steady rate of VTE recurrence unaffected by the cessation of anticoagulation. This intuitively suggests that decreasing the duration of anticoagulation may reduce the overall rate of hemorrhage while not appreciably changing the long-term rate of VTE recurrence. Extended anticoagulation appears to be safer for patients in the study population who are younger and without cancer on the basis of the current multivariate analysis. It may be especially valuable for patients with nonmodifiable risk factors, such as hypercoagulable disorders, but very few of these patients discontinued anticoagulation during the study period, making it difficult to evaluate the effect.



	Months	3	6	12	24
Malignancy	Deaths	74	91	110	120
	At risk	226	131	72	34
No Malignancy	Deaths	11	14	17	19
	At risk	365	472	229	91

[a]Log-rank test

Fig 3. Kaplan-Meier curve depicting overall survival. Survival is substantially lower in patients with malignancy.

Anticoagulant choice in this study population largely followed American College of Chest Physicians 2012 guidelines recommending vitamin K antagonists for patients without cancer and LMWH for patients with cancer.[9] Whereas a low incidence of hemorrhage was seen in patients without cancer (2.4%), updated 2016 guidelines recommend the use of NOACs for this subgroup because of the putative lower risk of hemorrhage.[10] In addition, studies of NOACs' cost-effectiveness show a cost savings compared with vitamin K antagonists.[13] Given the few patients (n = 18) receiving NOACs in this study, this study cannot support or oppose the recommendation. However, if indeed NOACs cause fewer bleeding events, the risk of anticoagulation would be lower and risk-benefit analysis may favor longer duration of therapy.

There are two additional unique findings of this study. First, although the overall incidence of subsequent PE was low at 1.2% (n = 13), PE was fatal in 23% of cases (n = 3). This alarming finding is somewhat mitigated by the very low incidence of fatal PE at 0.3% of the study population. Whereas previously Baumann Kreuziger et al noted that 10% of PEs were fatal in patients with CA-UEDVT in the RIETE registry, no other large study has shown such a high proportion of PEs that result in death.[2-6,12] In this study, all three patients had advanced cancer, making them fragile and susceptible to any further insult, such as PE. There was also no surveillance imaging for subsequent PEs; as a result, only symptomatic PEs were recorded, skewing the observed spectrum of cases toward the more severe. More aggressive anticoagulation would likely not decrease the proportion of PEs that are fatal as all three cases were being appropriately therapeutically anticoagulated. However, in two of the cases, the patients died days after the PE, and it is therefore possible that more aggressive treatment, including thrombolysis or thrombectomy, could lower the mortality rate.

The second unusual finding was the association between hemorrhage and recurrent VTE seen on multivariate analysis. On its face, bleeding and thrombosis seem to be in conflict, as they are usually thought

of as opposite ends of a spectrum. Using this framework, one can imagine a scenario in which a patient had an episode of hemorrhage prompting withdrawal of anticoagulation therapy. Without anticoagulation, the patient has a recurrent VTE. Another possible explanation is that patients with recurrent VTE were given a longer duration of anticoagulation compared with those without recurrent VTE, putting patients at higher cumulative risk of bleeding. Careful analysis of the timing of bleeding events and VTE recurrences in patients with both shows that in a minority of cases, anticoagulation cessation for bleeding precedes VTE recurrence, and in the rest of the cases, a bleeding event occurs well after VTE recurrence, while the patient is on an extended duration of anticoagulation. Together the two hypotheses do account for all cases of patients with both recurrent VTE and hemorrhage. Clinicians should therefore limit extended duration anticoagulation regimens if possible, for example, in cases in which the provoking event for recurrent VTE has resolved.

Limitations of this study are mainly related to external validity. Spain contributed the majority of patients, resulting in a study population with a low rate of obesity (14.6%) compared to U.S. series.[2] In addition, 71% of patients presented as outpatients compared with 27% in the study of Lee et al and 11% in the study of Hingorani et al; this likely explains the lower rates of postoperative status and immobilization observed in this study.[4,6] Another limitation is the variable definition of "catheter association." As defined by the RIETE registry, in this study the DVT was considered catheter associated only if it was diagnosed while the catheter was in place. Others have defined a UEDVT as catheter associated if it occurred at the site of a previous catheter even if that catheter had been removed before the UEDVT diagnosis.[2,3] Certainly by the latter definition, many of the UEDVTs in our study population would have been classified as catheter-associated DVTs; however, the RIETE registry does not collect such data to reclassify DVTs to compare the definitions. Additional limitations include those typically inherent in registry studies, including reliance on the electronic medical record and the possibility of VTE or bleeding events occurring that were not documented in the registry.

