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**Highlights**

- Arterial events are a major death cause in cancer patients with venous thrombosis
- Arterial events occur early after venous thrombosis in cancer patients
- The risk of arterial events should be considered in this clinical setting

**Clinical Research Study**

# Arterial Ischemic Events Are a Major Complication in Cancer Patients with Venous Thromboembolism

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[*]A full list of the RIETE investigators is given in the appendix.

**Running title: Arterial events in cancer patients with venous thromboembolism**

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**Abstract**

***Background*:** Venous thromboembolism is common in patients with malignancies, affecting up to 10% of this patient population. The association between arterial ischemic events and venous thromboembolism has been also established. However, the influence of arterial ischemic events on outcomes in cancer patients with venous thromboembolism has not been fully determined.

***Methods*:** The current study analyzed clinical characteristics, time-course, risk factors, incidence and severity of venous thromboembolism recurrences, arterial ischemic events and major bleeding in 5,717 patients with active cancer and venous thromboembolism recruited into RIETE (multi-center prospective registry of patients with objectively confirmed venous thromboembolism).

***Results*:** During anticoagulation course (median 7.3 months), 499 (8.7%) patients developed venous thromboembolism recurrences, 63 (1.1%) developed arterial events, and 346 (6.1%) suffered from major bleeding. Overall, major bleeding and arterial events appeared earlier (median 35 and 36 days, respectively) than venous thromboembolism recurrences (median 97 days). Thirty-day mortality rates after each event were: 20% after recurrent pulmonary embolism, 13% after recurrent deep vein thrombosis, 41% after major bleeding, 40% after myocardial infarction, 64% after ischemic stroke, and 83% after lower limb amputation. Bleeding was the leading cause of death (67 fatal bleeds), while cumulative mortality due to arterial ischemic events (n=27) was similar to that related to pulmonary embolism recurrences (n=26).

***Conclusions*:** In this study, arterial ischemic events and major bleeding appeared early after venous thromboembolism in patients with active cancer and were among frequent causes of their death. The risk and severity of arterial events need to be considered in this clinical setting.

**Keywords:** Arterial ischemic events, venous thromboembolism, bleeding, cancer

## Introduction

A number of studies revealed that patients with venous thromboembolism are at increased risk of developing subsequent arterial ischemic events, such as myocardial infarction or stroke(1-8). Prevention of such arterial ischemic events in addition to treating venous thromboembolismmay warrant combination therapy with antiplatelets and anticoagulants. Recent studies suggested an increased risk of arterial ischemic events in cancer patients(9, 10). Accurate identification of patients at increased risk for arterial ischemic events during the course of anticoagulation for venous thromboembolismmay help to select those who would potentially benefit from concomitant therapy with anticoagulants and antiplatelets.

Patients with active cancer and coexisting venous thromboembolism are an under-studied population who may suffer from various types of vascular events, including arterial ischemic events(11). With improvement in cancer therapies and patient survival rates, rising patient age and accumulation of cardiovascular risk factors throughout the lifetime, the probability of arterial or venous thromboembolic events has increased in this patient population. The extent of malignancy spread is related to the rising risk of thrombotic events(4). In addition, numerous new antineoplastic drugs(5, 6) and palliative therapies are associated with an increased risk for arterial thrombosis. However, patients with cancer are also at increased risk of bleeding while receiving anticoagulant therapy(12)

RIETE (Registro Informatizado de Enfermedad TromboEmbólica) is an ongoing, multicenter, international registry of patients with objectively confirmed acute venous thromboembolism. Data from this registry have been used to evaluate outcomes of cancer patients and acute venous thromboembolism in several settings(13-15). Notably, 23% of the RIETE patients are those with cancer(15). The aim of the current study was to determine the relative frequency, time-course, clinical characteristics and outcomes of cancer patients who developed arterial, venous and bleeding events during the course of anticoagulation for venous thromboembolism.

