haematologica
Journal of the Ferrata Storti Foundation

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Collaborative Groups: Spanish Society of Medical Oncology (SEOM).

Received: July 1, 2024.
Accepted: December 5, 2024.

Citation: Silvia García Adrián, Claudia Iglesias Pérez, Alberto Carmona-Bayonas, Laura Ortega Morán, Jaime Rubio Pérez, Purificación Martínez del Prado, Eva Martínez de Castro, Fernando Neria, Isaura Fernández Pérez, Marta García de Herreros, Marta Carmona Campos, Ignacio García Escobar, Rut Porta Balanyà, David Marrupe González, Paula Jiménez Fonseca, María Esperanza Guirao García, Manuel Sánchez Cánovas, José Muñoz Langa, Pedro Pérez Segura, Mª José Méndez Vidal and Andrés J. Muñoz Martín. Collaborative Groups: Spanish Society of Medical Oncology (SEOM). Cancer-related thrombosis: impact of biological sex on the risk of rethrombosis and bleeding. Haematologica. 2024 Dec 12. doi: 10.3324/haematol.2024.286152 [Epub ahead of print]

Cancer-related thrombosis: impact of biological sex on the risk of rethrombosis and bleeding

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Funding

The TESEO Registry is funded with an unrestricted grant from Sanofi, Rovi, Leo Pharma, and BMS-Pfizer. These institutions have not participated in any way in the study design, data analysis, or interpretation of results or in any decision having to do with this publication.

Conflict of interest

The authors declare that they have no conflict of interest/funding disclosure relating to the publication of this manuscript.

Contributions

SGA conceptualized the study, interpreted the data and wrote the manuscript. AMM, PJF, ACB, EMC, PPS and JML designed the study, contributed essential material and revised the manuscript. FN analyzed results and created figures. All authors contributed essential material and approved the final manuscript.

Acknowledgments

SEOM for sponsoring this study. The mFAR team for supporting the website registry. Priscilla Chase for editing and translating the manuscript.

Data sharing statement

Data available upon request to the corresponding author.

ABSTRACT:

Patients with cancer present a higher risk of rethrombosis and bleeding secondary to anticoagulant treatment than individuals without cancer. Given the lack of specific clinical trials, the decision regarding the optimal duration of treatment must consider multiple factors, including sex. The current study used data from the international, prospective TESEO Registry that includes consecutive patients diagnosed with cancer-associated thrombosis (CAT). Between July 2018 and December 2022, 2,823 patients were included in the TESEO Registry, 1,351 (48%) of whom were female. The most common venous thromboembolic event (VTE) in both sexes was pulmonary embolism (PE), with an incidence of 58.0% among men and 54.3% in women (p=0.045). After a median follow-up of 6.9 months (IQR, 1.9-14.4), the rethrombosis rate at the end of follow up was 10.0% in males and 15.0% in females (p=0.14). The location of the primary tumor in the gastrointestinal tract was associated with a greater risk of rethrombosis, whereas sex had no significant impact. Men presented twice as many major bleeds. Additional risk factors for major bleeding included situations of risk due to tumor site or thrombocytopenia, as well as the presence of active tumor bleeding at the time of VTE diagnosis. Overall survival was higher among women. Given the higher incidence of major bleeding among men, sex should be deemed a relevant factor when deciding on the duration of anticoagulant treatment in cancer patients.

Key words: cancer, sex, recurrent thrombosis, bleeding

Introduction

The interrelationship between cancer and venous thromboembolic events (VTE) stands out given its two-way nature, revealing significant increase in the risk of thrombotic complications in cancer patients, which can be as much as nine times that of the general population[1]. The frequency of VTE among these patients is modulated by a series of factors that include the type and stage of the cancer, the presence and extent of metastasis, the treatment received, as well as the specific demographic and clinical characteristics of the patient, such as age and existing comorbidities. Despite this, there is a paucity of information regarding the incidence of VTE broken down by sex among patients with cancer.

Individuals with cancer not only face an up to three-fold risk of rethrombosis compared to those without cancer, but also exhibit a greater risk of bleeding during anticoagulant treatment[2]. Clinical guidelines recommend maintaining anticoagulant therapy for at least six months, basing the decision to extend this period on an individualized assessment that considers the balance between the risk of rethrombosis and that of bleeding for each person.[3-6] Some factors, such as the presence of an active tumor and on-going oncological treatment are acknowledged as increasing the risk of rethrombosis, whereas the presence of renal failure, advanced age, thrombocytopenia, or certain tumor sites appear to elevate the risk of bleeding during anticoagulant therapy.

As for the influence of sex on the risk of rethrombosis and bleeding, the data are contradictory. Studies in general populations reveal a greater risk of VTE recurrence in men *versus* women, [7-11] whereas several studies conducted in subjects with cancer have failed to detect significant differences in the incidence of thrombotic recurrence based on sex.[12-15] As for the risk of bleeding in anticoagulated cancer patients due to cancer-associated thrombosis (CAT), while some publications evidence no significant sex-related differences,[12,16] others suggest a higher incidence of bleeding among males.[13,1718]

We have performed this study in an attempt to shed light on the impact of sex on the risk of rethrombosis and bleeding in cancer patients and taking into account the possible influence of other factors, such as the primary tumor site and certain cancer treatments.

Methods

Study design

TESEO is an observational, non-intervention, prospective, longitudinal registry promoted by the Spanish Society of Medical Oncology (SEOM, for its acronym in Spanish), in which 52 Spanish and two Portuguese centers participate. This registry consecutively includes patients diagnosed with CAT, both incidental and symptomatic, confirmed by imaging studies (doppler ultrasound,

CT angiography scans, scheduled CT to assess tumor response, etc.). The participants are followed up until their demise. Subjects with superficial venous thrombosis, as well as those in whom the VTE appears more than one month prior to the diagnosis of cancer or more than one month after concluding adjuvant cancer treatment are excluded.[19,20]

The study was conducted in compliance with current safety legislation and established in Spanish Organic Law 3/2018 and EU Regulation 2016/679 of the European Parliament and of the Council on the Protection of Personal Data. It was approved by the Research Ethics Committees of all the autonomous communities and participating centers, and it was classified as a prospective, post-marketing surveillance study by the Spanish Agency of Drugs and Medical Devices (*Agencia Española de Medicamentos y Productos Sanitarios*, AEMPS). Written Informed consent was obtained from all patients before their enrollment in the study.