This study focused on the subgroup of patients presenting with an isolated proximal non-CA-UEDVT and determined that the rates of recurrent DVT and subsequent PE were low, with subsequent fatal PE and fatal bleeding being extremely rare. Cancer was found to be a common risk factor for both bleeding and hemorrhagic complications of treatment, whereas advanced age was predictive of hemorrhage only. By analyzing the rate of recurrent VTE and hemorrhage through time, this study also begins to bring into question whether the recommended minimum duration of anticoagulation, 3 months, truly balances the risk of complications with the benefits of treatment.

CONCLUSIONS

Patients with isolated, proximal non-CA-UEDVT and malignant disease should be considered at higher risk of both VTE recurrence and hemorrhage, whereas older patients are at higher risk of hemorrhage. Further prospective study should be undertaken to best determine length of anticoagulation treatment for the varied populations of patients with UEDVT.

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AUTHOR CONTRIBUTIONS

Conception and design: DN, MMB, ML
Analysis and interpretation: MA, LW, CP, RL
Data collection: MMB
Writing the article: DN
Critical revision of the article: DN, MMB, MA, LW, CP, RL, ML
Final approval of the article: DN, MMB, MA, LW, CP, RL, ML
Statistical analysis: LW
Obtained funding: MMB
Overall responsibility: DN

REFERENCES

1. Monreal M, Lafoz E, Ruiz J, Valls R, Alastrue A. Upper-extremity deep vein thrombosis and pulmonary embolism: a prospective study. Chest 1991;99:280-3.
2. Levy MM, Albuquerque F, Pfeifer JD. Low incidence of pulmonary embolism associated with upper-extremity deep venous thrombosis. Ann Vasc Surg 2012;26:964-72.
3. Joffe HV. Upper-extremity deep vein thrombosis: a prospective registry of 592 patients. Circulation 2004;110:1605-11.
4. Hingorani A, Ascher E, Markevich N, Yorkovich W, Schutzer R, Mutyala M, et al. Risk factors for mortality in patients with upper extremity and internal jugular deep venous thrombosis. J Vasc Surg 2005;41:476-8.
5. Major KM, Bulic S, Rowe VL, Patel K, Weaver FA. Internal jugular, subclavian, and axillary deep venous thrombosis and the risk of pulmonary embolism. Vascular J 2016;16:73-9.
6. Lee JA, Zierler BK, Zierler RE. The risk factors and clinical outcomes of upper extremity deep vein thrombosis. Vasc Endovascular Surg 2012;46:139-44.
7. Kohler TR, Kirkman TR. Central venous catheter failure is induced by injury and can be prevented by stabilizing the catheter tip. J Vasc Surg 1998;28:59-65.

8. Illig KA, Doyle AJ. A comprehensive review of Paget-Schroetter syndrome. J Vasc Surg 2010;51:1538-47.
9. Kearon C, Akl EA, Comerota AJ, Prandoni P, Bounameaux H, Goldhaber SZ, et al. Antithrombotic therapy for VTE disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;14:419-96.
10. Kearon C, Akl EA, Ornelas J, Blaivas A, Jimenez D, Bounameaux H, et al. Antithrombotic therapy for VTE disease: CHEST Guideline and Expert Panel Report. Chest 2016;149:315-52.
11. Munoz FJ, Mismetti P, Poggio R, Valle R, Barron M, Guil M, et al. Clinical outcome of patients with upper-extremity deep vein thrombosis: results from the RIETE registry. Chest 2008;133:143-8.
12. Baumann Kreuziger L, Cote L, Verhamme P, Greenberg S, Caprini J, Munoz FJ, et al. A RIETE registry analysis of recurrent thromboembolism and hemorrhage in patients with catheter-related thrombosis. J Vasc Surg Venous Lymphat Disord 2015;3:243-50.e1.
13. Amin A, Bruno A, Trocio J, Lin J, Lingohr-Smith M. Comparison of differences in medical costs when new oral anticoagulants are used for the treatment of patients with non-valvular atrial fibrillation and venous thromboembolism vs warfarin or placebo in the US. J Med Econ 2015;18:399-409.

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APPENDIX (online only).

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