## Methods

RIETE enrolls consecutive patients with acute venous thromboembolism (an index event) confirmed by objective tests such as contrast venography or ultrasonography for suspected deep vein thrombosis; and pulmonary angiography, lung scintigraphy or helical computed tomography scan for pulmonary embolism. The design and methodology of the registry have been described elsewhere(16). Briefly, patients are excluded if they were participating in a therapeutic clinical trial with blinded therapy. In RIETE, participating physicians ensure that eligible patients are consecutively enrolled. Data are recorded in a computer-based case report form at each participating hospital and submitted to a centralized coordinating center through a secure website. The study coordinating center assigns patients a unique identification number to maintain patient confidentiality and is responsible for all data management. Data quality is regularly monitored electronically, including checks to detect inconsistencies or errors, which are resolved by

contacting the local coordinators. Data quality is also monitored by periodic visits to participating hospitals by contract research organizations that compare medical records with submitted data. All patients provided written or oral informed consent for participation in the registry, in accordance with local ethic committee requirements.

*Patients*

For this study, only venous thromboembolism patients with active cancer and with available information on risk factors for atherosclerosis and on the development of subsequent arterial ischemic events were selected. Such information was added to the RIETE data abstraction forms in February, 2009. Therefore, only patients recruited after this date were eligible for the current study. The primary outcomes were the relative frequency and severity of arterial ischemic events (i.e., ischemic stroke, myocardial infarction or limb amputation) appearing during the course of anticoagulant therapy. Secondary outcomes were the rate of pulmonary embolism recurrences, deep vein thrombosis recurrences, major bleeding and all-cause death. Myocardial infarction was defined as the presence of ischemic symptoms in combination with a transient increase of CK-MB or troponin, and/or typical electrocardiogram signs (development of pathologic Q-waves or ST-segment elevation or depression). Ischemic stroke was diagnosed if the patient had appropriate symptoms and signs for more than 24 hours, and had a brain computed tomography or magnetic resonance imaging study that showed a clinically-compatible lesion. Major bleeding was defined as an overt bleed that required a transfusion of 2 or more units of blood, 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 pulmonary embolism, in the absence of autopsy, was defined as any death appearing within 10 days of pulmonary embolism diagnosis, in the absence of any alternative cause of death. Fatal ischemic events, in the absence of autopsy, was defined as any death appearing within 10 days of myocardial infarction, ischemic stroke, limb amputation or mesenteric ischemia, in the absence of any alternative cause of death.

*Baseline variables*

The following parameters were recorded when the qualifying episode of venous thromboembolism was diagnosed: gender, age, and body weight and height; presence of coexisting conditions such as chronic heart or lung disease; concomitant therapies; recent major bleeding (<30 days prior to enrollment into RIETE); recent immobility (i.e., total bed rest with bathroom privileges for ≥4 days in the 2-month period prior to venous thromboembolism diagnosis), recent surgery (in the 2 months prior to venous thromboembolism), active cancer (defined as newly diagnosed cancer or cancer that is being treated [i.e. surgery, chemotherapy, radiotherapy, support therapy, or combined treatments]), hormonal therapy, pregnancy, puerperium, prior venous thromboembolism and recent travel; risk factors for atherosclerotic disease, including hypertension, diabetes, current smoking,

prior arterial ischemic disease, therapy with antiplatelets or statins at baseline, and laboratory data also at baseline, including whole blood counts and serum creatinine levels.

*Treatment and follow-up*

Patients were managed according to the clinical practice of each participating hospital (i.e., treatment was not standardized). The type, dose and duration of anticoagulant therapy were recorded. Patients were followed for up to a year in the outpatient clinics. During each visit, any signs or symptoms suggesting an ischemic event (chest pain, neurological deficit, limb or abdominal pain) or bleeding complications were registered. Each episode of clinically suspected ischemic event was investigated using appropriate methods (electrocardiography, laboratory tests, angiography or appropriate computed tomography scan). Most outcomes were classified as reported by the clinical centers. However, if the staff at the RIETE coordinating center were uncertain how to classify a reported outcome, the event in question was reviewed by the central adjudication committee (<10% of events).

