Incidence of major adverse cardiovascular events among patients with provoked and unprovoked venous thromboembolism: Findings from the Registro Informatizado de Enfermedad Tromboembólica Registry

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ABSTRACT

Objective: Overlap exists between the risk factors for coronary artery disease and venous thromboembolism (VTE). However, a paucity of data is available on the incidence of major acute cardiovascular events (MACE) and major adverse limb events (MALE) among patients presenting with VTE. Moreover, it is unknown whether the rate of cardiovascular outcomes differs among patients with unprovoked vs provoked VTE.

Methods: We analyzed the data from 2009 to 2017 in the Registro Informatizado de Enfermedad Tromboembólica registry, an ongoing, multicenter, international registry of consecutive patients with a diagnosis of objectively confirmed VTE. The query was restricted it to patients with data entry for the arterial outcomes. The baseline prevalence of coronary artery disease risk factors was compared between patients with provoked (ie, immobility, cancer, surgery, travel >6 hours, hormonal causes) and unprovoked VTE. After the initial VTE event, we followed up patients for the composite primary outcome of incident MACE (ie, stroke, myocardial infarction, unstable angina) and/or MALE (ie, major limb events). We used the χ^2 test for baseline associations and a Cox proportional hazard for multivariate analysis. We used IBM SPSS, version 24 (IBM Corp, Armonk, NY) for statistical analysis. A *P* value of <.05 was considered statistically significant.

Results: We analyzed the data from 41,259 patients with VTE, of whom 22,633 (55.6%) had experienced a provoked VTE. During follow-up, the patients with provoked VTE were more likely to develop MACE or MALE than were patients with unprovoked VTE (hazard ratio [HR], 1.3; 95% confidence interval [CI], 1.1-1.5). The association of arterial events with recent immobility (HR, 1.4; 95% CI, 1.5-12.1) and cancer (HR, 1.7; 95% CI, 1.4-1.9) was strong. After adjusting for multiple conventional cardiovascular risk factors, provoked VTE, compared with unprovoked VTE, was significantly associated with an increased hazard for MACE (HR, 1.4; 95% CI, 1.1-1.7). Cancer remained a significant adjusted predictor for both MACE (HR, 1.7; 95% CI, 1.4-2.1) and MALE (HR, 2.1; 95% CI 1.01-4.6) in those with provoked VTE.

Conclusions: Among patients with VTE, provoked cases, specifically those with cancer-associated VTE, have an increased risk of major arterial events. (J Vasc Surg: Venous and Lym Dis 2019;■:1-7.)

Keywords: Major adverse cardiovascular events; Major adverse limb events; Provoked; Venous thromboembolism; VTE

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Atherothrombosis and venous thromboembolism (VTE) have often been viewed as mechanistically separate entities, specifically with respect to the epidemiology, pathophysiology, and subsequent treatment strategies. Arterial thrombi usually develop in high shear stress areas, where plaques are formed, creating a platelet-rich product termed "white thrombus." In contrast, venous thrombi have been noted to form in low-flow, undamaged vessels, consisting mainly of fibrin and erythrocytes, creating "red thrombi."[1]

Recent studies have challenged the concept that VTE and atherosclerosis are completely separate entities, because patients with VTE have experienced more arterial events than did control subjects.[2,3] The common risk factors for atherosclerosis and VTE could overlap.[2] Atherosclerosis risk factors include hypertension, diabetes mellitus, cigarette smoking, obesity, hyperlipidemia, and the metabolic syndrome combination of obesity, hypertension, hyperglycemia, and hyperlipidemia. The key risk factors for VTE surgery have included immobilization, cancer, estrogen use, thrombophilia, and pregnancy.[1,4-7] Prandoni et al[3] suggested that atherosclerosis could induce VTE or that they share common risk factors. In a recent study of patients with VTE and active cancer, arterial ischemic events emerged as a major cause of mortality.[8] The differences in the underlying thrombosis triggers and persistent thrombophilia could plausibly also affect the likelihood of atherosclerotic progression. However, a paucity of long-term data is available on incident arterial events between patients with provoked vs unprovoked VTE, which could affect the preventive considerations after a thrombotic event.

