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The risk for recurrences in non-cancer patients with a symptomatic upper extremity deep vein thrombosis. Analysis of three RIETE cohorts.

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Keywords:	deep vein thrombosis (DVT), pulmonary embolism (PE), pacemaker, Upper extremity deep vein thrombosis, Recurrent venous thromboembolism
Abstract:	Abstract Background. The natural history of patients with a pacemaker-related upper extremity deep vein thrombosis (UEDVT) has not been consistently studied. Methods. We used the RIETE registry data to compare the outcomes during anticoagulation and after its discontinuation in non-cancer patients with symptomatic UEDVT associated to a pacemaker, other catheters or no catheter. The major outcome was the composite of symptomatic pulmonary embolism or recurrent DVT. Results. As of February 2022, 2,578 patients with UEDVT were included: 156 had a pacemaker-related UEDVT, 557 other catheters, and 1,865 had no catheter. During anticoagulation, 61 patients (2.3%) developed

	recurrent VTE, 38 had major bleeding (1.4%) and 90 died (3.4%). After its discontinuation, 52 patients (4.4%) had recurrent VTE and 6 major bleeding (0.5%). On multivariable analysis, there were no differences among subgroups in the rates of VTE recurrences or major bleeding during anticoagulation. After its discontinuation, patients with a pacemaker-related UEDVT had a higher risk for VTE recurrences than those with no catheter (adjusted OR: 4.59; 95%CI: 1.98-10.6). Conclusions. Patients with pacemaker-related UEDVT are at increased risk for VTE recurrences after discontinuing anticoagulation. If our findings are validated in adequately designed trials, this might likely justify changes in the current recommendations for the duration of anticoagulation.

Dear Editor,

I am writing to submit our manuscript entitled, **"The risk for recurrences in non-cancer patients with a symptomatic upper extremity deep vein thrombosis. Analysis of three RIETE cohorts."** *for consideration for* publication as a research article in VASCULAR MEDICINE.

Current guidelines of antithrombotic therapy recommend that in patients with catheter-associated upper-extremity deep vein thrombosis (UEDVT), anticoagulant therapy can be discontinued after 3 months if the catheter is removed. If it is not removed, the guidelines suggest that anticoagulation should be considered for a minimum of 3 months, or continued as long as the catheter remains. In patients with a pacemaker related UEDVT, there is scarce information to provide insight whether they should be regarded a transient or persistent risk factor.

We used the RIETE registry data to compare outcomes during anticoagulation and after its discontinuation in patients with symptomatic UEDVT related to a pacemaker (n=156), a venous catheter (n=560) or neither (n=1,865). On multivariable analysis, there were no differences among subgroups in the rates of VTE recurrences or major bleeding during anticoagulation. After its discontinuation, patients with a pacemaker-related UEDVT had a significantly higher risk for VTE recurrences than those with catheter-related UEDVT or spontaneous UEDVT. If our findings were validated in adequately designed trials, this might justify changes in the current recommendations for the duration of therapy.

This manuscript describes original work and is not under consideration by any other journal. All authors approved the manuscript and this submission.

Thank you for receiving our manuscript and considering it for review. We appreciate your time and look forward to your response.

Kind regards,

Manuel Jesús Núñez Fernández, on behalf of all authors

The risk for recurrences in non-cancer patients with a symptomatic upper extremity deep vein thrombosis. Analysis of three RIETE cohorts.

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Introduction.

Based on extrapolation of randomized trials from lower extremity deep vein thrombosis (DVT) and small cohort studies, current guidelines from the European Society of Vascular Surgery recommend that in patients with catheter-associated upper-extremity DVT (UEDVT) [1], anticoagulant therapy can be discontinued after three months if the catheter is removed. If the catheter is not removed, the guidelines suggest that anticoagulation should be considered for a minimum of three months, or continued as long as the catheter remains.

Since the placement of the first permanent transvenous pacemaker in 1965, asymptomatic UEDVT has been frequently associated with this procedure [2-5]. The symptomatic form in which swelling and pain prevail in the arm is much less frequent [6-7]; when it develops, UEDVT may lead to severe local morbidity and can be a source of pulmonary embolism (PE) [8-10].

In patients with a pacemaker-related UEDVT, there is scarce information to provide insight into the association between transvenous leads and UEDVT over time to elucidate whether they should be regarded a transient or persistent risk factor. Although anticoagulant treatment is the most widely used, the adequate duration is not known, nor are the complications associated with the treatment, or its suspension. An answer to this question would provide clarity as to whether anticoagulation may be discontinued after the initial 3 months of treatment for a first DVT or extended anticoagulant therapy should be considered.