*Statistical analysis*

Categorical variables were reported as frequencies and quantitative variables were reported as mean or median with appropriate measures of dispersion. ANOVA analysis and nonparametric tests were used to compare means and medians of continuous variables Rates of arterial ischemic events, venous thromboembolism recurrences and major bleeding were assessed and the corresponding Kaplan Meier survival curves were constructed. Time zero was the date of diagnosis of incident venous thromboembolismand participants were censored at the time of discontinuation of anticoagulation, at the time of death or at the last date for which outcome data were available. We defined the case-fatality rate of ischemic events as the proportion of all ischemic events (non-fatal and fatal) that were fatal. We defined the case-fatality rate of recurrent pulmonary embolism as the proportion of all recurrent pulmonary embolism events (non-fatal and fatal) that were fatal. We defined the case-fatality rate of major bleeding as the proportion of all major bleeding events (non-fatal and fatal) resulting in fatal bleeding. All analyses were completed with the PASW Statistics 18, and a p-value <0.05 was considered statistically significant.

**Results**:

From February 2009 to June 2017 *34,082* patients were recruited to RIETE. Of these, *5,717* (17%) had active cancer and were evaluated for arterial events during the course of anticoagulation for venous thromboembolism (median, 7.3 months). Over a median follow-up duration of 5.0 months, 63 patients (1.1%) developed an arterial ischemic event (ischemic stroke 42, myocardial infarction 15, lower-limb amputation 6), 499 (8.7%) experienced recurrent venous thromboembolism (recurrent pulmonary embolism 222, deep vein thrombosis 277) and 346 (6%) suffered from major bleeding.

Patients subsequently presenting with arterial ischemic events exhibited a greater burden of cardiovascular risk factors at baseline (i.e., arterial hypertension, diabetes mellitus), compared with patients with recurrent venous thromboembolism but no arterial events during follow-up (Table 1). Further, prior ischemic events such as myocardial infarction, stroke or peripheral artery disease were significantly more frequent among patients with arterial events during the follow-up compared to patients with recurrent venous thrombosis (Table 1). Thirty one percent of patients with arterial events were already receiving antiplatelet drugs at the time of the venous thromboembolism index event. The proportion of patients treated with antiplatelets at baseline was significantly lower among patients without subsequent arterial events or compared to patients who suffered from major bleeding (Table 1). Importantly, only 6% of patients were on antiplatelet therapy when they developed an acute ischemic event.

The median time from the venous thromboembolism index event to an arterial event was significantly shorter than that to a venous thromboembolism recurrent event (36 days vs. 97 days, $p<0.01$) and similar to the time to a major bleeding event (Table 1). All the evaluated events were more frequent among patients with metastatic disease (Table 2). The most prevalent malignancy among patients with arterial events was lung cancer (30%) followed by pancreatic, genitourinary and gastrointestinal cancers (18% each) (Table 2). The prevalence of arterial events was the highest among patients with pancreatic and lung cancers [11/226 (4.9%) and 19/888 (2.1%), respectively].

Most of the patients with arterial events, venous thromboembolism recurrences or major bleeding were initially treated with low molecular weight heparin. Only 4 (6.3%) patients who developed arterial events were treated with antiplatelet drugs after the venous thromboembolism index event (Table 3). At 30 days of follow-up after the evaluated event, 37/63 (59%) patients with arterial events died, with ischemic stroke being the cause of death in the majority of them. Within the same time frame, 81 patients (16%) from the recurrent venous thromboembolism cohort and 142 (41%) from the major bleeding cohort died. Remarkably, the cause of death in 64 of the latter 142 patients was bleeding. Overall, 28 patients died of pulmonary embolism, 67 died of bleeding and 27 died of ischemic events (ischemic stroke 20, myocardial infarction 5, limb amputation 2) (Table 4). The rate of pulmonary embolism recurrences exceeded the rate of ischemic events, but the mortality due pulmonary embolism was similar to the mortality due to arterial ischemic events (28 vs. 27 deaths, respectively).

At one year of follow-up, bleeding was the leading fatal event in the study population, while the cumulative mortality due to arterial ischemic events was similar to that related to pulmonary embolism recurrence (Figure 1).

**Discussion:**

Our study characterized the frequency, time course and severity of arterial ischemic events appearing during the course of anticoagulation in patients with venous thromboembolism and cancer. Remarkably, the present study demonstrated that arterial ischemic events occurred early upon the diagnosis of cancer as well as shortly after the index venous thromboembolism event. The former finding is in line with a recent analysis of a large Medicare database(11). Our data confirmed that the rate of pulmonary embolism recurrences during anticoagulation was higher than the rate of ischemic events (222/5717 (3.9%) vs. 63/5717 (1.1%), respectively). While arterial events were less frequent than recurrent venous thromboembolism, they were characterized by a severe course and a poor outcome. Indeed, although the case-fatality rate of recurrent pulmonary embolism was lower than that of arterial ischemic events, the total mortality due to pulmonary embolism recurrences was similar to the mortality due to ischemic events (28 vs. 27 deaths, respectively).

