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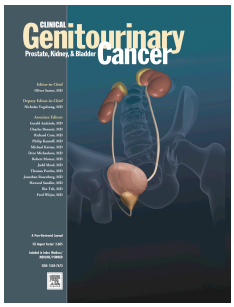

Venous thromboembolism risk in patients with locoregional urothelial tract tumors

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MicroAbstract

There is limited data on venous thromboembolism (VTE) risk in locoregional urothelial tract tumors (UTT) patients. We performed a multicenter, retrospective study of 1732 patients assessing VTE rate, associative factors, and impact on survival in this population. Our study identified a high VTE rate (7.6%) and several factors associated with increased risk including non-urothelial histology, renal dysfunction, and cardiovascular disease.

ABSTRACT

Background: Venous thromboembolism (VTE) is common in cancer patients, but there is limited data in urothelial tract tumors (UTT) patients. We previously identified several associative factors for increased VTE rates in patients with metastatic UTT. In this study, we assessed the frequency, associative factors, and impact on survival of VTE in locoregional UTT patients.

Methods: Locoregional bladder, upper urinary tract, or urethral cancer patients were included in this multi-center study from 29 academic institutions. Patients with <cT2, >N1, or M1 disease at diagnosis were excluded. Patients with incomplete clinical staging or miscoded/missing data were excluded. Cumulative, unadjusted VTE incidence was calculated from time of diagnosis of muscle-invasive disease, excluding VTEs diagnosed in the metastatic setting. Chi-squared statistics tested differences in VTE rates across baseline and treatment-related factors. Significant covariates were incorporated into a multivariate, logistic regression model. Overall survival stratified by VTE was estimated using Kaplan-Meier methods and evaluated using the log-rank test.

Results: 1732 patients were eligible. There were 132 VTEs (7.6%). On multivariate analysis, non-urothelial histology ($p<0.001$), clinical Nx stage ($p<0.001$), cardiovascular disease (CVD) ($p=0.01$), and renal dysfunction ($p=0.04$) were statistically significant baseline factors associated with VTE. Using surgery alone as reference, surgery with perioperative chemotherapy ($p=0.04$) and radiation with concurrent chemotherapy ($p=0.04$) also were significant.

Conclusions: The VTE incidence of 7.6% in locoregional disease is comparable to our previously reported rate in the metastatic setting (8.2%). Similar to our findings in metastatic UTT, non-urothelial histology, renal dysfunction, and CVD was associated with increased VTE risk.

INTRODUCTION

Patients with urothelial tract tumors (UTT) have an increased risk of venous thromboembolism (VTE). Although the Khorana score, a risk-stratification model for VTE, considers malignancies of the urothelial tract high risk for VTE, UTT only represented a minor subset of patients in their analysis.[1] Some risk factors for cancer-associated thrombosis that have been consistently shown to be associated with VTE are immobility, aggressive tumor biology, surgery, and systemic chemotherapy, particularly cisplatin-based regimens.[2-7] More recently, our group identified multiple associative factors from a large, international, retrospective database of patients with UTT.[8] However, this study focused exclusively on patients with metastatic disease, and the associative factors identified may not be applicable to the locoregional disease setting.

VTE rates in patients with locoregional UTT may be different compared to patients with metastatic disease.[9,10] One might expect metastatic disease patients to have higher VTE rates for multiple reasons. Generally, patients with metastatic disease have larger tumor volumes which may lead to release of more thrombogenic cytokines, cause mechanical vascular compression, receipt of systemic chemotherapy, and declining performance status. Conversely, patients with muscle-invasive localized disease that are undergoing radical cystectomy also have the significant increased risk factor of VTE of undergoing a major pelvic surgery with limited mobility.[11]

Extended (28-day) postoperative thromboprophylaxis in patients undergoing abdominal or pelvic cancer surgery has been shown to decrease VTE rates.[12] However, this information was not disseminated in a widespread fashion through clinical guidelines until more recently.[13,14] Although clear benefit has been shown, the uptake of the practice of prophylactic anticoagulation prior to radical cystectomy likely has had poor uptake.[15,16] Therefore, we set out to describe the risk of VTE for patients with locoregional UTT, identify associative factors for patients in this setting, determine the risk of different systemic perioperative chemotherapy regimens, and determine association, if any, of VTE on overall survival.

MATERIALS AND METHODS

Study Design and Patient Population

Data were collected and abstracted from the Retrospective International Study of Cancers of the Urothelium (RISC) database, a multi-center study of the management and outcomes of patients with UTT with at least muscle-invasive disease. As previously described, the RISC database is comprised of data that were gathered from 29 international centers and stored via a secure, password-protected platform.[17] The institutional review board at all participating institutions approved the study.