RIETE (**R**egistro **I**nformatizado de **E**nfermedad **T**rombo**E**mbólica) is an ongoing registry of patients with symptomatic, objectively confirmed acute DVT or PE (Clinicaltrials.gov NCT: 02832245). It started in Spain in 2001, and 6 years later the database was translated into English with the aim to expand the registry to other countries. ~~ultimately allowing physicians worldwide to use their database to select the most appropriate therapy for their patients.~~ Data from this registry has been used to evaluate outcomes after acute venous thromboembolism

(VTE), such as the frequency of recurrent VTE, bleeding and mortality, and risk factors for these outcomes [11,12]. In the current analysis, we aimed to compare the incidence rate of VTE recurrences developing during anticoagulation or after its discontinuation in patients with an acute symptomatic: 1) pacemaker-related UEDVT; 2) catheter-related UEDVT; or 3) neither pacemaker nor catheter related (spontaneous) UEDVT.

Methods

We enrolled in RIETE consecutive patients with symptomatic, acute DVT or PE. DVT were confirmed by compression ultrasonography or contrast venography. PE were confirmed by ventilationperfusion lung scintigraphy, helical CT-scan or angiography. If patients currently participated in a therapeutic clinical trial with a blinded therapy were excluded. All patients (or their relatives) provided written or oral consent for their participation in the registry, in accordance with local ethics committee requirements.

Study design

Given the high association between cancer and VTE recurrences, we excluded patients with active cancer, or with history of cancer prior to the diagnosis of DVT. The major outcome was the incidence rate of VTE recurrences, defined as the composite of symptomatic (objectively confirmed) PE and/or DVT recurrences (in the ipsilateral arm, contralateral or in the lower-limb). When an episode of clinically suspected recurrent VTE was suspected, the investigation consisted on repeat compression ultrasonography, lung scintigraphy, helical-CT scan or pulmonary angiography, as appropriate. Secondary outcomes were major bleeding and death. Major bleeding was defined as a bleed that required two or more units of blood transfusion, was retroperitoneal, spinal or intracranial, or was fatal. Fatal bleeding was defined as any death occurring within 10 days of a major bleeding episode, in the absence of an alternative cause of death. Fatal PE, in the absence of an autopsy, was defined as any death

appearing within 10 days of a PE event, in the absence of any alternative cause of death.

Baseline variables

The following parameters were recorded in RIETE: patient's characteristics; VTE signs and symptoms at baseline; clinical status including any coexisting or underlying conditions such as hypertension, diabetes, atrial fibrillation, peripheral artery disease, ischemic stroke, chronic heart failure or chronic lung disease, recent (<30 days before) major bleeding, anemia or renal insufficiency; concomitant disorders; additional risk factors for VTE; blood tests at baseline (including hemoglobin, leukocyte and platelet count; creatinine clearance levels), the treatment received upon VTE diagnosis (drugs, doses and duration); concomitant drugs (including corticosteroids, antiplatelets or statins) and the outcomes. Anemia was defined as hemoglobin levels <13 g/dL for men and <12 g/dL for women. The RIETE registry restricted all values of these variables to the nearest recorded to the time of VTE diagnosis. We imputed missing values where necessary.

Treatment and follow-up

Patients were managed according to the clinical practice of each participating hospital (i.e., there was no standardization of treatment). The type, dose and duration of anticoagulant therapy were recorded. The decision to treat patients in hospital or at home was left to the attending physicians. After hospital discharge, patients were followed-up in the outpatient clinic (or telephone interviews with patients who could not show up for a clinic visit). During each visit, any signs or symptoms suggesting VTE recurrences or major bleeding were noted.

Statistical analysis

Continuous variables were reported with the mean, standard deviation, median and

interquartile range, and categorical variables with absolute frequencies and percentages. Differences between groups were assessed by the Chi-squared test for categorical variables and a T test for continuous data. The risk for VTE recurrences appearing during the course of anticoagulant therapy, and after its discontinuation was separately assessed using logistic regression models. Covariates entering into the model were selected by a significance level of P <0.10 on univariable analysis or by a well known association reported in the literature. The doses of anticoagulant drugs were not included because its choice might have been influenced by the physician's assessment of a patient's risk of bleeding or recurrent VTE. Adjusted odds ratio (OR) with 95% confidence intervals (CIs) were estimated. A SPSS software (version 25, SPSS Inc., Chicago, Illinois) was used for the statistical management of the data, and a two-sided p <0.05 was considered to be statistically significant.

Results

From March 2001 to March 2022, there were 4,505 patients with UEDVT in RIETE. Of these, 1,924 (43%) had cancer (active cancer 1,312, history of cancer 612) and were excluded for this study. Among the remaining 2,581 patients, 156 (5.9%) had a pacemaker-related UEDVT, 557 (22%) had UEDVT related to other catheters (central venous catheters 404, peripheral 153~~, stent 3~~) and 1,865 (72%) had UEDVT with no catheter. Overall, 256 patients presented with concomitant UEDVT and PE (5.1%, 8.1% and 11%, respectively).