Study objectives and variables

The main objective of the study was to evaluate the impact of sex on the incidence of rethrombosis and major bleeding in the TESEO Registry population. Rethrombosis was defined as the appearance of a second thrombotic event following proper management of the index VTE or progression of the previous episode despite appropriate anticoagulant therapy. Bleeding severity was graded as per the International Society of Thrombosis and Hemostasis (ISTH) criteria as minor, clinically relevant, or major.[21]

Secondary objectives included analyzing the type of VTE, the type of anticoagulant therapy administered, as well as survival and cause of death. Overall survival (OS) was defined as the time between the diagnosis of the VTE until patient demise for any cause.

Patients' demographic variables were collected (age, sex, comorbidity, etc.), clinical and molecular characteristics of the neoplasms (such as the site of the primary tumor, stage, histological type, location of metastasis, bleeding risk) were recorded, along with the cancer treatment administered, the characteristics of the VTE and its treatment, as well as the evolution of the CAT (rethrombosis, bleeding, and death).

Statistical analysis

The continuous variables are presented as medians and interquartile range (IQR), while the categorical variables are expressed as absolute and relative frequencies. The statistical comparisons were performed by means of the χ^2 test (or Fisher's exact test when needed) for the categorical variables and the Welch Two Sample t-test for continuous variables.

We used Fine-Gray proportional subdistributions hazards models to identify predictors of rethrombosis and major bleeding, both within six months after the initial VTE and throughout the follow-up, with death as a competing risk.

Survival rates were calculated by means of the Kaplan-Meier estimator. Log-rank tests were applied to compare survival rates based on sex and type of VTE.

All statistical analyses were performed with the R v4.3.2 software package. Significant differences were considered to be present when the p value was <0.05.

Results

Demographic and clinical profiles of patients and characteristics of VTE

Between July 2018 and December 2022, 2,866 patients were included in the TESEO Registry. Of them, 43 were excluded from analysis due to lack of essential clinical information in the database. Finally, 2,823 subjects were considered for this analysis, of whom 1,351 (48%) were women. The most common tumor sites among females were breast (20.9%), lung (16.5%), and colorectal (16.5%), whereas the leading tumor locations in males were lung (27.6%), colorectal (21.7%), and pancreatic-biliary (12.7%). Table 1 illustrates that arterial hypertension, dyslipemia, and smoking were more prevalent among men, while women exhibited a higher incidence of obesity and worse functional status. The men exhibited more advanced tumor stages and greater presence of active tumor at the time of diagnosis of the VTE compared to the women. No pregnancies were reported in the women at the time of VTE diagnosis. When diagnosed with VTE, 27.0% of the females had a central venous catheter VTE (71% Port-a-Cath, 28% peripherally inserted central catheter) compared to 21.4% of the males (66% Port-a-Cath, 32% peripherally inserted central catheter); this difference was statistically significant (p=0.003).

In both men and women, the most common VTE was pulmonary embolism (PE) (58.0% and 54.3% respectively; p=0.045), followed by deep vein thrombosis (DVT) (37.9% vs 40.6%; p=0.136), with more than 9% of the subject simultaneously presenting PE and DVT in both groups. No significant differences were found between sexes with respect to the incidence of splanchnic thrombosis; nevertheless, central catheter-associated thromboses were significantly more frequent in women (Table 2). PE severity, incidence of bilateral PE (46.5% and 49.2% respectively; p=0.299), location (central: 31.3% *vs.* 32.4%; peripheral: 42.6% *vs.*44.0%; both: 26.1% *vs.*23.6%), and the presence of right ventricular dysfunction (9.1% compared to 10.6%; p=0.329) revealed no significant differences across the sexes. Almost half (47%) of the individuals with PE were incidental at the time of diagnosis, with no differences based on sex.

Most of VTE were treated with low molecular weight heparin (LMWH) both in the initial phase (first 5-10 days), 90% of the cases, as well as during maintenance (95%); again, with no differences noted based on sex. Only 55 patients received long-term direct oral anticoagulant (DOAC) treatment and a mere 14 were treated with vitamin K antagonists (Table 3). The choice of antithrombotic therapy was uninfluenced by the person's sex. The median duration of anticoagulant treatment was 5.0 months in men (IQR 1.5-11.0) and 5.6 months in women (IQR 1.8-11.7).

Analysis of rethrombosis and bleeding

With a median follow up of 6.1 months (IQR 1.8-14.3) among males and 7.4 months (IQR 2.1-16.7) among women, the incidence of rethrombosis was 6.5% (7.1% in men and 5.8% in women; p = 0.178). As evidenced in Table 4, no significant differences were observed in the cumulative incidence of rethrombosis between men and women. Of the 103 men with rethrombosis, 51 (49.5%) presented PE (with 3 cases of simultaneous DVT), compared to 32 of the 78 women (41.0%); this difference failed to achieve statistical significance (p=0.256). DVT was the second most frequent location of recurrence (28.1% in males *vs.* 32.1% in women; p=0.571), followed by splanchnic thrombosis (8.7% vs 11.5%; p=0.533) and catheter-associated thrombosis (6.8% *vs.* 7.7%; p=0.817). Of the 181 rethromboses, most occurred in subjects with digestive tumors (36 colorectal, 3 esophageal, 11 gastric, and 37 biliary/pancreatic), followed by lung carcinoma (40 cases) and breast cancer (18 cases). Eighty percent of the rethromboses (n = 145) occurred in adenocarcinomas in contrast to 6.6% in squamous cell carcinoma, and 2.2% in small cell carcinoma. Forty-one percent of the cases (n=74) had discontinued anticoagulant therapy prior to rethrombosis for different reasons, including the end of scheduled treatment (n=36), bleeding (n=10), patient decision (n=9), palliative management (n=6), and other reasons (n=13).

The univariate analysis evidenced that being <70 years of age increased the risk of rethrombosis at six months of VTE diagnosis. When evaluating the risk of rethrombosis at the end of follow up, primary tumor location in the digestive tract was identified as the only independent risk factor (sHR 1.87; 95% CI 1.21-2.89), whereas sex revealed no significant impact on this risk (*Online Supplementary Table S1*).