Major arterial events included major acute cardiovascular events (MACE) and major adverse limb events (MALE). MACE represent a composite of myocardial infarction, revascularization, cerebrovascular accidents, and aortic events.[9] MALE is a key endpoint for revascularization therapies in critical limb ischemia—inclusive of amputation (transtibial or above) or any major vascular reintervention (ie, thrombectomy, thrombolysis, or major surgical procedure [new bypass graft, jump/interposition graft revision]) in the index limb.[10]

Subsequent cardiovascular events (including MACE and MALE) could variably occur in patients with precedent VTE.[8] Among the distinct subgroups, a comparison of those with provoked VTE vs those with unprovoked VTE is of particular importance because of the prognostic and treatment implications.[11]

The aim of the present study was to measure the prevalence of cardiovascular risk factors in patients with provoked vs unprovoked VTE and to compare the incidence of the composite primary outcome of MACE and/or MALE in these two groups using the data from Registro Informatizado de Enfermedad Tromboembólica (RIETE), a large multicenter prospective registry of patients with VTE.

ARTICLE HIGHLIGHTS

- **Type of Research:** Multicenter retrospective analysis of prospectively collected data in the Registro Informatizado de Enfermedad Tromboembólica registry
- **Key Findings:** Of 41,259 patients with venous thromboembolism (VTE), 55.6% had provoked VTE and were more likely to develop major adverse cardiac events (MACE) and major adverse limb events (MALE) than were patients with unprovoked VTE (hazard ratio [HR], 1.3; 95% confidence interval [CI], 1.1-1.5). The association of MALE with recent immobility (HR, 1.4; 95% CI, 1.5-12.1) and cancer (HR, 1.7; 95% CI, 1.4-1.9) was strong. After adjusting for cardiovascular risk factors, provoked VTE was associated with MACE (adjusted HR, 1.4; 95% CI, 1.1-1.7), and cancer predicted for both MACE (adjusted HR, 1.7; 95% CI, 1.4-2.1) and MALE (adjusted HR, 2.1; 95% CI, 1.01-4.6) in provoked VTE.
- **Take Home Message:** Patients with provoked VTE, specifically those with cancer-associated VTE have an increased risk of MACE/MALE.

METHODS

All data and supporting materials have been described in the present report. RIETE is an ongoing, multicenter, international registry of consecutive patients with a diagnosis of objectively confirmed VTE. The registry was originally started in Spain in 2001 with the goal of gathering a large sample of patients with VTE, with specific attention to those excluded from the typical randomized trials of anticoagulation therapy (including those with severe renal insufficiency, liver failure, recent major bleeding, pregnancy, disseminated cancer, or thrombocytopenia and the elderly). The aim was to understand the common factors of their presentation, management pattern and outcomes, and the factors associated with better or worse patient outcomes. RIETE includes 207 investigators from 179 participating centers.

At each participating center, the patients are screened by the site investigator and evaluated for eligibility. The investigators were required to enroll consecutive patients. Periodic audits of the sites confirmed the consecutiveness. No duplicates are permitted, and patients who have been enrolled in blinded treatment trials are ineligible. The inclusion criteria for RIETE are as follows: acute objectively confirmed deep venous thrombosis or acute objectively confirmed pulmonary embolism (PE); data available for ≥54 core variables; and a minimum of 3 months of follow-up. The exclusion criteria are as follows: enrollment in any treatment trial (VTE or other conditions) in a blinded fashion, previous enrollment in the registry, and the lack, or withdrawal, of patient consent.[12]

Table I. Basic demographic variables for provoked and unprovoked venous thromboembolism (*VTE*)