Still, major bleeding was the most common life-threatening outcome [346/5717 (6.1%)] and mortality due to bleeding complications in our series (67 deaths) was higher than the combined mortality due to pulmonary embolism recurrences or ischemic events (55 deaths in total).

Notably, concomitant therapy with anticoagulants and antiplatelets is known to increase the risk of bleeding, while anticoagulants alone may be insufficient for patients at high risk for arterial events(17, 18). In our series, one out of every nine cancer patients with venous thromboembolism had prior symptomatic arterial disease, and many of them were using antiplatelet therapy at the time venous thromboembolism diagnosis (i.e., when they were enrolled into RIETE). Importantly, antiplatelets have been continued in only 20% of these patients, who present a therapeutic dilemma because they are perceived to be at substantial risk of bleeding if concomitant therapy with anticoagulants and antiplatelets is prescribed, and of recurrent ischemic events if antiplatelets are discontinued. Hence, our findings warrant further evaluations with an ultimate goal to optimize management in this complicated clinical setting, utilizing tailored therapy and careful monitoring. To that end, accurate identification of patients at increased risk for arterial events, applying precise risk stratification, is needed.

Assessment of cardiovascular risk factors is crucial for optimal management of patients with arterial ischemic events(19). Currently, there are no guidelines for thromboprophylaxis for myocardial infarction or stroke in patients with venous thromboembolism and cancer (17, 20, 21). In our cohort, only 6.3% of cancer patients with venous thromboembolism were receiving antiplatelets at the time when an arterial ischemic event was diagnosed, compared to 31% of patients who were on antiplatelets at the time of the venous thromboembolism index event occurrence. Thus, it is most likely that antiplatelets were stopped in the majority of patients (15/19) after the diagnosis of a venous thromboembolism index event and prior to the arterial ischemic event. The discontinuation of antiplatelet therapy could be related to clinicians' concern of increasing bleeding risk while treating patients with anticoagulation. In this scenario, stoppage of antiplatelet agents could be a contributing factor to early ischemic events in the follow-up.

The present study revealed that all the evaluated events (arterial ischemic events, major bleeding and recurrent venous thromboembolism) were more frequently found in patients with advanced metastatic cancer. These findings are supported by previous reports on an increased hazard ratio for arterial events in patients with metastasis compared to patients with a more localized disease(11, 22). Among possible underlying pathological mechanisms could be increased hypercoagulability due to high levels of circulating microvesicles(23, 24), elevated heparanase procoagulant activity(25), alteration in platelet activity and endothelial function(26). More aggressive chemotherapy in advanced cancer also leads to an increased risk for thrombotic events(27). Emerging of targeted therapies and immunotherapy could play a role in increasing the risk of thrombotic events(28). At the same time, the risk for bleeding is also increasing in patients with advanced cancer due to chemotherapy and related thrombocytopenia.

In our study, more patients with lung and pancreatic cancer suffered from arterial ischemic events, which could to be partly attributable to smoking, a common risk factor for these entities. A recently published study demonstrated an increased risk of arterial events (myocardial infarction and stroke) at one month from lung cancer diagnosis(11).
While it is well-established that venous thromboembolism could be indicative of the presence of cancer, the latest study by Sundbøll et al. has demonstrated that lower limb arterial thrombosis could also be a marker of occult cancer and is reported to be associated with increased mortality in certain cancer types(29).

Current guidelines suggest consideration of venous thromboembolism thromboprophylaxis in ambulatory patients with lung or pancreatic cancer receiving chemotherapy(30, 31). A recent study based on data from the Danish National Patient Registry found comparable risks of developing thromboembolism or bleeding in atrial fibrillation patients with and without cancer, regardless of prescribed anticoagulant type(32). However, the optimal management of cancer patients with venous thromboembolism who are also at risk for arterial ischemic events requires further evaluation.