As shown in Table 4, the incidence of any kind of bleeding and the incidence of major bleeding were significantly higher in males**.** The adjusted multivariate analysis (*Online Supplementary Table S2*) evidenced that being male doubled the risk of major bleeding at the end follow up (sHR 2.34; 95% CI 1.36-4.04; p=0.002), but not at 6 months of VTE diagnosis (sHR 1.85; 95% CI 0.87-3.94; p=0.11). Other factors associated with greater risk of major bleeding at the end of follow up were the presence of a situation of risk for bleeding (due to tumor location and/ or

presence of thrombocytopenia) and the existence of tumor bleeding at the time of VTE diagnosis (*Online Supplementary Table S2*). Tumor stage, age, thrombocytopenia, use of antiangiogenic therapies, and glomerular filtration rate <60 ml/ min (none of the 31 patients with glomerular filtration <30 ml/ min had major bleeding) did not increase the risk of major bleeding (Online Supplementary Table S2). Of the 77 individuals with major bleeding, most had digestive tumors (17 colorectal, 4 esophageal, 6 gastric, 7 biliary/ pancreatic, and 2 GIST), followed by carcinoma of the breast (11 cases), lung (9 cases), and urological tumors (5 cases). The location of the primary tumor in the breast was also associated with a higher risk of major bleeding at the end of follow up in the multivariate analysis (sHR 2.75; 95% CI 1.18-6.38; p = 0.019). No significant differences were noted (p=0.563) regarding the median number of days between VTE diagnosis and bleeding among males (53 days; IQR 18.0-163.5) or women (72 days; IQR 16.8-175.5). There were 13 cases of fatal bleeding among the women, largely in patients with colorectal (n=4), pulmonary (n=2), and ovarian (n=2) carcinoma, and 11 cases among men, predominantly in those with digestive (n = 4), pulmonary (n = 2), and urological (n = 2) tumors.

Analysis of survival

At the time of analysis, mortality was slightly greater among males than females, with 55.2% and 51.5% of the participants deceased, respectively. Median OS was 11.0 months for men (95% CI 9.9-12.5) in contrast to 13.5 months for women (95% CI 12.4-15.3), revealing a significant advantage for females (p=0.0062) (Figure 1). The leading cause of death was tumor progression, present in 76% of all cases, with no differences across sexes (Table 4). Survival was greater in patients who developed catheter-associated thrombosis with respect to other forms of VTE, in both sexes (Figure 2).

Discussion

The association between thrombosis and cancer has been widely acknowledged and, while more clinical trials are being conducted that evaluate anticoagulant treatments in this population in particular, the optimal duration of anticoagulant therapy in the oncological patient has yet to be fully elucidated. This dilemma is due to the more than well-known increased risk of rethrombosis in these patients, together with an added bleeding risk attributable to the tumors and cancer treatments.

In this context, the evidence from real life data in ample populations and, in particular, prospective series, has begun to play a critical role with the real-world evidence (RWE) emerging as a possible answer to the questions as yet unresolved by clinical trials. In fact, international regulatory agencies are beginning to use this RWE for various purposes.

In recent years, several real-life registries of patients with thrombosis have been consolidated, notably the RIETE (the Spanish acronym for the Computerized Registry of Thrombo-Embolic Disease), an international registry that collects consecutive cases of acute VTE. The fact that the RIETE cover a larger population notwithstanding, it includes an important segment of oncological patients that has yielded interesting information concerning the evolution of CAT. Several of the RIETE publications have examined the impact of sex on rethrombosis and bleeding, focusing exclusively on subjects with symptomatic PE and DVT.[12,13,22] In contrast, the TESEO Registry covers any type of VTE, including incidental and symptomatic events.

Our findings failed to reveal sizeable differences in the incidence of DVT as the first event based on sex, though it did show a slightly higher incidence of PE among males. Nonetheless, the incidence of central catheter-associated thrombosis was significantly greater in women, possible given that these devices are used more in this sex. Although women with breast cancer have typically exhibited a low risk of thrombosis, the surge in the use of catheters in this group has brought with it more VTE in recent years. Of the 277 catheter-associated thromboses, 26.0% (n=72) occurred in cases of colorectal carcinoma, with breast cancer (22.4%, n=62) being the second tumor most frequently associated with this kind of VTE.

Some studies indicate that PE may be more serious in women than in men, with a higher incidence of centrally located embolisms, massive PE, and secondary right ventricle dysfunction.[13,23,24] These findings were not confirmed by our study in which we found no significant differences in terms of the extension of the PE, presence of symptoms, or of cardiac dysfunction.

Several studies in populations that are not exclusively oncological have identified a higher risk of rethrombosis among males with respect to women, albeit the specific causes of this difference are complex and probably multifactorial[7-11]. It has been suggested that a significant proportion of initial VTE in females develop in relation to exposure to hormonal factors and that the risk of recurrence decreases when these factors are eliminated, such as when contraceptive treatments are discontinued. In our study, no association was found between sex and the risk of rethrombosis. Research carried out in the cancer population has also detected that the risk of recurrence does not vary significantly according to sex.[12,13,15] Nevertheless, it did confirm that the presence of digestive primary tumors markedly increments the risk of rethrombosis. This endorses earlier studies concerning the higher incidence of VTE recurrence in individuals with gastrointestinal tumors compared to other primary sites. [14,25] Unlike other studies, our analysis no detected a significant difference in the risk of rethrombosis depending on the tumor stage,[14,15,26] or between incidental and suspected thrombotic events, with 7% of recurrences in the former versus 6% in the latter. [15,27] The absence of an increased risk of rethrombosis in patients with stage IV disease in our univariate and multivariate analyses may be due to the

adjustment for death as a competing risk in the Fine-Gray model. By accounting for death as a competing event, the association between stage IV disease and rethrombosis may be attenuated. However, when we applied the Cox proportional hazards model-which does not consider competing risks-stage IV disease was associated with a higher risk of rethrombosis (*Online Supplementary Table S3*)