Demographic variable	All (N = 41,259)	Provoked VTE group (n = 22,633)	Unprovoked VTE group (n = 18,626)	OR (95% CI)	*P* value
Age >65 years	23,883 (57.9)	12,573 (55.6)	11,310 (60.7)	0.9 (0.8-0.97)	<.01
Male gender	20,142 (48.8)	10,025 (44.3)	10,117 (54.3)	0.7 (0.6-0.7)	<.01
BMI >30 kg/m^2	8806 (29.7)	4316 (26.3)	4490 (33.8)	0.8 (0.8-0.9)	<.01
Comorbidities					
History of CAD	2778 (7.3)	1571 (7.5)	1207 (7.0)	1.03 (0.9-1.2)	.09
History of cerebral ischemia	2615 (6.8)	1568 (7.4)	1046 (6.1)	1.1 (1.06-1.1)	<.01
PAD	1453 (3.8)	813 (3.9)	640 (3.7)	1.02 (1.0-1.1)	.48
Diabetes	5806 (15.2)	3309 (15.7)	2497 (14.5)	1.04 (1.02-1.1)	.01
Hypertension	17,971 (46.9)	9270 (44)	8701 (50.4)	0.9 (0.87-0.90)	<.01
Current smoker	5659 (15.1)	2881 (14.0)	2778 (16.5)	0.9 (0.89-0.94)	<.01
CHF	3004 (7.3)	1755 (7.8)	1249 (6.7)	1.1 (1.03-1.1)	<.01
Previous VTE	6276 (15.2)	2612 (11.5)	3664 (19.7)	0.7 (0.7-0.8)	<.01
Known thrombophilia	1073 (2.9)	427 (2.2)	646 (3.9)	0.7 (0.7-0.8)	<.01
Medication					
Antiplatelets	6733 (17.2)	3673 (17.1)	3060 (17.4)	0.98 (0.9-1.04)	.5
Statins	8019 (21.1)	4078 (19.5)	3941 (23.1)	0.9 (0.89-0.93)	<.01
Presentation					
PE only	21,806 (52.9)	11,781 (52.1)	10,025 (53.8)	0.97 (0.9-0.99)	<.01

BMI, Body mass index; *CAD*, coronary artery disease; *CHF*, congestive heart failure; *CI*, confidence interval; *OR*, odds ratio; *PAD*, peripheral artery disease; *PE*, pulmonary embolism.
Data are presented as number (%).

The initial VTE event was confirmed by the findings from objective tests (ie, contrast venography or compression ultrasonography for suspected deep vein thrombosis; pulmonary angiography, lung scintigraphy, or helical computed tomography scan for suspected PE).[12] Patients were excluded if they were participating in a therapeutic clinical trial. The patients' cases were managed according to the clinical practice of each participating hospital, and the patients were not subject to any predetermined intervention. All subjects (or their legal power of attorney, if indicated) had provided written consent for their participation in the REITE registry. The institutional review board of each recruiting site approved the study protocol and informed consent forms.

The arterial outcomes data were added in February 2009 to the RIETE database. Therefore, for the present study, we focused on patients included from February 2009 to December 2017 and included those who had data available for arterial events. Our operational definition of MACE did not include aortic events.

Study variables and data quality. The following parameters were recorded when the qualifying episode of VTE had been diagnosed: patient age, sex, and body mass index (BMI); history of coronary artery disease (CAD), cerebral ischemia, peripheral artery disease, diabetes, hypertension, current smoking, a history of VTE, thrombophilia history, previous use of antiplatelet agents (eg, aspirin or other platelet inhibitors), and the presence of chronic heart or lung disease. We classified provoked VTE as that in those patients with a history of cancer, recent surgery, immobility (≥4 days), travel >6 hours, and hormonal changes (including pregnancy, puerperium, and estrogen hormonal therapy). Risk factors such as hypertension, diabetes, smoking, and a history of previous coronary, cerebrovascular or peripheral artery disease, and congestive heart failure (CHF) predispose to the development of CAD.[1,4-7]

The main outcome was the composite of MACE and/or MALE, which were prospectively collected after the VTE diagnosis. MACE were defined as the development of ischemic stroke, myocardial infarction, or unstable angina after the incident VTE. MALE were defined as amputation (transtibial or above) or any major vascular reintervention (ie, thrombectomy, thrombolysis, or major surgical procedure [new bypass graft, jump/interposition graft revision]).