*Study limitations*

Our study has a number of limitations. First, RIETE is an observational registry. Patients were not treated with a standardized regimen; treatment varied with local practices and is likely to have been influenced by a physician's assessment of a patient's risk of bleeding or arterial events. Further, the choice of continuing low molecular weight heparin or switching to vitamin K antagonists was confounded by the patient's clinical condition, as were the choices related to continuation or cessation of antiplatelet therapies. Factors including type, extent and rate of progression of cancer, the nature of the initial venous thromboembolism event, type of concomitant

chemotherapy, affordability of the treatment, predicted life expectancy, and patient preference would have all influenced the choice to continue or discontinue low molecular weight heparin. However, in RIETE detailed information was available related to treatment duration with anticoagulants and complications assessed in this study. While we cannot provide inferences about comparative effectiveness of antithrombotic regimens, the above limitation is unlikely to have affected our estimates for the relative frequency or outcomes related to our studied patient subgroups. Second, RIETE by design does not currently have a biobank and as such, we could not have a systematic assessment of biomarkers (e.g., for thrombophilia testing). Finally, our study may have underestimated the relative frequency of venous and arterial events, since we looked at symptomatic venous thromboembolism recurrences and arterial events, but there could have been a number of asymptomatic events that were missed.

*Future directions*

Future studies should focus on refined risk assessment for arterial thrombosis in various cancer subtypes as well as approaches to advance management of venous thromboembolism patients with cancer who are at risk of arterial ischemic events. Appropriate choice of antithrombotic therapy to optimize the prevention of ischemic events and minimize the hemorrhagic events remains a conundrum that may be addressed by better risk stratification, and tailored monitored treatment strategies.

In conclusion, arterial ischemic events have been found to be a major complication in patients with venous thromboembolism and active cancer. As the mortality rate is highest among patients who suffer from an arterial event, randomized controlled studies are urgently needed in this high-risk patient population.

**Figure legend**

**Figure 1. Unadjusted cumulative mortality due to pulmonary embolism recurrences, bleeding or ischemic arterial events**

**Author Contributions**

Benjamin Brenner: designed research, interpreted the data, wrote the paper, approved the final version of the paper
Behnood Bikdeli: designed research, interpreted the data, wrote the paper, approved the final version of the paper
Inna Tzoran: recruited patients, performed research, interpreted the data, approved the final version of the paper
Olga Madridano: recruited patients, performed research, approved the final version of the paper
Raquel López-Reyes: recruited patients, performed research, approved the final version of the paper
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Antonella Tufano: recruited patients, performed research, approved the final version of the paper
Juan José López Núñez: recruited patients, performed research, approved the final version of the paper
Javier Trujillo-Santos: recruited patients, performed research, interpreted the data, approved the final version of the paper
Manuel Monreal: recruited patients, designed research, interpreted the data, wrote the paper, approved the final version of the paper and obtained funding

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**Disclosure of Conflicts of Interest**
The authors declare no conflicts of interest relevant to this submission.

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**Table 1. Clinical characteristics.**