Our study stands out in that it reveals a greater incidence of bleeding in males compared to women, a finding that diverges from that of some studies performed in non-exclusively oncological populations that point toward a higher risk of bleeding among females during anticoagulant therapy. [28-30] Nevertheless, research focused on cancer patients reflect results similar to ours. [13,17,31] In the general population, uterine bleeding, common in women of reproductive age, is a typical cause of bleeding. [32,33] Nonetheless, it is important to bear in mind that, in subjects with cancer, most VTE in females are diagnosed in menopause, whether physiological (78% of women in our series were more than 55 years of age) or induced by cancer treatments. Martin-Martos et al. observed a lower risk of fatal bleeding in women with cancer included in the RIETE Registry compared to males (RR 0.69; 95% CI 0.47-0.99), as well as a trend toward a lower incidence of major bleeding that failed to achieve statistical significance. [13] A specific sub-analysis within the TICAT study of patients treated with LWMH for at least 12 months demonstrated a greater risk of clinically relevant bleeding in males (HR 2.97; 95% CI 1.01-8.1). [17] In contrast, in individuals who are anticoagulated other than for VTE, Raposeiras et al. found a lower incidence of bleeding in women and a higher incidence of bleeding in individuals with active cancer in a population of more than 1,100 cancer patients anticoagulated due to atrial fibrillation. [31]

In our series, more than 90% of the subjects were treated with LWMH both during the initial phase, as well as during maintenance, an approach that differs from that observed in RIETE Registry studies, in which a considerable proportion of cases (40% of patients in the study by Martin Martos et al.[13]) received treatment with antivitamin K, probably given that recruitment for said registry began in 2001. The limited use of DOACs in our population is worthy of note, which is attributable to the lack of financial coverage for this indication in Spain. Consequently, in light of the fact that DOAC and antivitamin K use was practically anecdotal in our study, the type of anticoagulant therapy was not included as a bleeding risk factor in the analysis. Apropos of bleeding risk by sex in patients with cancer receiving DOACs, Bosch and cols. examined gastrointestinal bleeding risk factors in subjects with gastrointestinal tumors who received edoxaban in the Hokusai VTE Cancer study.[18] They found a higher proportion of males in the group with bleeding compared to the control group (79% vs 64%; p=0.27).

Our study demonstrates the evolution of a sizable cohort of subjects with CAT treated in daily clinical practice, outside the controlled conditions of a clinical trial. Be that as it may, it presents

limitations inherent to observational studies. To begin with, as with other studies based on real-life registries, the incidence of VTE recurrence may be underestimated radiological testing to confirm VTE recurrences if the result will not entail a change in therapeutic attitude. Secondly, the impact of DOACs on the risk of recurrence or bleeding cannot be determined due to the few patients who received them in our series. Third, subjects were classified according to their biological sex, without factoring in their sexual orientation. On the other hand, the representation of hematological tumors is limited (only 18 cases), a reflection of the scant participation of hematologists in the registry.

Despite these limitations, our research provides valuable insights in an area with little clinical evidence. It guides professionals on which patients might benefit from prolonged anticoagulation beyond six months, inasmuch as the mean duration of anticoagulant therapy in our study exceeded eight months. Subjects with digestive or pulmonary tumors, and metastatic spread[14,15,25,26] are at greater risk for VTE recurrence, which suggests that they might be eligible to maintain anticoagulation, as long the risk of bleeding is carefully considered. This risk appears to be greater in individuals with tumors who already exhibited bleeding at the time of VTE diagnosis, in those with tumors at high risk for bleeding given their location (infiltration of digestive, bronchial, or vesical mucosa) or in the presence of thrombocytopenia, and in males. It is worth noting a higher than expected incidence of major bleeding in women with breast cancer in our study, indicating that the benefit of maintaining prolonged anticoagulation may be lower in this group.

In short, given the absence of clinical trials to inform decision-making, the decision as to whether to extend anticoagulation or not must be made on a case-by-case basis, bearing in mind all the possible factors that increase the risk of rethrombosis and bleeding, including biological sex as one of such relevant factors.

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	Overall N = 2,823	**Male** N = 1,472	**Female** N = 1,351	**p-value**[1]
Age (Mean ± SD)	64.9 ± 11.4	65.2 ± 10.9	64.6 ± 11.8	0.139
Race. N (%)				
Caucasian	2,768 (98.1%)	1,446 (98.2%)	1,322 (97.9%)	0.266
Other	55 (1.9%)	26 (1.8%)	29 (2.1%)	
Chronic arterial hypertension. N (%)	1,192 (42.3%)	652 (44.4%)	540 (40.0%)	0.018
Dyslipidemia. N (%)	1,015 (36.0%)	561 (38.2%)	454 (33.6%)	0.011
BMI > 30. N (%)	586 (21.2%)	260 (18.1%)	326 (24.5%)	<0.001
Performance status, ECOG. N (%)				0.024
0-1	2,043 (72.4%)	1,092 (74.2%)	951 (70.4%)	
≥ 2	780 (27.6%)	380 (25.8%)	400 (29.6%)	
Smoking status. N (%)				<0.001
Active smoker	448 (17.2%)	273 (19.9%)	175 (14.1%)	
Ex-smoker	1,095 (41.9%)	777 (56.7%)	318 (25.6%)	
Never smoker	1,068 (40.9%)	321 (23.4%)	747 (60.2%)	
History of inherited thrombophilia. N (%)	15 (0.5%)	4 (0.3%)	11 (0.8%)	0.048
Immobilization. N (%)	211 (7.6%)	122 (8.3%)	141 (10.4%)	0.052
Central venous catheter. N (%)	673 (24.0%)	312 (21.4%)	361 (27.0%)	<0.001
Previous VTE. N (%)	211 (7.6%)	110 (7,6%)	101 (7.6%)	0.98
TNM Stage. N (%)				<0.001
I	79 (2.8%)	28 (1.9%)	51 (3.8%)	
II	200 (7.1%)	84 (5.7%)	116 (8.6%)	
III	534 (18.9%)	269 (18.3%)	265 (19.6%)	
IV	2,010 (71.2%)	1,091 (74.1%)	919 (68.0%)	
Primary tumor location. N (%)				
Lung	629 (22.3%)	406 (27.6%)	223 (16.5%)	<0.001
Colorectal	543 (19.2%)	320 (21.7%)	223 (16.5%)	<0.001
Pancreas and bile duct	358 (12.6%)	187 (12.7%)	169 (12.5%)	0.876
Breast	291 (10.3%)	9 (0.6%)	282 (20.9%)	<0.001
Gynecological	200 (7.1%)	----	200 (14.8%)	----
Bladder	103 (3.6%)	81 (5.5%)	22 (1.6%)	<0.001
CNS tumors	73 (2.6%)	50 (3.4%)	23 (1.7%)	<0.005
Prostate	62 (2.2%)	62 (4.2%)	----	----
Head and neck	59 (2.1%)	50 (3.4%)	9 (0.7%)	<0.001
Esophagus/ stomach	49 (1.7%)	42 (2.9%)	7 (0.5%)	<0.001
Kidney	47 (1.7%)	32 (2.2%)	15 (1.1%)	0.027
Melanoma	23 (0.8%)	17 (1.2%)	6 (0.4%)	<0.036
Testicular	21 (0.7%)	21 (1.4%)	----	----
Hematological	18 (0.6%)	7 (0.5%)	11 (0.8%)	0.259
Other	349 (12.4%)	187 (12.7%)	161 (11.9%)	0.525
Recent major surgery (30 days). N (%)	63 (2.2%)	26 (1.8%)	37 (2.7%)	0.081
Active tumor disease. N (%)	2,393 (84.8%)	1,278 (86.8%)	1,115 (82.5%)	0.002
Prior anticoagulant therapy. N (%)	87 (3.1%)	67 (4.5%)	20 (1.5%)	<0.001