We defined myocardial infarction as the presence of ischemic symptoms combined with a transient increase in CK-MB (creatine kinase-muscle/brain) or troponin and/or typical electrocardiographic signs (ie, development of pathologic Q-waves or ST-segment elevation or depression). Ischemic stroke was diagnosed if the patient had had the appropriate symptoms and signs for >24 hours and had brain computed tomography or magnetic resonance imaging findings that showed a clinically compatible lesion. Critical limb ischemia was defined as chronic ischemia at rest or the presence of gangrene or ulcers in 1 or both legs attributable to arterial occlusive disease.[13]

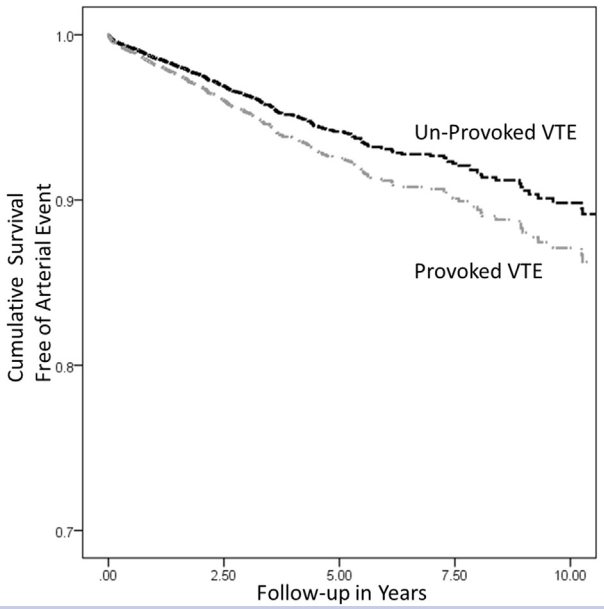

Fig. Cumulative survival free of an arterial event. Survival of provoked vs unprovoked venous thromboembolism (*VTE*) groups free of any arterial events (major adverse cardiac events [MACE] and major adverse limb events [MALE]). The provoked VTE group (defined as VTE secondary to cancer, surgery, immobility, travel, or hormonal changes) had decreased survival compared with the unprovoked VTE group (provoked VTE: 2.5 years, 19,543; 5 years, 2225; 7.5 years, 535; 10 years, 330; and unprovoked VTE: 2.5 years, 15,387; 5 years, 2303; 7.5 years, 580; 10 years, 356; $P < .01$).

The local primary investigators ensured that eligible patients had been consecutively enrolled. Data were recorded into a computer-based case report form at each participating hospital and submitted to a centralized coordinating center through a secure website. Data encryption was used to enhance confidentiality and security. The data quality was regularly monitored and documented electronically to detect inconsistencies or errors. The data quality was also monitored by periodic visits to the participating hospitals by contract research organizations, which compared the medical records with the data in the web database. The patient identities remained confidential and were identified by a unique number assigned by the RIETE central coordinating center.

Statistical analysis. We used descriptive statistics to summarize the distribution of baseline parameters. Continuous variables are expressed as the mean ± standard deviation or the median and interquartile range (IQR), as appropriate. Categorical variables are expressed as the absolute numbers and percentages. We categorized all continuous variables in quartiles, unless otherwise specified. To compare the baseline differences in cardiovascular risk factors at baseline, we used the Student *t*-test and Mann-Whitney *U* test for continuous variables and the χ^2 test or the Fisher exact test for categorical variables. We analyzed the arterial outcomes as a composite MALE and MACE outcome, as well as independently, using Cox proportional hazards models. We then created 3 different models based on the adjusted conventional cardiovascular risk factors and cardiovascular therapy. Model 1 was adjusted of age, gender, and BMI. Model 2 was adjusted for all the risk factors included in model 1 plus diabetes mellitus, smoking, and hypertension. Finally, model 3 was adjusted for all the risk factors included in model 2 plus a history of CAD, a history of ischemic stroke, the presence of peripheral artery disease, the use of statin therapy, and the use of antiplatelet therapy.