Patients with a pacemaker-related UEDVT were more likely to be men, much older and more likely to have hypertension, atrial fibrillation, chronic heart failure, prior myocardial infarction or to be using antiplatelet drugs or statins at baseline than those with UEDVT secondary to other catheters, or those with no catheter. 1,193 (46.2%) were women. The proportion of women in each subgroup was: 30% of patients with VTE associated with pacemaker, 43% of those with VTE associated to other catheters, and 49% with spontaneous

(non-catheter related) upper extremity DVT (Table 1).

Among 1,492 patients diagnosed with UEDVT as outpatients, 839 (56%) required hospitalization to treat the DVT (50%, 64% and 56%, respectively), as shown in Table 2. Most patients in all three subgroups (90%, 83% and 82%, respectively) received initial therapy with low-molecular-weight heparin (LMWH). Then, 54% of patients with a pacemaker-related UEDVT switched to vitamin K antagonists, 32% kept receiving LMWH and 12% switched to direct oral anticoagulants. The duration of anticoagulation was longer in patients with a pacemaker-related UEDVT (median, 148 days) than in those in the other 2 subgroups (median, 102 and 130 days, respectively). The duration of follow-up after discontinuing anticoagulation was also longer in patients with a pacemaker-related UEDVT than in those in the other 2 subgroups (median, 445 vs. 295 and 178 days, respectively).

During the course of anticoagulation, 18 patients (0.7%) developed symptomatic PE, 43 (1.6%) had DVT recurrences (ipsilateral UEDVT 27, contralateral 11, lower-limb DVT 5), 38 (1.4%) suffered major bleeding (gastrointestinal 13, intracranial 4) and 90 (3.4%) died (fatal PE 6, fatal bleeding 4). Among the 6 patients who died of PE, 2 died of the index PE and 4 died of recurrent PE. During anticoagulation, no patient with a pacemaker-related UEDVT developed symptomatic PE, and the rate of DVT recurrences in patients with a pacemaker-related DVT was close to the rate of DVT recurrences in the other 2 subgroups (Table 3). All VTE recurrences in patients with a pacemaker-related UEDVT appeared beyond the third month of anticoagulant therapy. At variance with this, all VTE recurrences in patients with UEDVT related to other catheters appeared within the first 3 months (Supplementary Figure 1). The rate of major bleeding in patients with a pacemaker-related UEDVT was similar to the rate of major bleeding in patients with no catheter, and much lower than in those with UEDVT related to other catheters.

After discontinuing anticoagulant therapy, 10 patients (0.8%) developed symptomatic PE,

42 (3.6%) had DVT recurrences (ipsilateral UEDVT 23, contralateral 16, lower-limb DVT 3), 6 (0.5%) suffered major bleeding (gastrointestinal 3, intracranial 1) and 47 (4.0%) died (no fatal PE nor fatal bleeding). Among patients with a pacemaker-related UEDVT, all VTE recurrences (either symptomatic PE or DVT recurrences) appeared within the first 90 days after discontinuing anticoagulation, half of them (3 of 6) within the first 30 days (Supplementary Figure 2). On the other side, less than half of the VTE recurrences in patients with UEDVT related to other catheters (4 of 10) or no catheter (9 of 19) appeared within the first 3 months. The rate of symptomatic PE was significantly higher in patients with a pacemaker-related DVT than in those with no catheters, and non-significantly higher than in those with other catheters (Table 3).

Variables entering in the multivariable analyses were: age, sex, body weight, inpatient condition, chronic lung disease or heart failure, hypertension, diabetes, recent major bleeding, additional risk factors for VTE, initial VTE presentation (isolated UEDVT or with concomitant PE), prior VTE, anemia, platelet count, creatinine clearance levels at baseline and type of catheter (pacemaker, other catheters or no catheters). On multivariable analysis, there were no differences among subgroups in the risk for VTE recurrences (considering together symptomatic PE and DVT recurrences) during the course of anticoagulation, but patients with a pacemaker-related UEDVT (adjusted OR: 4.59; 95%CI: 1.98-10.6) or UEDVT secondary to other catheters (adjusted OR: 2.60; 95%CI: 1.35-4.98) were at increased risk for VTE recurrences after its discontinuation (Table 4).

Discussion

Previous studies reported that symptomatic UEDVT occurred in 0.3-0.5% of the patients mainly within the first month after pacemaker implantation 6-7, though may occur up to multiple years after. Recently Duijzer et al., report a review and meta-analysis collected 72

patients with symptomatic UEDVT related with pacemaker along 34 years (from 1985 to 2019). The authors requested "further research to elucidate whether trans-venous leads should be considered a transient or persistent risk factor" [10].