[1]Welch Two Sample t-test; Pearson's Chi-squared test; Fisher's exact test

VTE: venous thromboembolic event, SD: standard deviation, BMI: Body Mass Index, ECOG: Eastern Cooperative Oncology Group, CNS: central nervous system

Table 1. Clinical characteristics of the patients and VTE risk factors

	Overall N = 2,823	**Male** N = 1,472	**Female** N = 1,351	**p-value**[1]
Type of VTE. N (%)				
PE	1,588 (56.2%)	855 (58.0%)	733 (54.3%)	**0.045**
DVT	1,107 (39.2%)	558 (37.9%)	549 (40.6%)	0.136
DVT and/ or PE	2,433 (86.2%)	1,272 (86.4%)	1,161 (85.9%)	0.714
Simultaneous PE + DVT	262 (9.3%)	141 (9.5%)	121 (8.9%)	0.573
Splanchnic thrombosis	207 (7.3%)	125 (8.5%)	82 (6.1%)	0.343
Catheter-associated thrombosis	277 (9.8%)	121 (8.2%)	156 (11.7%)	**0.003**
VTE diagnostic type. N (%)				0.143
Unsuspected /Incidental	1,380 (48.9%)	739 (50.2%)	641 (47.5%)	
Suspected	1,441 (51.1%)	732 (49.8%)	709 (52.5%)	

[1]*Welch Two Sample t-test; Pearson's Chi-squared test; Fisher's exact test*

PE: Pulmonary Embolism; DVT: Deep vein thrombosis; VTE: venous thromboembolic event

Table 2. Type of thrombotic event by sex

	Male N = 1,472	**Female** N = 1,351
Initial therapy. N (%)		
LMWH	1324 (89.9%)	1216 (90.0%)
UFH	90 (6.1%)	83 (6.1%)
DOAC	13 (0.9%	19 (1.4%)
No therapy	43 (2.9%)	31 (2.3%)
Unknown	2 (0.1%)	2 (0.2%)
Long-term therapy. N (%)		
LMWH	1392 (94.5%)	1284 (95.0%)
DOAC	26 (1.8%)	29 (2.3%)
Vitamin K antagonist	9 (0.6%)	5 (0.3%)
No therapy	43 (3.0%)	31 (2.3%)
Unknown	2 (0.1%)	2 (0.1%)
Duration of anticoagulation.		
Mean, months (± SD)	8.0 (± 9.0)	8.8 (± 9.7)
Median, months (IQR)	5.0 (1.5-11.0)	5.6 (1.9-11.7)
Anticoagulation discontinuation. N (%)	293 (20.5%)	288 (21.9%)
Causes of discontinuation. N (%)		
Treatment complete	123 (42.0%)	157 (54.5%)
Patient's decision	14 (4.8%)	14 (4.9%)
Bleeding	58 (19.8%)	31 (10.8%)
Other complications	13 (4.4%)	15 (5.2%)
Palliative care	67 (22.9%)	51 (17.7%)
Other	18 (6.1%)	20 (6.9%)

LMWH: Low-Molecular Weight Heparin; UFH: Unfractionated Heparin; DOAC: Direct Oral anticoagulant; SD: standard deviation; IQR: interquartile range

Table 3. Anticoagulant therapy by sex

	Male N = 1,472	**Female** N = 1,351	**p-value**[1]
Recurrent VTE. % (95% CI)			0.14
Cumulative incidence at 6 months	4.5% (3.5%-5.7%)	2.8% (2.0%-3.9%)	
Cumulative incidence at 12 months	6.7% (5.4%-8.2%)	4.9% (3.8%-6.3%)	
Cumulative incidence at the end of follow up	10.0% (8.1%-12.0%)	15.0% (4.8%-32.0%)	
Any bleeding. % (95% CI)			**0.009**
Cumulative incidence at 6 months	9.7% (8.2%-11.0%)	7.3% (5.9%-8.8%)	
Cumulative incidence at 12 months	12.0% (9.9%-13.0%)	8.8% (7.2%-10.0%)	
Cumulative incidence at the end of follow up	15.0% (13.0%-17.0%)	12.0% (9.3%-15.0%)	
Major bleeding. % (95% CI)			**0.026**
Cumulative incidence at 6 months	1.8% (1.2%-2.7%)	0.7% (0.3%-1.3%)	
Cumulative incidence at 12 months	2.7% (1.9%-3.7%)	1.4% (0.8%-2.2%)	
Cumulative incidence at the end of follow up	12.0% (4.8%.23.0%)	6.0% (3.2%-9.9%)	
Death. N (%)	805 (55.2%)	691 (51.5%)	**0.046**
Cause of death. N (%)			0.971
Cancer	612 (76.0%)	527 (76.3%)	
Mixed causes, VTE probably involved	98 (12.1%)	80 (11.6%)	
Infection	40 (5.0%)	36 (5.2%)	
VTE	12 (1.5%)	12 (1.7%)	
Fatal bleeding	11 (1.4%)	13 (1.9%)	
Other, VTE probably not involved	32 (4.0%)	23 (3.3%)	