RESULTS

We analyzed the data from 41,259 patients with VTE. Of these 41,259 patients, 22,633 (55.6%) had experienced a provoked VTE event. In the patients with provoked VTE, cancer was identified as a risk factor for 23.6%, recent surgery for 10.8%, immobility for 21.6%, and pregnancy/hormonal therapy for 7.3%. In the provoked VTE group, 57.9% of the patients were aged >65 years compared with 60.7% in the unprovoked VTE group ($P < .01$). Male

Table II. Arterial outcomes in provoked venous thromboembolism (*VTE*) group compared with those with unprovoked VTE[a]

	Any arterial event		MACE		MALE	
Provoked VTE group	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Overall	1.3 (1.1-1.5)	<.001	1.3 (1.1-1.5)	.03	1.73 (0.98-3.1)	.06
Surgery	0.64 (0.5-0.9)	.003	0.7 (0.5-0.9)	.006	0.4 (0.1-1.8)	.25
Immobility	1.7 (1.5-2.1)	<.001	1.7 (1.5-2.1)	<.001	1.7 (0.98-3.1)	.05
Travel >6 hours	0.5 (0.3-0.97)	.39	0.6 (0.3-1.04)	.06	NA	.6
Hormonal therapy	0.2 (0.1-0.4)	<.001	0.2 (0.1-0.4)	<.001	NA	.6
Pregnancy	0.1 (0.001-1.6)	.09	0.1 (0.001-1.8)	.1	NA	NA
Puerperium	0.1 (0.001-3.1)	.15	0.1 (0.001-3.5)	.2	NA	NA
Cancer	1.7 (1.4-1.9)	<.001	1.6 (1.4-1.9)	<.001	1.8 (1.0-3.09)	.04

CI, Confidence interval; *HR*, hazard ratio; *MACE*, major adverse cardiac events; *MALE*, major adverse limb events; *NA*, not applicable.
[a]Data are presented for cumulative arterial, MACE, and MALE outcomes in the provoked VTE group for each identified provoked VTE risk factor.

Table III. Arterial events adjusted for cardiovascular risk factors

	Model 1		Model 2		Model 3	
Event	Adjusted HR	*P* value	Adjusted HR	*P* value	Adjusted HR	*P* value
Any arterial	1.48 (1.2-1.8)	<.001	1.47 (1.2-1.8)	<.001	1.39 (1.1-1.7)	<.01
MACE	1.43 (1.1-1.7)	<.001	1.39 (1.1-1.7)	.002	1.35 (1.09-1.67)	<.01
MALE	1.5 (0.8-2.9)	.1	1.3 (0.6-2.4)	.5	1.1 (0.6-2.3)	.6

CI, Confidence interval; *HR,* hazard ratio; *MACE,* major adverse cardiac events; *MALE,* major adverse limb events.
Data are presented for arterial events adjusted for cardiovascular risk factors: model 1, age, gender, and body mass index; model 2, factors included in model 1 plus diabetes mellitus, smoking, and hypertension; and model 3, factors included in models 1 and 2 plus previous myocardial infarction, a history of cerebrovascular accident, peripheral artery disease, statin therapy, and antiplatelet therapy.

patients constituted 48.8% of the provoked VTE group compared with 54.3% in the unprovoked VTE group ($P < .01$). Almost one third of the patients (29.7%; $P < .01$) were obese (BMI >30 kg/m^2) and 15.2% had diabetes ($P < .01$). Previous VTE had occurred in 15.2% of the patients (11.5% in the provoked VTE group and 19.7% in the unprovoked VTE group; $P < .01$), and 7.3% of the patients had a history of CAD ($P = .09$). PE was the initial presentation in 52.9% of the patients ($P < .01$; Table I). The median follow-up after the initial VTE event was 266 days (IQR, 60-737 days). The median follow-up period was 233 days (IQR, 111-527 days) for the provoked events and 337 days (IQR, 166-688 days; $P < .01$) for the unprovoked events.