In our cohort of 156 patients with a symptomatic pacemaker-related UEDVT, along 21 years, there was a 2-fold higher incidence of VTE recurrences (the composite of symptomatic PE or DVT recurrences) after discontinuing anticoagulation that persisted after adjusting for potentially confounding factors. Compared to the other two subgroups of patients, the incidence rate of VTE recurrences in patients with a pacemaker-related UEDVT was higher and appeared early after discontinuing anticoagulant therapy, thus suggesting they could likely benefit from prolonging the duration of anticoagulation. Certainly, patients with a pacemaker-related UEDVT were older, more likely to be using antiplatelets concomitantly or to have renal insufficiency, and thus might have been considered to also be at high-risk for bleeding during anticoagulation. However, their incidence rate of major bleeding was similar to that in the other two subgroups.

During the course of anticoagulation, no patient with a pacemaker-related UEDVT in our cohort developed symptomatic PE, as compared to 6 patients with UEDVT secondary to other catheters and 12 with non-catheter related UEDVT. Interestingly, 6 of these 18 patients (33%) died of the PE. Thus, the clinical relevance of PE in patients with UEDVT should not be underestimated. Interestingly, no patient with a pacemaker-related UEDVT developed DVT recurrences during the first 3 months of therapy, the time when most recurrences had appeared in the other two subgroups of patients. However, the incidence rate of recurrent DVT in patients with a pacemaker related UEDVT increased quickly beyond the third month of therapy. The explanation for the previously mentioned data is that pacemakers, with few exceptions, will never be removed, and therefore their responsibility as a pathogenic factor in venous thrombosis will persist over time. It would be reasonable for these patients with

symptomatic UVDT-Pacemaker to be included in the group with venous thromboembolic disease related to a permanent risk factor. Therefore, the extension of anticoagulant treatment could be considered if there is no high risk of bleeding. The results of our study show that prolonging anticoagulant treatment in this group of patients is not associated with a higher risk of bleeding.

During anticoagulation, overall rates of recurrence (2.4%), major bleeding (1.4%) and mortality (3.4%) are lower than those previously documented in case series and reviews [13-21]. The referenced publications include patients with cancer, a condition that justifies higher percentages of recurrence (between 5.1% and 7.5%), major bleeding (between 3.1-6.7%), and mortality in the first months (between 11%-27%).

Our study has a number of limitations that should be emphasized. First, the sample size of patients with a pacemaker-related UEDVT in our cohort is rather small. And the amount of those who were followed-up after discontinuing anticoagulant therapy was even smaller. It is therefore dangerous to draw conclusions from a such sample size. However, ours is the largest cohort of patients with a pacemaker-related UEDVT published thus far. Second, unfortunately in RIETE we gather no information on the number of leads (i.e., dual or single lead pacemaker), to assess its influence on the development of symptomatic pacemaker-related UEDVT. Unlike catheters which offer option of removal, device therapies are often permanent and removal introduces additional risk for vascular injury, and need for device therapy either via subcutaneous or intracardiac if possible. Third, ours is an observational study where the therapeutic decisions (and the decision to discontinue or no) were left to the criteria of the attending physicians. Thus, our findings may be only considered as hypothesis-generating. However, to our knowledge there are no randomized controlled clinical trials comparing different therapeutic options in patients with a pacemaker-related UEDVT.

In summary, patients with a pacemaker-related UEDVT are at increased risk for VTE

recurrences after discontinuing anticoagulation. If our findings were validated in adequately designed trials, this might likely justify changes in the current recommendations for the duration of anticoagulant therapy.

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Table 1. Baseline characteristics of patients with upper-extremity deep vein thrombosis, according to the study subgroups.

	Pacemaker	Other catheters	No catheter
Patients, N	***156***	***557***	***1,865***
Demographics,			
Male gender	109 (70%)	318 (57%)†	958 (51%)‡
Age (mean years±SD)	71±13	55±18‡	51±21‡
Age >80 years	38 (24%)	34 (6.1%)‡	218 (12%)‡
Body weight (mean kg±SD)	76±13	75±20	74±16
Outpatients	119 (76%)	203 (36%)‡	1,170 (63%)‡
Initial DVT presentation,			
Concomitant PE	8 (5.1%)	45 (8.1%)	203 (11%)*
Concomitant diseases,			
Hypertension	75 (48%)	183 (33%)‡	470 (25%)‡
Diabetes	32 (21%)	110 (20%)	167 (8.9%)‡
Atrial fibrillation	11 (7.0%)	21 (3.8%)	43 (2.3%)†
Prior myocardial infarction	27 (17%)	41 (7.4%)‡	96 (5.1%)‡
Prior ischemic stroke	11 (7.0%)	23 (4.1%)	80 (4.3%)
Peripheral artery disease	7 (4.5%)	23 (4.1%)	30 (1.6%)*
Prior artery disease	37 (24%)	71 (13%)†	176 (9.4%)‡
Chronic heart failure	41 (26%)	43 (7.7%)‡	108 (5.8%)‡
Chronic lung disease	13 (8.3%)	68 (12%)	106 (5.7%)
Recent major bleeding	1 (0.6%)	61 (11%)‡	34 (1.8%)
Risk factors for VTE,			
Recent surgery	28 (18%)	170 (31%)†	116 (6.2%)‡
Recent immobility ≥4 days	15 (9.6%)	185 (33%)‡	221 (12%)
Pregnancy or postpartum	0	7 (1.3%)	39 (2.1%)
Estrogens use	3 (1.9%)	11 (2.0%)	198 (11%)‡
None of the above	110 (71%)	193 (35%)‡	1,310 (70%)
Prior VTE	6 (3.8%)	50 (9.0%)*	227 (12%)‡
Blood tests,			
Anemia	49 (31%)	386 (69%)‡	499 (27%)
Platelet count <100,000/μL	3 (1.9%)	19 (3.4%)	26 (1.4%)
CrCl levels <60 mL/min	56 (36%)	169 (30%)	319 (17%)‡
Concomitant drugs,			
Antiplatelet therapy	48 (31%)	84 (15%)‡	217 (12%)‡
Statins	51 (33%)	81 (15%)‡	235 (13%)‡
Corticosteroids	6 (3.8%)	112 (20%)‡	94 (5.0%)