| | No events | Arterial events | VTE recurrences | Major bleeding |
|---|---|---|---|---|
| ***Patients, N*** | ***4,809*** | ***63*** | ***499*** | ***346*** |
| **Clinical characteristics,** | | | | |
| Gender (male) | 2,455 (51%) | 36 (57%) | 275 (55%) | 195 (56%) |
| Age (years±SD) | 67±13 | 68±11 | 64±13‡ | 69±13‡ |
| Body weight (kg±SD) | 73±15 | 72±14 | 74±15 | 73±15 |
| Body mass index (±SD) | 27.0±5.2 | 25.5±4.3 | 27.0±5.2 | 26.6±5.3 |
| Waist circumference (cm±SD) | 97.9±14.8 | 107.5±6.4 | 101.0±11.6 | 100.3±12.6 |
| Recent major bleeding | 137 (2.8%) | 2 (3.2%) | 14 (2.8%) | 23 (6.6%)‡ |
| **Risk factors for arterial events,** | | | | |
| Current smoking | 560 (12%) | 11 (18%) | 67 (14%) | 46 (14%) |
| Arterial hypertension | 2,101 (45%) | 38 (60%)* | 221 (52%) | 174 (52%)* |
| Diabetes mellitus | 765 (17%) | 21 (33%)‡ | 96 (19%) | 74 (22%)* |
| **Risk factors for VTE,** | | | | |
| Surgery | 801 (17%) | 7 (11%) | 48 (9.6%)‡ | 49 (14%) |
| Immobility ≥4 days | 654 (14%) | 14 (22%)* | 76 (15%) | 78 (23%)‡ |
| Estrogen use | 373 (7.8%) | 3 (4.8%) | 33 (6.6%) | 22 (6.4%) |
| None of the above (unprovoked) | 3,138 (65%) | 41 (65%) | 353 (71%)* | 215 (62%) |
| Prior VTE | 509 (11%) | 5 (7.9%) | 68 (14%)* | 43 (12%) |
| **Blood tests,** | | | | |
| CrCl levels (mL/min) | 82±39 | 82±43 | 83±36 | 74±39‡ |
| Anemia | 2,861 (60%) | 42 (67%) | 291 (58%) | 255 (74%)‡ |
| Leukocyte count >11,000/µL | 1,018 (21%) | 22 (35%)† | 146 (29%)‡ | 104 (30%)‡ |
| Abnormal platelet count | 505 (11%) | 6 (9.5%) | 64 (13%) | 52 (15%)† |
| Total cholesterol levels (mg/dL) | 179.1±47.0 | 178.1±51.1 | 184.3±49.5 | 170.1±50.8 |
| Triglycerides (mg/dL) | 141.8±101.3 | 154±69.2 | 149.5±121.5 | 130.9±57.1 |
| **Prior ischemic events,** | | | | |
| Myocardial infarction | 252 (5.5%) | 9 (14%)† | 41 (8.3%)* | 34 (10%)‡ |
| Stroke | 238 (5.1%) | 8 (13%)† | 21 (4.2%) | 33 (9.8%)‡ |
| Peripheral artery disease | 150 (3.3%) | 5 (7.9%)* | 22 (4.4%) | 15 (4.5%) |
| Any of the above | 554 (12%) | 17 (27%)‡ | 73 (15%)* | 70 (20%)‡ |
| **Concomitant drugs at baseline** | | | | |
| Antiplatelets | 612 (14%) | 19 (31%)‡ | 80 (17%) | 67 (20%)† |

| | | | | |
|---|---|---|---|---|
| Corticosteroids | 634 (14%) | 14 (23%) | 78 (16%) | 60 (18%)* |
| NSAIDs | 347 (7.9%) | 6 (9.7%) | 49 (10%) | 34 (10%) |
| Statins | 929 (20%) | 22 (36%)† | 116 (24%) | 89 (26%)† |
| **Initial VTE presentation,** | | | | |
| Pulmonary embolism | 2,598 (54%) | 42 (67%)* | 268 (54%) | 231 (67%)‡ |
| **Time elapsed to the events,** | | | | |
| Days to event (mean±SD) | - | 101±138 | 160±233 | 96±193 |
| Days to event (median, IQR) | - | 36 (136) | 97 (156)† | 35 (96) |