The defined cardiovascular risk factors, including diabetes (odds ratio [OR], 1.04; 95% CI, 1.02-1.1; $P < .01$), a history of stroke (OR, 1.09; 95% CI, 1.06-1.1; $P = .01$), the presence of CHF (OR, 1.07; 95% CI, 1.03-1.1; $P < .01$), and current smoking (OR, 0.91; 95% CI, 0.89-0.94; $P < .01$), were more common in the provoked VTE group. The proportion of patients with a history of CAD (OR, 1.03; 95% CI, 0.9-1.2; $P = .09$) or peripheral artery disease (OR, 1.02; 95% CI, 0.97-1.1; $P = .48$) was not different between the two groups. Treatment with CAD preventative therapies such as statins (OR, 0.9; 95% CI, 0.89-0.93; $P < .01$) were less common in the provoked VTE group. In the provoked VTE group, cancer was identified as a risk factor for the VTE events in 23.6% of patients; however, surgery (10.8%) and immobility (21.6%) were also common. Patients with provoked VTE were more likely to develop any arterial complication (MACE and/or MALE) than were those with unprovoked VTE (hazard ratio [HR], 1.3; 95% CI, 1.1-1.5; $P < .01$). Of the patients with provoked VTE, 28% were more likely to develop MACE (HR, 1.3; 95% CI, 1.1-1.5; $P < .03$), although no statistically significant differences were found for MALE (HR, 1.7; 95% CI, 1.0-3.1; $P \leq .06$; Fig 1).

When we explored the specific triggers for provoked VTE, strong associations were identified between immobility and cancer and the occurrence of MACE and/or MALE. Patients who had presented with provoked VTE secondary to immobility were more likely to develop any arterial event (MACE and/or MALE; HR, 1.7; 95% CI, 1.5-2.1; $P < .01$) and MACE (HR, 1.7; 95% CI, 11.5-2.1; $P < .01$). Moreover, patients with provoked VTE and cancer were also more likely to develop MACE and/or MALE (HR, 1.7; 95% CI, 1.4-1.9; $P < .01$) and MACE alone (HR, 1.6; 95% CI, 1.4-1.9; $P < .01$). However, limb arterial events were also more likely to occur (HR, 1.8; 95% CI, 1.01-3.1; $P < .04$; Table II).

On multivariate analysis using the predefined adjustments for multiple conventional cardiovascular risk factors, provoked VTE was still associated with the occurrence of MACE (HR, 1.39; 95% CI, 1.1-1.7; $P < .001$; Table III). Immobility-associated provoked VTE remained a predictor for arterial events (HR, 1.4; 95% CI, 1.1-1.8; $P < .01$). Cancer remained an adjusted predictor for a major arterial event (MACE and/or MALE; HR, 1.7; 95% CI, 1.4-2.2; $P < .001$) and both MACE (HR, 1.7; 95% CI, 1.4-2.1; $P < .01$) and MALE (HR, 2.1; 95% CI, 1.01-4.6; $P < .46$) alone.

DISCUSSION

Using a large prospectively collected database, we have described the differences in the prevalence of major cardiovascular risk factors between patients with provoked vs unprovoked VTE. In our study, the prevalence of diabetes and CHF was greater in the patients with provoked VTE than in those with unprovoked VTE, comparable with previous studies.[14,15] Provoked VTE was associated with an increased risk of major arterial events (MACE and/or MALE) compared with unprovoked VTE in both unadjusted and multivariable adjusted analyses. These events were strongly associated in patients with cancer and/or immobility but not other causes of VTE. Cancer remained an adjusted predictor for both MACE and MALE.

Recent studies have revealed that patients with VTE have an increased risk of subsequent ischemic events such as stroke and myocardial infarction.[16-18] Madridano et al[19] studied 23,370 patients with acute VTE in the RIETE registry and concluded that during the course of anticoagulation, the mortality due to PE recurrence was lower than that due to arterial ischemic events. Moreover, in their study, the predictors for ischemic events were also associated with major bleeding.[19] Thus, identifying patients for whom the

benefit/risk ratio is more favorable with the current antithrombotic strategies and using safer alternative antithrombotic strategies that could mitigate the risk of thrombotic events without elevating the hemorrhagic risk drastically would be beneficial in the patient cohort with VTE and arterial events.[19]