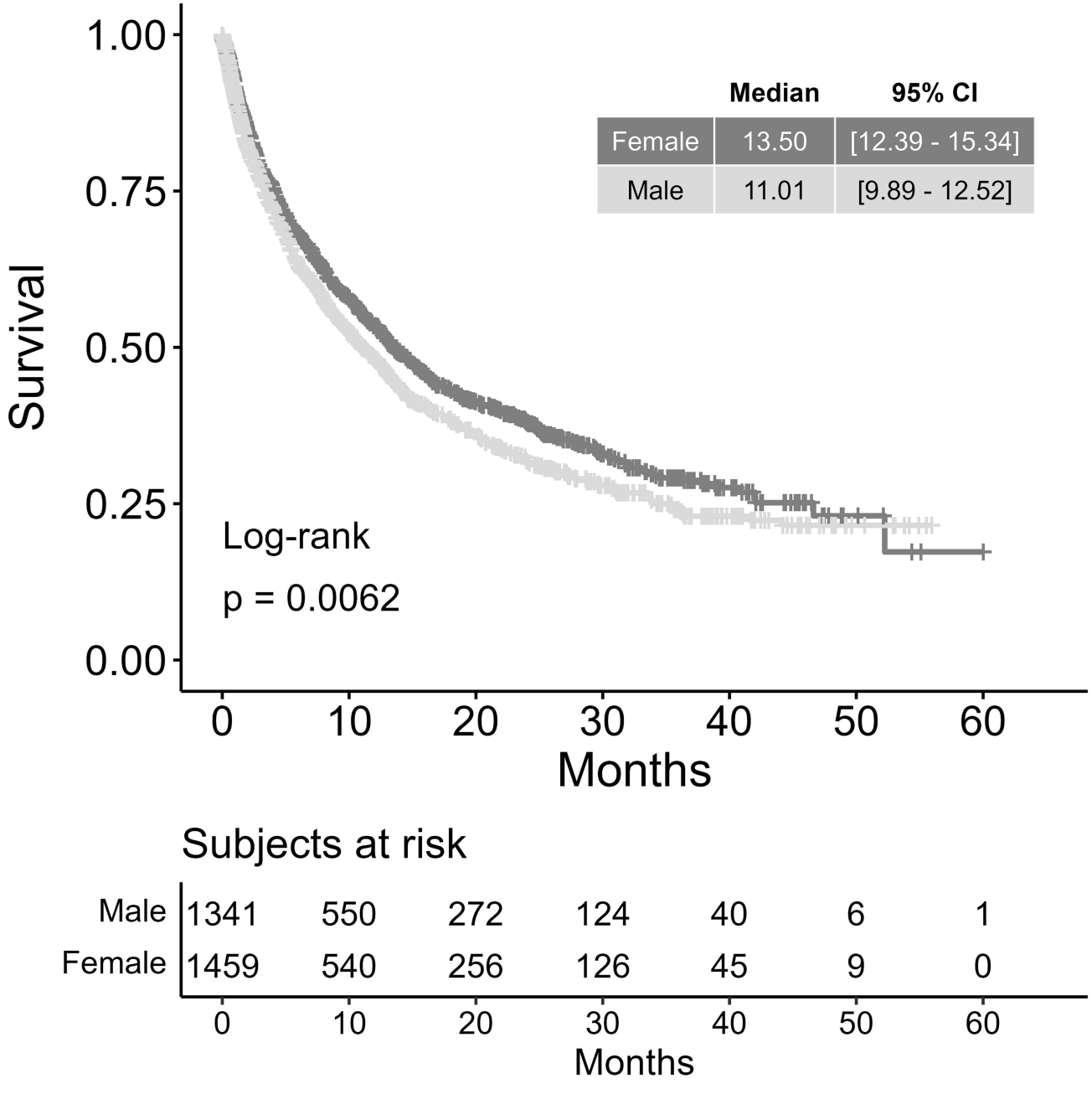
[1]*Gray's Test; Pearson's Chi-squared test.*

95% CI: 95% Confidence Interval. VTE: venous thromboembolic event

Table 4: Clinical outcome by sex

Figure 1. Survival by sex

Figure 2. Survival by type of VTE A: Kaplan-Meier curve comparing survival from time of cancer diagnosis to demise according to type of VTE (all patients, excluding patients with simultaneous VTE). B: Kaplan-Meier curve comparing survival from time of cancer diagnosis to demise according to type of VTE (male, excluding patients with simultaneous VTE). C: Kaplan-Meier curve comparing survival from time of cancer diagnosis to demise according to type of VTE (female, excluding patients with simultaneous VTE).


Median
95% CI
Female
13.50
[12.39 - 15.34]
Male
11.01
[9.89 - 12.52]
Survival
1.00
0.75
0.50
0.25
0.00
Log-rank
p = 0.0062
0
10
20
30
40
50
60
Months
Subjects at risk
Male
1341
550
272
124
40
6
1
Female
1459
540
256
126
45
9
0
0
10
20
30
40
50
60
Months