Patients diagnosed with cT2-T4, cN0-N1 (including Nx), and M0 (including Mx) cancer of the bladder, renal pelvis, ureter, and urethra were eligible for analysis.

Urothelial and non-urothelial histologies (i.e., adenocarcinoma, micropapillary, neuroendocrine, sarcomatoid, and squamous) were included. Patients were classified as having non-urothelial histology if they had purely or predominately variant histology. Patients with primarily urothelial carcinoma with a component of non-urothelial histology were categorized as urothelial histology. Patients without complete clinical staging at the time of diagnosis or miscoded/missing data were excluded from the study.

Patient, tumor, and treatment-related factors were assessed for their association with VTE incidence. Patient characteristics that were collected include age, race, gender, presence of renal dysfunction (investigator-designated), history of cardiovascular disease (CVD), CVD risk factors, congestive heart failure, and chronic obstructive pulmonary disease. CVD encompassed coronary artery disease, peripheral vascular disease, and/or a cerebrovascular accident. Cardiovascular risk factors included diabetes mellitus, hypertension, and/or hyperlipidemia. Tumor characteristics assessed were primary tumor location, histologic subtype, clinical T-stage at diagnosis, and clinical N-stage at diagnosis. Primary treatment modality was categorized into five variables for analysis: 1) surgery alone, 2) surgery with perioperative chemotherapy, 3) radiation therapy alone, 4) radiation therapy with concurrent chemotherapy, and 5) no primary local treatment modality utilized. Surgical interventions included in the analysis were radical (both open and robotic) or partial cystectomy, nephrectomy, nephrouretectomy, ureterectomy, and urethrectomy. Lastly, in the patients that

were treated with surgery in combination with perioperative chemotherapy, we assessed the association of VTE based on chemotherapy regimens. We specifically evaluated three chemotherapy regimens: 1) gemcitabine and cisplatin, 2) gemcitabine and carboplatin, and 3) methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) or cisplatin, methotrexate, and vinblastine (CMV).

Statistical Analysis

Cumulative, 3-month, and 6-month absolute VTE incidence rates were calculated from the date of diagnosis to the VTE date. Since we were interested in understanding VTE risk in the locoregional disease setting, VTEs that occurred after a patient developed metastatic disease were excluded. VTE rates based on demographic and baseline characteristics were compared using chi-squared tests. In assessing the association of VTE based on treatment modality, we recognized that treatment decisions may also be affected by baseline characteristics and extent of disease. Therefore, we evaluated whether there were differences in these clinical characteristics when stratified by treatment modality. In addition to age, covariates that were significant ($P \leq .05$) in the univariate analysis and/or significantly different across treatment modalities were included in a multivariate logistic regression analysis. Odds ratios (OR) were calculated for each factor in the multivariate model. Kaplan-Meier estimation and the log-rank test was utilized to assess overall survival stratified by whether the patient experienced a VTE.

RESULTS

Study Population and Patient Characteristics

The RISC database is comprised of 3025 patients, of which 1732 were eligible for analysis in this study (Figure 1). Of the 1732 patients, 1716 (99.1%) were diagnosed with muscle-invasive disease between January 1, 2000, and May 31, 2013. Only 16 (0.9%) patients were diagnosed between January 1, 1990, and December 31, 1999. Baseline characteristics of the study cohort are shown in Table 1. The mean age of the study cohort at the time of diagnosis was 67.4 years. The majority of patients had urothelial histology (90.0%), and the primary tumor was located in the bladder in 89.4% of cases. Most patients (70.6%) underwent surgical intervention as their primary treatment modality. Surgery in combination with perioperative chemotherapy represented the primary treatment modality in 37.0% of patients, and 33.6% were treated with surgery alone. The median overall survival of the study cohort was 3.0 years with a median duration of follow-up of 1.7 years.

Cumulative Incidence of VTE and Association with Clinical Characteristics

VTE incidence over time is shown in Figure 2. Altogether, there were 132 VTE events for a cumulative VTE incidence of 7.6%, with the preponderance of events occurring within 6 months of the date of diagnosis of muscle-invasive disease (77.3%). Unadjusted VTE incidence rates stratified by clinical characteristics are shown in Table 2. Baseline characteristics that were associated with VTE on univariate analysis were non-urothelial histology ($P<0.001$), presence of CVD

(P=0.004), renal dysfunction (P=0.02), and clinical Nx at diagnosis (P<0.001). Furthermore, with surgery alone as the reference, surgery with perioperative chemotherapy (P=0.05), radiation therapy alone (P=0.04), and radiation therapy with concurrent chemotherapy (P=0.01) were associated with an increased VTE incidence.