One of the strongest findings from our study was that the presence of cancer-associated VTE was strongly associated with incident MACE/MALE relative to other causes of VTE. Brenner et al[8] analyzed the data from 5717 patients in the RIETE registry and concluded that arterial ischemic events and major bleeding appeared early after venous thromboembolism in those with active cancer and were the frequent cause of death. The 30-day mortality rates after each event were 20% after recurrent PE, 13% after recurrent deep vein thrombosis, 41% after major bleeding, 40% after myocardial infarction, 64% after ischemic stroke, and 83% after lower limb amputation.[8] Several factors contributed to this finding. Koene et al[20] argued that cancer and cardiovascular disease share many similar risk factors, including obesity, diabetes, hypertension, diet, and alcohol use. However, the effect found in our study remained after controlling for the conventional risk factors. The use of statins (OR, 0.9; $P < .001$) was less common in the provoked VTE group. Both cancer and cardiovascular disease share inflammation in common as a critical culprit in the pathogenesis of both diseases. Although the complete steps of this process remain unknown, inflammation contributes to both cancer onset and progression.[21] In addition, smoking is a major risk factor for both cancer and CAD development and progression, and as much as 30% of all cardiovascular disease in the United States and 40% of cancer-related deaths can be attributed to cigarette smoking. However, our study was not powered to control for the types of cancer more likely to be associated with tobacco use.[22,23] Finally, the treatment of cancer can also include radiotherapy, another factor known to trigger the progression of arterial disease.[24]

The identification of patients at risk can lead to earlier interventions, which can prevent arterial outcomes. Lin et al[25] concluded that statins are related to the improvement in survival of patients with stage IV non-small-cell lung cancer, with improvements in overall survival (HR, 0.76; 95% CI, 0.73-0.79) and lung cancer-specific survival (HR: 0.77, 95% CI: 0.73—0.81). Another possible intervention would be the use of antiplatelet therapy; however, the use of antiplatelet therapy must be balanced against the risk of bleeding. The PIONEER study compared three groups of patients with atrial fibrillation undergoing percutaneous coronary intervention.[26] Group 1 had received rivaroxaban and P2Y12 inhibitor monotherapy. Group 2 had received rivaroxaban 2.5 mg twice daily and dual antiplatelet therapy. Finally, group 3 had received warfarin and dual antiplatelet therapy. Significant bleeding occurred in 16.8% of patients in group 1 vs 18.0% in group 2 and 26.7% in group 3 (HR, 0.59; $P < .001$ for group 1 vs group 3; HR, 0.63; $P < .001$ for group 2 vs group 3).[26]

The present study had some limitations. The complexity of the care of patients with cancer could have caused a surveillance bias and selective diagnosis of arterial events in this group. Although recent studies have argued that VTE and CAD share common risk factors, the topic has remained controversial.[3] Given that our study was of data collected from a registry, reporting biases could exist. Given that the main outcomes were hard events, it appears unlikely that surveillance bias alone could explain our findings. In addition, patients with unprovoked VTE will be more likely to continue receiving antithrombotic therapy in the long term. It is plausible that this could have also masked the probability of new arterial outcomes in the long term; thus, the greater probability of events in the patients with provoked VTE. Finally, we only controlled for known cardiovascular risk factors present at the VTE diagnosis. Thus, we do not know whether the patients with provoked VTE might have engaged in a more conscious cardiovascular lifestyle after the initial diagnosis.

CONCLUSIONS

In the cohort of patients with VTE and arterial events in the RIETE registry, we have demonstrated that major cardiovascular risk factors were more common in those with provoked VTE. Moreover, the patients with provoked VTE were more likely to develop MACE/MALE than were those in the unprovoked VTE group. Immobility and cancer were strongly associated with the occurrence of arterial events, and only cancer remained as an adjusted predictor for both MACE and MALE. Limited data are available on how to prevent arterial outcomes in patients with cancer and VTE. Further studies are necessary to better understand the underlying mechanism and clinical effects. The role of medications such as statins, direct anticoagulants, or antiplatelet therapy remains to be investigated. Further studies are needed to investigate the role or therapies that can reduce the role of atherosclerotic risk factors in patients with VTE and cancer.

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AUTHOR CONTRIBUTIONS

Conception and design: IG, AT, MM
Analysis and interpretation: IG, AT, MM
Data collection: IG, LC, OI, BenB, AT, BehB, CF, JP, RO, RQ, MM
Writing the article: IG, AT, MM
Critical revision of the article: IG, LC, OI, BenB, AT, BehB, CF, JP, RO, RQ, MM
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IG and AT contributed equally to this article and share co-first authorship.

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APPENDIX (online only).

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