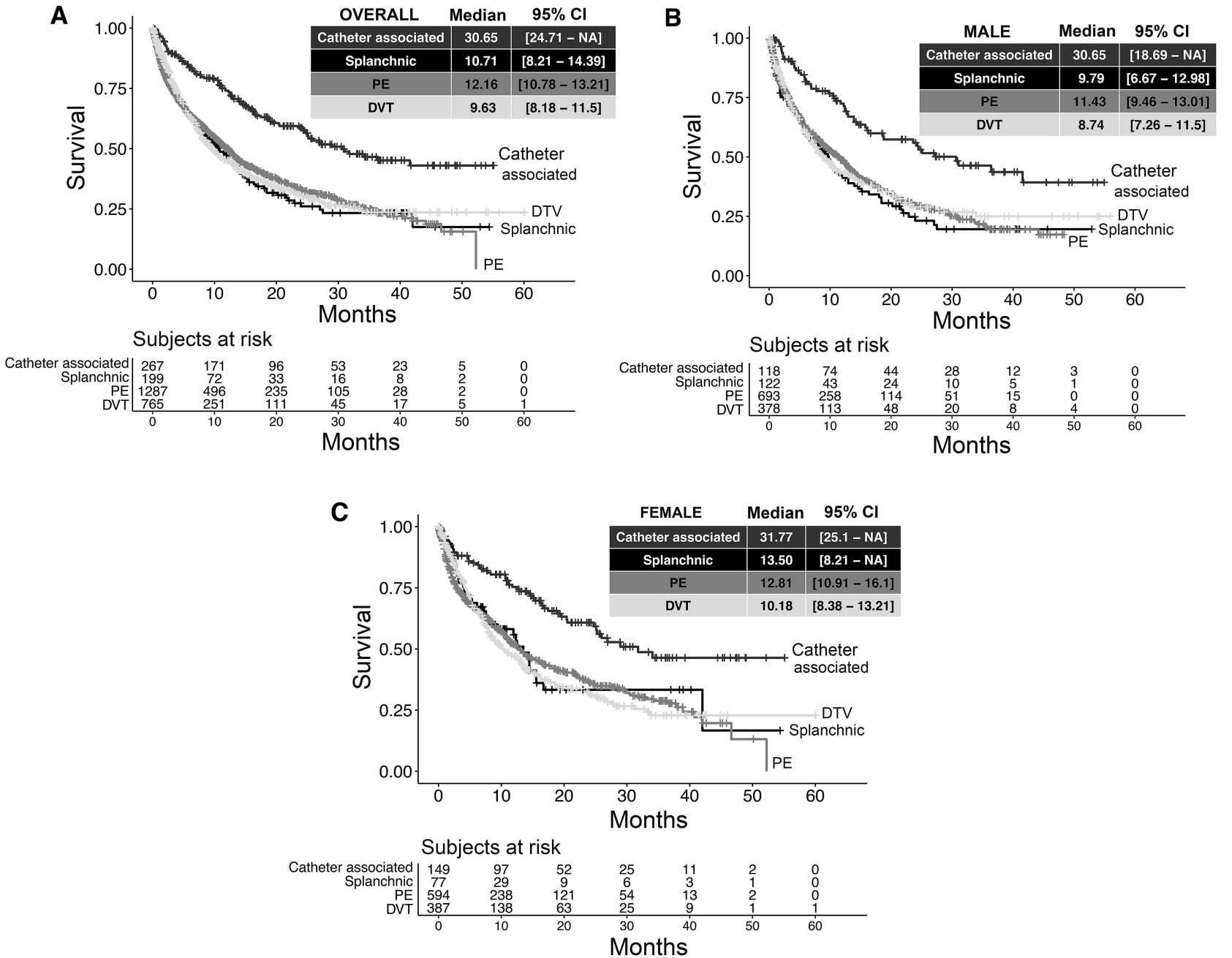

A
OVERALL Median 95% CI
Catheter associated 30.65 [24.71 – NA]
Splanchnic 10.71 [8.21 – 14.39]
PE 12.16 [10.78 – 13.21]
DVT 9.63 [8.18 – 11.5]
Survival
Months
Catheter associated
DTV
Splanchnic
PE
Subjects at risk
Catheter associated 267 171 96 53 23 5 0
Splanchnic 199 72 33 16 8 2 0
PE 1287 496 235 105 28 2 0
DVT 765 251 111 45 17 5 1
B
MALE Median 95% CI
Catheter associated 30.65 [18.69 – NA]
Splanchnic 9.79 [6.67 – 12.98]
PE 11.43 [9.46 – 13.01]
DVT 8.74 [7.26 – 11.5]
Subjects at risk
Catheter associated 118 74 44 28 12 3 0
Splanchnic 122 43 24 10 5 1 0
PE 693 258 114 51 15 0 0
DVT 378 113 48 20 8 4 0
C
FEMALE Median 95% CI
Catheter associated 31.77 [25.1 – NA]
Splanchnic 13.50 [8.21 – NA]
PE 12.81 [10.91 – 16.1]
DVT 10.18 [8.38 – 13.21]
Subjects at risk
Catheter associated 149 97 52 25 11 2 0
Splanchnic 77 29 9 6 3 1 0
PE 594 238 121 54 13 2 0
DVT 387 138 63 25 9 1 1

Table S1. Univariate analysis and multivariate analysis adjusted for risk of rethrombosis (Fine-Gray proportional subdistributions hazards model)

	At 6 months of follow up				At the end of follow up			
	Univariate		Adjusted multivariate		Univariate		Adjusted multivariate	
	sHR (95% CI)	p-value	sHR (95% CI)	p-value	sHR (95% CI)	p-value	sHR (95% CI)	p-value
Male sex	1.17 (0.68-2.02)	0.57			1.25 (0.93-1.67)	0.14	1.22 (0.90-1.67)	0.20
Age > 70 years	0.48 (0.24-0.96)	**0.039**	0.45 (0.23-0.91)	**0.025**	0.82 (0.60-1.13)	0.23		
TNM stage								
Stage I-III	---				---			
Stage IV	0.82 (0.46-1.47)	0.51			1.03 (0.75-1.42)	0.86		
Tumor location								
Other	---		---		---		---	
Lung	1.47 (0.60-3.59)	0.40	1.52 (0.62-3.72)	0.36	1.52 (0.93-2.49)	0.097	1.46 (0.90-2.35)	0.13
Urological	1.06 (0.52-2.23)	0.94	1.21 (0.32-4.55)	0.78	1.08 (0.52-2.23)	0.84	0.99 (0.48-2.03)	0.98
Breast	0.78 (0.21-2.91)	0.71	0.79 (0.21-2.96)	0.72	1.41 (0.79-2.56)	0.26	1.53 (0.82-2.84)	0.18
Digestive	1.82 (0.82-4.00)	0.14	1.99 (0.90-4.44)	0.088	1.87 (1.21-2.89)	**0.005**	1.80 (1.16-2.77)	**0.008**
Initial VTE								
Unsuspected	---				---			
Suspected	1.24 (0.72, 2.15)	0.43			0.87 (0.65, 1.17)	0.35		

sHR: Sub-distribution Hazard Ratio. CI: Confidence Interval.