*p <0.05; †p <0.01; ‡p <0.001

**Table 2. Cancer characteristics.**

| | No events | Arterial events | VTE recurrences | Major bleeding |
|---|---|---|---|---|
| ***Patients, N*** | ***4,809*** | ***63*** | ***499*** | ***346*** |
| **Time from cancer diagnosis** | | | | |
| Mean months (±SD) | 23±44 | 6.1±16* | 17±38* | 20±43 |
| <6 months before VTE | 2,460 (51%) | 46 (73%)‡ | 272 (55%) | 194 (56%) |
| <3 months before VTE | 1,758 (37%) | 39 (62%)‡ | 209 (42%)† | 150 (43%)† |
| **Metastases** | | | | |
| Yes | 2,228 (49%) | 41 (65%)† | 318 (64%)‡ | 223 (65%)‡ |
| **Sites of cancer,** | | | | |
| Genitourinary | 1,103 (23%) | 11 (18%) | 108 (22%) | 96 (28%)* |
| Gastrointestinal | 1,009 (21%) | 11 (18%) | 85 (17%)* | 83 (24%) |
| Breast | 755 (16%) | 4 (6.3%)* | 46 (9.2%)‡ | 24 (6.9%)‡ |
| Lung | 618 (13%) | 19 (30%)‡ | 119 (24%)‡ | 52 (15%) |
| Hematologic | 406 (8.4%) | 1 (1.6%) | 32 (6.4%) | 15 (4.3%)† |
| Pancreas | 169 (3.5%) | 11 (18%)‡ | 30 (6.0%)† | 16 (4.6%) |
| Central nervous system | 155 (3.2%) | 1 (1.6%) | 14 (2.8%) | 13 (3.8%) |
| Other | 452 (9.4%) | 3 (4.8%) | 45 (9.0%) | 34 (9.8%) |
| **Therapy for cancer,** | | | | |
| Chemotherapy | 2,025 (42%) | 20 (32%) | 195 (39%) | 117 (34%)† |
| Radiotherapy | 238 (4.9%) | 1 (1.6%) | 22 (4.4%) | 19 (5.5%) |
| Chemo- and radiotherapy | 477 (9.9%) | 4 (6.3%) | 57 (11%) | 25 (7.2%) |
| Hormonal therapy | 632 (13%) | 6 (9.5%) | 44 (8.8%)† | 31 (9.0%)* |
| None of the above | 1,500 (31%) | 31 (49%)† | 188 (38%)† | 152 (44%)‡ |
| Not reported | 159 (3.3%) | 2 (3.2%) | 8 (1.6%)* | 12 (3.5%) |