Comparisons between patients with pacemakers vs. other subgroups:
*p <0.05; †p <0.01; ‡p < 0.001.
Abbreviations: SD, Standard deviation; PE, pulmonary embolism; VTE, venous thromboembolism; CrCl, Creatinine clearance.

Table 2. Treatment strategies.

	Pacemaker	Other catheters	No catheter
Patients, N	***156***	***557***	***1,865***
Outpatients requiring hospitalization	60/119 (50%)	130/203 (64%)*	649/1,170 (56%)
Initial therapy,			
Low-molecular-weight heparin	140 (90%)	462 (83%)*	1,532 (82%)*
Mean daily doses (IU/kg/day)	166±38	160±51	172±44
LMWH doses <120 IU/kg/day	19 (14%)	102 (22%)*	219 (14%)
Unfractionated heparin	6 (3.8%)	57 (10%)*	73 (3.9%)
Direct oral anticoagulants	7 (4.5%)	19 (3.4%)	111 (6.0%)
Rivaroxaban	4 (2.6%)	14 (2.5%)	79 (4.2%)
<30 mg daily	1 (33%)	3 (21%)	13 (16%)
Apixaban	3 (1.9%)	6 (1.1%)	31 (1.7%)
<20 mg daily	1 (33%)	2 (40%)	15 (48%)
Fondaparinux	2 (1.3%)	4 (0.7%)	72 (3.9%)
<7.5 mg daily	0	0	6 (8.3%)
Thrombolytic drugs	1 (0.6%)	4 (0.7%)	47 (2.5%)
Long-term therapy,			
Vitamin K antagonists	85 (54%)	198 (36%)‡	1,004 (54%)
Low-molecular-weight heparin	50 (32%)	264 (47%)‡	470 (25%)
Mean daily doses (IU/kg/day)	142±41	136±51	156±47
LMWH doses <120 IU/kg/day	14 (28%)	105 (40%)	102 (22%)
Direct oral anticoagulants	19 (12%)	64 (12%)	330 (18%)
Rivaroxaban	5 (3.2%)	38 (6.8%)	187 (10%)†
<20 mg daily	0	2 (5.3%)	8 (4.3%)
Apixaban	10 (6.4%)	20 (3.6%)	101 (5.4%)
<10 mg daily	2 (20%)	2 (10%)	13 (13%)
Dabigatran	1 (0.6%)	4 (0.7%)	31 (1.7%)
Edoxaban	3 (1.9%)	2 (0.4%)	11 (0.6%)
Duration of therapy,			
Mean days ± SD	303±410	151±181	218 ± 305
Median days (IQR)	148 (99-273)	102 (91-148)	130(96-224)‡
Follow-up after discontinuing therapy,			
Mean days ± SD	612±565	503±544	415±618
Median days (IQR)	445 (182-962)	295 (95-814)	178 (53-536)

Comparisons between patients with pacemakers vs. other subgroups:
*p <0.05; †p <0.01; ‡p < 0.001.
Abbreviations: IU, International units; SD, Standard deviation; IQR, inter-quartile range.

Table 3. Clinical outcomes during anticoagulation and after its discontinuation.