Table S2. Univariate analysis and multivariate analysis adjusted for risk of major bleeding (Fine-Gray proportional subdistributions hazards model)

	At 6 months of follow up				At the end of follow up			
	Univariate		Adjusted multivariate		Univariate		Adjusted multivariate	
	sHR (95% CI)	p-value	sHR (95% CI)	p-value	sHR (95% CI)	p-value	sHR (95% CI)	p-value
Male sex	1.95 (0.92-4.13)	0.083	1.85 (0.87-3.94)	0.11	1.73 (1.08-2.75)	0.022	2.34 (1.36-4.04)	**0.002**
Kidney function								
Glomerular filtration ≥ 60 ml/ min	----				----			
Glomerular filtration 30- 59 ml/ min	1.45 (0.55-3.78)	0.45			1.30 (0.68-2.46)	0.43		
Glomerular filtration < 30 ml/ min	0				0			
Age > 70 years	0.70 (0.32-1.57)	0.39			0.82 (0.50-1.34)	0.43		
Active tumor disease	2.59 (0.62-10.9)	0.19			1.85 (0.85-4.0)	0.12		
TNM stage								
Stage I-III	----				----			
Stage IV	0.98 (0.46-2.13)	0.96			1.06 (0.64-1.75)	0.81		
Bleeding risk	3.33 (1.57-7.08)	**0.002**	2.08 (0.88-4.90)	0.094	4.08 (2.57-6.49)	**<0.001**	3.45 (2.05-5.80)	**<0.001**
Active bleeding cancer	7.07 (2.70-18.5)	**<0.001**	4.08 (1.37-12.2)	**0.012**	5.08 (2.49-10.54)	**<0.001**	2.32 (1.04-5.21)	**0.041**
Tumor location								
Other	----				----		----	
Lung	0.77 (0.21-2.85)	0.69			0.54 (0.24-1.21)	0.14	0.46 (0.20-1.09)	0.078
Urological	1.13 (0.22-5.81)	0.89			0.88 (0.32-2.39)	0.8	0.58 (0.21-1.62)	0.3
Breast	1.24 (0.30-5.19)	0.77			1.42 (0.66-3.04)	0.37	2.75 (1.18-6.38)	**0.019**
Digestive	1.88 (0.70-5.10)	0.21			1.23 (0.68-2.21)	0.49	1.04 (0.56-1.91)	0.91
Platelets < 100000 counts/ µl	1.54 (0.47-5.03)	0.48			1.18 (0.51-2.71)	0.70		
Antiangiogenic Therapy	1.59 (0.48-5.22)	0.45			1.00 (0.41-2.48)	> 0.999		

sHR: Sub-distribution Hazard Ratio. CI: Confidence Interval.

Table S3. Univariate analysis and multivariate analysis adjusted for risk of rethrombosis (Cox proportional hazards model)

	At 6 months of follow up				At the end of follow up			
	Univariate		Adjusted multivariate		Univariate		Adjusted multivariate	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Male sex	1.64 (1.07-2.50)	**0.023**			1.33 (0.99-1.78)	0.059	1.2 (0.87-1.66)	0.264
Age > 70 years	0.65 (0.40-1.05)	0.078	0.6 (0.37-0.98)	**0.039**	0.86 (0.63-1.19)	0.377		
TNM stage								
Stage I-III	---				---		---	
Stage IV	1.35 (0.85-2.16)	0.204			1.56 (1.13-2.16)	**0.008**	1.49 (1.07-2.07)	**0.019**
Tumor location								
Other	---		---		---		---	
Lung	1.90 (0.93-3.86)	0.076	1.96 (0.97-3.99)	0.062	1.84 (1.12-3.01)	**0.016**	1.65 (1.01-2.74)	**0.047**
Urological	1.19 (0.42-3.39)	0.74	1.36 (0.48-3.88)	0.562	1.11 (0.54-2.30)	0.778	0.95 (0.45-1.99)	0.885
Breast	0.65 (0.21-2.00)	0.448	0.65 (0.21-2.01)	0.451	1.08 (0.59-1.97))	0.808	1.21 (0.65-2.24)	0.550
Digestive	2.36 (1.26-4.44)	**0.007**	2.68 (1.42-5.06)	**0.002**	1.86 (1.20-2.88)	**0.005**	1.74 (1.11-2.70)	**0.015**
Initial VTE								
Unsuspected	---				---			
Suspected	1.39 (0.92, 2.10)	0.117	1.51 (0.99-2.28)	0.054	0.93 (0.70-1.25)	0.638		

HR: Hazard Ratio. CI: Confidence Interval.

Table S4. Univariate analysis and multivariate analysis adjusted for risk of major bleeding (Cox proportional hazards model)

	At 6 months of follow up				At the end of follow up			
	Univariate		Adjusted multivariate		Univariate		Adjusted multivariate	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Male sex	2.31 (1.29-4.13)	**0.005**	2.14 (1.17-3.90)	**0.014**	1.81 (1.13-2.89)	**0.013**	2.32 (1.31-4.11	**0.004**
Kidney function								
Glomerular filtration ≥ 60 ml/ min	----				----			
Glomerular filtration 30- 59 ml/ min	1.36 (0.64-2.88)	0.429			1.35 (0.71-2.56)	0.359		
Glomerular filtration < 30 ml/ min	0				0			
Age > 70 years	0.77 (0.42-1.39)	0.384			0.86 (0.53-1.42)	0.564		
Active tumor disease	3.36 (1.05-10.8)	**0.041**	2.52 (0.78-8.15)	0.124	2.48(1.13-5.42)	0.023	2.00 (0.90-4.44)	0.089
TNM stage								
Stage I-III	----				----			
Stage IV	1.08 (0.60-1.94)	0.79			1.42 (0.86-2.36)	0.175		
Bleeding risk	4.21 (2.43-7.29)	**<0.001**	2.31 (1.17-4.56)	**0.016**	4.69 (2.94-7.48)	**<0.001**	3.41 (1.97-5.89)	**<0.001**
Active bleeding cancer	8.02 (3.9-16.4)	**<0.001**	3.58 (1.47-8.71)	**0.005**	6.3 (3.13-12.7)	**<0.001**	2.42 (1.05-5.54)	**0.037**
Tumor location								
Other	----				----			
Lung	0.82 (0.32-2.07)	0.667			0.61 (0.27-1.38)	0.237	0.41 (0.17-1.01)	0.052
Urological	1.15 (0.36-3.68)	0.810			0.90 (0.33-2.46)	0.836	0.56 (0.20-1.56)	0.264
Breast	1.21 (0.44-3.32)	0.718			1.16 (0.54-2.51)	0.703	2.23 (0.96-5.21)	0.062
Digestive	1.50 (0.73-3.10)	0.273			1.24 (0.69-2.23)	0.477	0.97 (0.53-1.78)	0.923
Platelets< 100000 counts/ µl	1.9 (0.81-4.44)	0.138			1.31 (0.57-3.02)	0.524		
Antiangiogenic Therapy	0.85 (0.26-2.71)	0.779			1.04 (0.42-2.57)	0.939		

HR: Hazard Ratio. CI: Confidence Interval.