Multivariate analysis of association of baseline characteristics, primary treatment modality, and perioperative chemotherapy regimen with VTE

On multivariate analysis, non-urothelial histology (OR: 2.62, 95% CI 1.64-4.17, P<0.001), clinical Nx at diagnosis (OR: 2.17, 95% CI 1.47-3.20, P<0.001), presence of CVD (OR: 1.74, 95% CI 1.16-2.62, P=0.01), and renal dysfunction (OR: 1.7, 95% CI 1.02-2.98, P=0.04) were still significantly associated with VTE (Table 3). In addition to the statistically significant covariates noted above, clinical T-stage and age were incorporated into the multivariate model when assessing the association between primary treatment modality and VTE. With surgery as the reference, surgery in combination with perioperative chemotherapy (OR: 1.65, 95% CI 1.03-2.64, P=.04) and radiation therapy with concurrent chemotherapy was associated with an increased incidence of VTE (OR: 2.03, 95%CI 1.02-4.03, P=0.04). The highest absolute VTE rate based on perioperative chemotherapy regimen was seen in patients treated with gemcitabine and cisplatin at 8.2% (30/365) (Table 4). Patients treated with gemcitabine and carboplatin or MVAC/CMV had a VTE rate of 7.3% (6/182) and 5.6% (7/125), respectively. On multivariate analysis, when using gemcitabine and cisplatin as the reference, there

was no statistical difference in VTE rates based on perioperative chemotherapy regimen.

Survival

There was no difference in overall survival in patients who had a VTE compared to patients who did not have a VTE (P=0.28). The overall survival curves stratified by VTE are superimposed for the first year from the date of diagnosis, with separation of the curves after 1 year with more deaths in the group of patients who had a VTE (Figure 3). A landmark analysis at 2 years from the date of diagnosis demonstrates a trend towards worse overall survival in patients who had a VTE (P=0.09).

DISCUSSION

Based on a validated risk model for VTE, genitourinary malignancies (except for prostate cancer) are considered high-risk for VTE.[1] However, many clinical characteristics may modulate an individual cancer patient's risk for VTE. Multiple studies have demonstrated that patients with higher stage disease, such as those with metastatic disease, have increased VTE rates.[9,10] Conversely, in the locoregional disease setting, surgical intervention is a well-established VTE risk factor.[2,11] However, it is not clear which patient population is at the highest risk of VTE when all clinical factors are taken into consideration. Our group previously reported a VTE rate of 8.2% in patients with metastatic UTT.[8] In the current analysis, we identified a VTE rate that was marginally lower at 7.6% in patients with locoregional UTT. Taken together, these data suggest that there may be a slightly greater VTE rate in metastatic disease patients, though the difference is

nominal, perhaps abrogated by the increased risk that surgery and associated immobility provide. Therefore, UTT patients are at high risk of VTE regardless of whether they have locoregional or metastatic disease and should be counseled about their increased risk prior to initiating therapy.

In addition to surgery, treatment with cytotoxic chemotherapy can also increase VTE rates. The strongest evidence for this association is with cisplatin.[3-7] Both perioperative and radio-sensitizing chemotherapy in patients with UTT predominately utilize cisplatin-containing regimens. Accordingly, in our analysis, patients who were treated with surgery in combination with perioperative chemotherapy (8.4%) or radiation in combination with chemotherapy (12.3%) had higher VTE rates than patients treated with surgery alone (5.5%). When we evaluated VTE rates of the various chemotherapy regimens in the perioperative setting, no statistically significant difference in VTE was identified. We recognize this may be a result of insufficient power as the number of events in this analysis was relatively low. Unexpectedly, with surgery alone as the reference, the odds of having a VTE were highest in patients treated with radiation alone (OR: 1.76, p=0.10) or radiation in combination with chemotherapy (OR: 2.03, p=0.04), even when controlling for age, clinical T-stage, clinical N-stage, renal dysfunction, histology, and CVD. There is very limited contemporaneous data on the association of radiation therapy with VTE in cancer patients. One prospective, observational study of multiple malignancies demonstrated a 2.3-fold increased risk of VTE in patients treated with radiation therapy.[18] Alternatively, the increased VTE rate seen in patients who were treated with radiation therapy may be a result

of selection bias. Patients treated with radiation often have worse functional status than patients who undergo surgical intervention, which may have contributed to the increased VTE rate. Thus, this finding will require confirmation in future large, population-based studies.