	Pacemaker		Other Catheters		No catheter	
	N	Events per 100 patient-years	N	Events per 100 patient-years	N	Events per 100 patient-years
On anticoagulation,						
Patients, N		***156***		***557***		***1,865***
Symptomatic PE	0	-	6	2.63 (1.06-5.46)	12	1.03 (0.56-1.75)
Recurrent DVT	3	2.33 (0.59-6.35)	6	2.66 (1.08-5.53)	34	3.05 (2.16-4.20)
Ipsilateral UEDVT	2	1.56 (0.26-5.14)	1	0.44 (0.02-2.19)	24	2.09 (1.37-3.07)
Contralateral UEDVT	1	0.78 (0.04-3.84)	2	0.89 (0.15-2.93)	7	0.61 (0.27-1.21)
Lower-limb DVT	0	-	2	0.89 (0.15-2.93)	3	0.26 (0.07-0.71)
VTE recurrences, any	3	2.33 (0.59-6.35)	12	5.33 (2.89-9.07)	46	4.13 (3.07-5.44)
Major bleeding	2	1.56 (0.26-5.14)	19	8.40 (5.21-12.9)†	17	1.38 (0.82-2.19)
Site of bleeding,						
Gastrointestinal	0	-	7	3.07 (1.34-6.08)*	6	0.51 (0.21-1.07)
Hematoma	1	0.78 (0.04-3.84)	6	2.62 (1.06-5.44)	2	0.17 (0.03-0.56)
Intracranial	0	-	1	0.44 (0.02-2.16)	3	0.26 (0.07-0.70)
Retroperitoneal	0	-	2	0.87 (0.15-2.88)	2	0.17 (0.03-0.57)
Pericardial	1	0.78 (0.04-3.84)	0	-	0	-
Death	4	2.84 (0.90-6.85)	30	13.1 (8.97-18.4)†	56	4.79 (3.65-6.17)
Causes of death,						
Pulmonary embolism	0	-	2	0.87 (0.15-2.88)	4	0.34 (0.11-0.82)
Initial PE	0	-	0	-	2	0.17 (0.03-0.56)
Recurrent PE	0	-	2	0.87 (0.15-2.88)	2	0.17 (0.03-0.56)
Bleeding	0	-	4	1.74 (0.55-4.20)	0	-
Off anticoagulation,						
Patients, N		***59***		***275***		***837***
Symptomatic PE	3	3.20 (0.81-8.71)	3	0.80 (0.20-2.17)	4	0.42 (0.13-1.02)*
Recurrent DVT	5	5.71 (2.09-12.6)	12	3.79 (2.15-6.20)	25	2.76 (1.83-4.02)
Ipsilateral UEDVT	4	4.57 (1.45-11.0)	4	1.09 (0.35-2.63)	15	1.66 (0.96-2.67)
Contralateral UEDVT	1	1.14 (0.06-5.63)	8	2.18 (1.01-4.14)	7	0.77 (0.34-1.53)
Lower-limb DVT	0	-	0	-	3	0.33 (0.10-1.90)
VTE recurrences, any	8	9.71 (4.51-18.4)	17	4.65 (2.80-7.29)	29	3.22 (2.19-4.56)*
Major bleeding	1	1.02 (0.05-5.01)	3	0.81 (0.21-2.21)	2	0.21 (0.04-0.70)
Site of bleeding,						
Gastrointestinal	1	1.02 (0.05-5.01)	1	0.27 (0.01-1.33)	1	0.11 (0.01-0.52)
Intracranial	0	-	0	-	1	0.11 (0.01-0.52)
Death	3	3.03 (0.77-8.26)	22	5.82 (3.74-8.66)	22	2.32 (1.49-3.45)
Causes of death,						
Pulmonary embolism	0	-	0	-	0	-
Bleeding	0	-	0	-	0	-

Comparisons between patients with pacemakers vs. other subgroups: $^{*}p < 0.05$; $^{\dagger}p$
Differences between pacemaker-related EUDVT and other subgroups: $^{*}<0.05$; $^{\dagger}p < 0.01$.
Abbreviations: PE, pulmonary embolism; DVT, deep vein thrombosis; VTE, venous thromboembolism.