*p <0.05; †p <0.01; ‡p <0.001

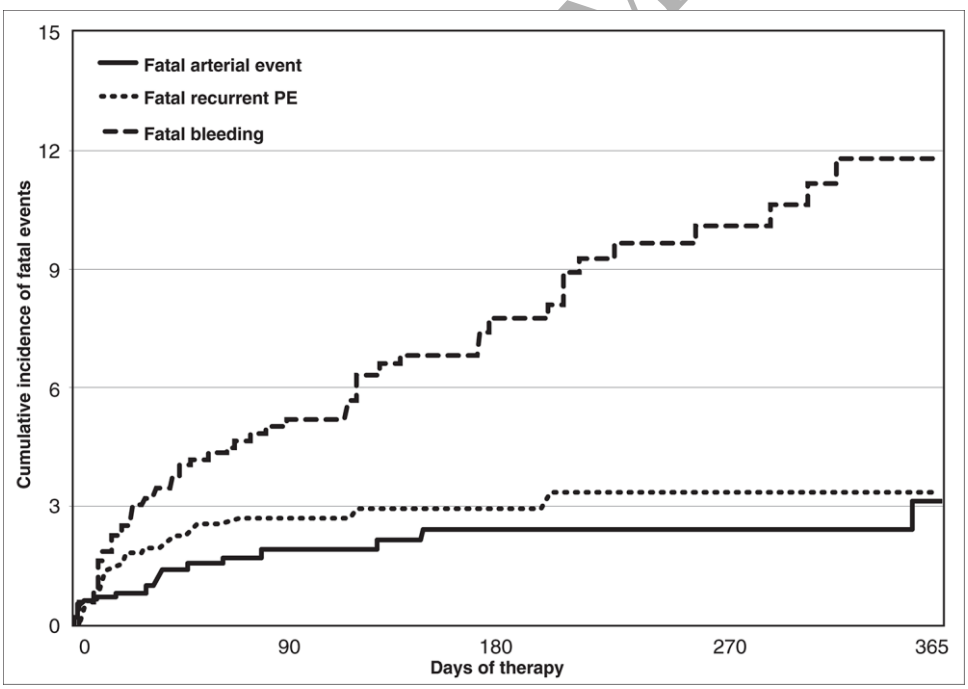
**Table 3. Treatment strategies.**

| | No events | Arterial events | VTE recurrences | Major bleeding |
|---|---|---|---|---|
| ***Patients, N*** | ***4,809*** | ***63*** | ***499*** | ***346*** |
| ***Duration of therapy,*** | | | | |
| Mean months (±SD) | 7.6±10 | 7.5±12 | 8.1±9.2 | 4.0±6.4‡ |
| Median months (IQR) | 5.2 (5.5) | 3.1 (8.5)* | 5.2 (7.6) | 1.9 (4.3)‡ |
| ***Initial therapy,*** | | | | |
| Unfractionated heparin | 209 (4.3%) | 2 (3.2%) | 21 (4.2%) | 30 (8.7%) |
| LMWH | 4,283 (89%) | 56 (89%) | 452 (91%) | 289 (84%) |
| Mean LMWH dose (IU/kg/day) | 168±45 | 162±47 | 165±51 | 170±59 |
| Fondaparinux | 111 (2.3%) | 1 (1.6%) | 0 | 6 (1.7%) |
| DOACs | 41 (0.9%) | 0 | 1 (0.2%) | 1 (0.3%) |
| Thrombolytics | 29 (0.6%) | 0 | 7 (1.4%) | 6 (1.7%) |
| Inferior vena cava filter | 86 (1.8%) | 3 (4.8%) | 10 (2.0%) | 3 (0.9%) |
| ***Long-term therapy,*** | | | | |
| LMWH | 3,251 (68%) | 40 (64%) | 361 (72%) | 186 (54%) |
| Mean LMWH dose (IU/kg/day) | 151±45 | 153±44 | 152±43 | 143±50 |
| Vitamin K antagonists | 759 (16%) | 5 (7.9%) | 65 (13%) | 39 (11%) |
| DOACs | 92 (1.9%) | 1 (1.6%) | 2 (0.4%) | 4 (1.2%) |
| Fondaparinux | 96 (2.0%) | 0 | 1 (0.2%) | 3 (0.9%) |
| **Therapy at the event,** | | | | |
| Unfractionated heparin | - | 3 (4.8%) | 7 (1.4%) | 22 (6.4%) |
| LMWH | - | 51 (81%) | 357 (72%) | 251 (73%) |
| Fondaparinux | - | 0 | 2 (0.4%) | 7 (2.0%) |
| Vitamin K antagonists | - | 3 (4.8%) | 59 (12%) | 41 (12%) |
| DOACs | - | 2 (3.2%) | 5 (1.0%) | 9 (2.6%) |
| Thrombolytics | - | 0 | 1 (0.2%) | 2 (0.6%) |
| Antiplatelets | - | 4 (6.3%) | 13 (2.6%) | 3 (0.9%)† |
| Other | - | 0 | 55 (11%)† | 11 (3.2%) |

Arterial events are the reference group when comparisons of therapy at the event are made.
*p <0.05; †p <0.01; ‡p <0.001

**Table 4. Thirty-day outcomes after each of the events.**

| | Myocardial infarction | Ischemic stroke | Lower limb amputation | Recurrent PE | Recurrent DVT | Major bleeding |
|---|---|---|---|---|---|---|
| ***Patients, N*** | ***15*** | ***42*** | ***6*** | ***222*** | ***277*** | ***346*** |
| ***Events,*** | | | | | | |
| Ischemic stroke | - | - | - | 1 (0.5%) | 3 (1.1%) | 1 (0.3%) |
| Myocardial infarction | - | - | - | 1 (0.5%) | 1 (0.4%) | 1 (0.3%) |
| Lower limb amputation | - | 1 (2.4%) | | 1 (0.5%) | 0 | 0 |
| Recurrent PE | - | 2 (4.8%) | - | 7 (3.2%) | 5 (1.8%) | 7 (2.0%) |
| Recurrent DVT | - | - | - | 3 (1.4%) | 3 (1.1%) | 9 (2.6%) |
| Major bleeding | - | 1 (2.4%) | - | - | - | - |
| | | | | | | |
| Death | 6 (40%) | 27 (64%) | 5 (83%) | 44 (20%) | 37 (13%) | 142 (41%) |
| *Causes of death,* | | | | | | |
| Myocardial infarction | 5 (33%) | - | - | - | - | - |
| Ischemic stroke | - | 17 (40%) | 1 (17%) | - | 2 (0.7%) | - |
| Limb amputation | - | - | 2 (33%) | - | - | - |
| Pulmonary embolism | - | 1 (2.4%) | - | 25 (11%) | - | 2 (0.6%) |
| Bleeding | - | - | - | 2 (0.9%) | 1 (0.4%) | 64 (18%) |
| Disseminated cancer | - | 5 (12%) | - | 15 (6.8%) | 23 (8.3%) | 43 (12%) |
| Other reasons | 1 (6.7%) | 4 (9.5%) | 2 (33%) | 7 (3.2%) | 11 (4.0%) | 33 (9.5%) |



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