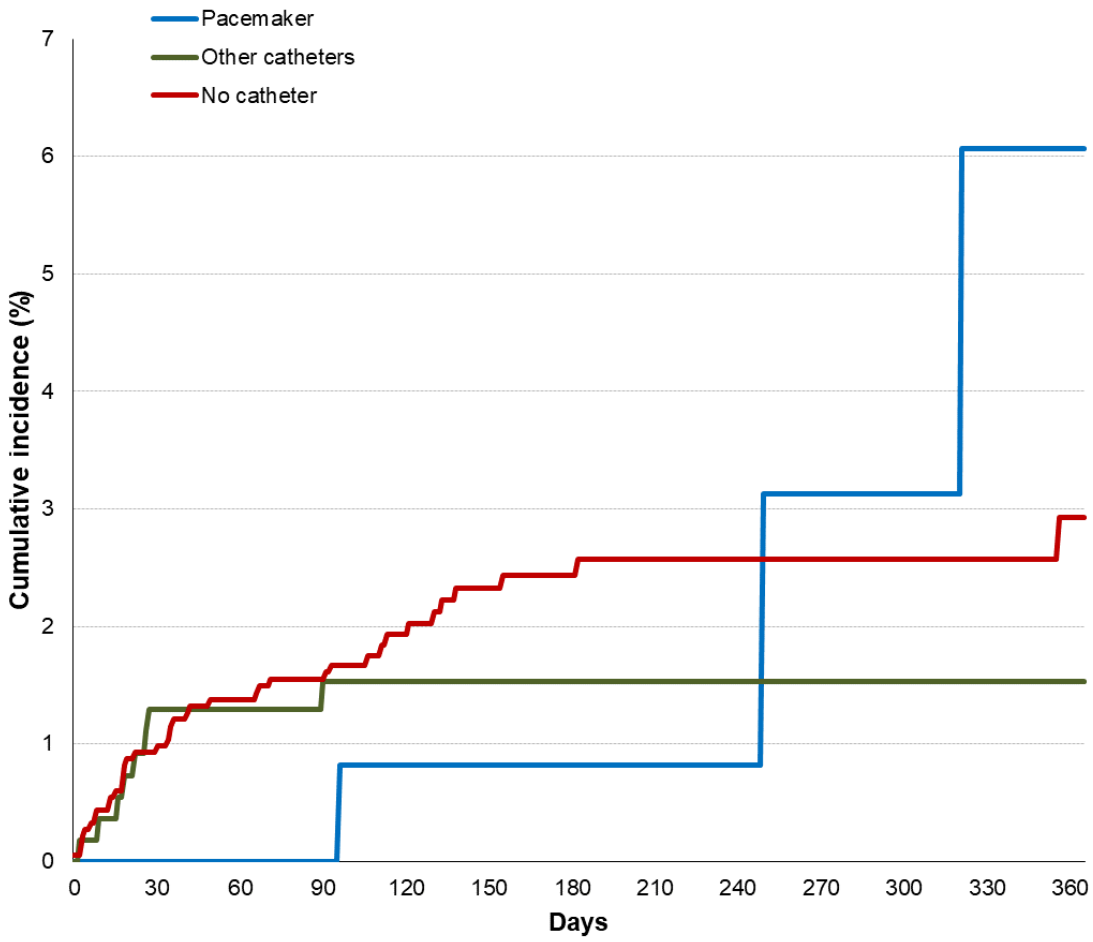
Table 4. Uni- and multivariable analyses for VTE recurrences during and after discontinuing anticoagulant therapy.

	During anticoagulation		Off anticoagulation	
	Univariable OR (95% CI)	Multivariable OR (95% CI)	Univariable OR (95% CI)	Multivariable OR (95% CI)
Demographics,				
Gender (males)	1.04 (0.63-1.73)	-	1.34 (0.77-2.34)	-
Age ≥50 years	1.09 (0.66-1.81)	-	1.48 (0.85-2.56)	-
Body weight ≥70 kg	0.82 (0.49-1.36)	-	0.77 (0.44-1.33)	-
Inpatients	1.17 (0.69-1.97)	-	1.32 (0.75-2.30)	-
Underlying conditions,				
Chronic lung disease	0.20 (0.03-1.48)	0.21 (0.03-1.50)	1.04 (0.37-2.95)	-
Chronic heart failure	1.61 (0.72-3.58)	-	1.10 (0.39-3.12)	-
Hypertension	1.31 (0.77-2.22)	-	1.49 (0.84-2.62)	-
Diabetes	1.08 (0.51-2.30)	-	1.72 (0.87-3.41)	-
Recent major bleeding	1.82 (0.65-5.12)	-	0.48 (0.07-3.58)	-
Additional risk factors,				
Transient risk factors	0.48 (0.26-0.87)*	0.53 (0.29-0.98)*	0.45 (0.24-0.85)*	0.35 (0.18-0.69)†
Prior VTE	2.44 (1.33-4.48)†	2.30 (1.24-4.26)†	1.57 (0.69-3.57)	-
Blood tests,				
Anemia	1.11 (0.66-1.87)	-	1.00 (0.57-1.75)	-
Platelet count <50,000/uL	10.4 (2.17-50.2)*	0.72 (0.31-1.69)	4.20 (0.48-36.6)	-
CrCl levels <60 mL/min	0.71 (0.36-1.41)	-	1.62 (0.88-2.99)	-
Concomitant drugs,				
Antiplatelets	0.68 (0.29-1.58)	-	1.30 (0.62-2.72)	-
Initial VTE presentation,				
Concomitant PE	1.56 (0.76-3.20)	1.47 (0.71-3.03)	1.48 (0.57-3.84)	-
Study subgroups,				
Spontaneous	Ref.	Ref.	Ref.	Ref.
Pacemaker	0.76 (0.23-2.46)	-	4.37 (1.91-10.0)†	4.59 (1.98-10.6)‡
Venous catheter	0.85 (0.45-1.61)	-	1.82 (0.99-3.37)	2.60 (1.35-4.98)†

*p <0.05; †p <0.01; ‡p < 0.001.

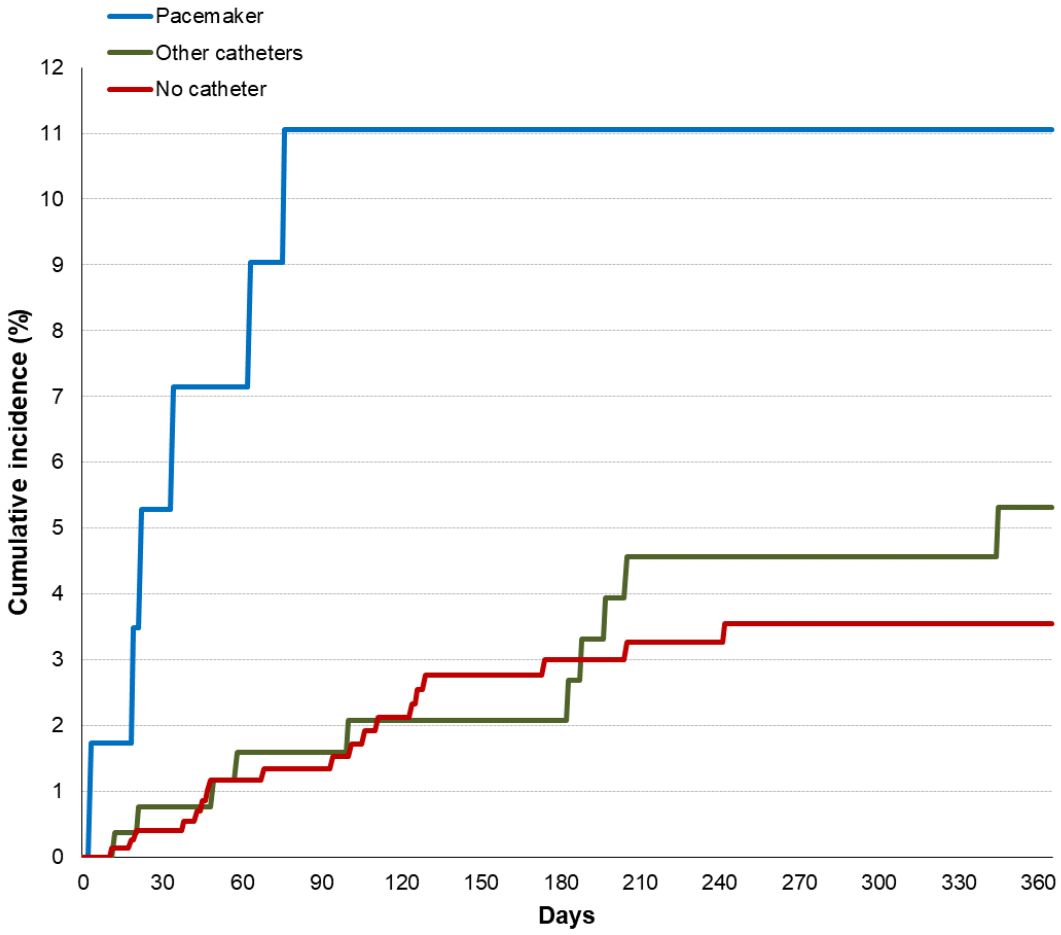
Abbreviations: OR, odds ratio; CI, confidence intervals; VTE, venous thromboembolism; CrCl, creatinine clearance; PE, pulmonary embolism.

Supplementary Figure 1. VTE recurrences during the course of anticoagulant therapy.



Days		10	30	90	180	270	365
Pacemaker	***At-risk patients***	156	155	150	106	53	48
	Outcomes	0	0	0	1 (0.8%)	2 (3.1%)	3 (6.1%)
Other Catheters	***At-risk patients***	549	533	478	272	80	69
	Outcomes	2 (0.4%)	7 (1.3%)	8 (1.5%)	8 (1.5%)	8 (1.5%)	8 (1.5%)
No catheter	***At-risk patients***	1,849	1,807	1,726	1,211	569	507
	Outcomes	8 (0.4%)	18 (1.0%)	28 (1.5%)	38 (2.4%)	39 (2.6%)	40 (2.9%)

Supplementary Figure 2. VTE recurrences after discontinuing anticoagulant therapy.



Days		10	30	90	180	270	365
Pacemaker	***At-risk patients***	58	55	48	41	38	34
	Outcomes	1 (1.7%)	3 (5.3%)	6 (11.1%)	6 (11.1%)	6 (11.1%)	6 (11.1%)
Other Catheters	***At-risk patients***	273	265	235	187	151	146
	Outcomes	0	2 (0.8%)	4 (1.6%)	5 (2.1%)	9 (4.6%)	10 (5.3%)
No catheter	***At-risk patients***	812	746	622	473	360	332
	Outcomes	0	3 (0.4%)	9 (1.3%)	17 (3.0%)	19 (3.5%)	19 (3.5%)

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APPENDIX

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