In addition to treatments associated with increased VTE rates, several patient and tumor-related characteristics were also associated with elevated risk of VTE. In the multivariate analysis of the current study, non-urothelial histology, renal dysfunction, and the presence of CVD were demonstrated to be associated with increased VTE rates, which is reassuringly similar to the findings in our prior analysis of patients with metastatic disease.[8]

Multiple studies have demonstrated that VTEs in cancer patients are associated with worse overall survival.[19,20] Though our study did not demonstrate a statistically significant difference in overall survival, there was a trend toward worse overall survival in patients who had a VTE within 2 years of diagnosis of muscle-invasive disease. One possible explanation is that VTEs may be acting a as surrogate for more aggressive disease. However, as demonstrated in the overall survival curve, the difference in survival between the two groups decreases beyond 2 years from the date of diagnosis. One would expect to continue to see more deaths in the VTE group even beyond 2 years if VTEs were solely a marker of aggressive tumor biology. Alternatively, patients may have died of complications of treatment of the VTE anticoagulation, the VTE itself, or a recurrent VTE. Indeed, cancer patients have been shown to have higher rates of recurrent VTE and major bleeding than non-cancer patients.[21]

There are several limitations to this study. First, this is a retrospective analysis which is limited by the inherent unmeasured confounders and biases of such analyses. Second, we do not have data on whether patients received postoperative thromboprophylaxis, although we suspect the numbers of patients who received anticoagulation were likely low. Another limitation is that patients with either upper tract or urethral UTT are often under-staged at diagnosis which may have had an impact on the results. Additionally, assessment of cancer-specific survival is limited in this analysis as the cause of death was not known in a substantial number of patients. Also, we did not have reliable data on a patient's ECOG performance status, thus it was not included in the analysis. Likewise, we did not have data on whether patients had a prior history of VTE, which is an established risk factor for future thrombotic events. Lastly, certain clinical factors were investigator-designated (e.g., renal dysfunction, hypertension, diabetes mellitus) instead of utilizing a uniform definition.

The results from this study demonstrate that VTE in locoregional UTT is not arbitrary, and overall rates are not dramatically different than prior publications in metastatic disease patients. This supports that this disease setting should also be considered high risk for VTE and emphasizes the need for adherence to thromboprophylaxis guidelines. Specific attention should be paid to patients with non-urothelial histology, cardiovascular disease, or renal dysfunction, as these patients had particularly high VTE rates. Furthermore, additional studies evaluating the association of radiation therapy and various chemotherapy regimens with VTE in UTT should be undertaken. Lastly, the underlying

mechanisms driving VTE development in cancer patients have not been well elucidated and should be a focus of future research.

Clinical Practice Points

- Venous thromboembolism is a common complication in patients with locoregional urothelial tract tumors
- Patients with non-urothelial histology, renal dysfunction, or cardiovascular disease are at particularly high risk for venous thromboembolism
- The high rate of venous thromboembolism in urothelial tract tumor patients supports the development of primary thromboprophylaxis clinical trials
- Ultimately, a better understanding of the underlying mechanisms driving venous thromboembolism is critical for appropriate management of this patient population

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FIGURE LEGENDS

Figure 1: Flow chart of patient inclusion and exclusion criteria.

Figure 2: Cumulative incidence of VTE of study cohort.

Figure 3: Kaplan-Meier plot of overall survival (OS) of patients who had a venous thromboembolic event (VTE) and no venous thromboembolic event (No VTE). P-values are a result of the log-rank test.

Table 1: Baseline characteristics of study cohort

Characteristic	N (%)
Age: Mean +/- SD	67.4 +/- 10.8
Gender	
Male	1332 (76.9)
Female	396 (22.9)
Unknown	4 (0.2)
Race	
Caucasian	1591 (91.9)
Black	62 (3.6)
Asian	24 (1.4)
Hispanic	24 (1.4)
Other/Unknown	31 (1.8)
Histology	
Urothelial	1559 (90.0)
Non-urothelial	166 (9.6)
Unknown	7 (0.4)
Primary Tumor Location	
Bladder	1549 (89.4)
Upper Tract	138 (8.0)
Urethra	12 (0.7)
Unknown	33 (1.9)
Clinical T Stage	
T2	1145 (66.1)
T3	403 (23.3)
T4	184 (10.6)
Clinical N Stage	
N0	1084 (62.6)
N1	175 (10.1)
Nx	473 (27.3)
Primary Treatment	
Surgery/Chemotherapy	640 (37.0)
Surgery	582 (33.6)
Radiation/Chemotherapy	114 (6.6)
Radiation	145 (8.4)
None/Unknown	251 (14.5)

Table 2: Clinical characteristics and association with VTE

Characteristic	VTE/N (%)	p-value
Histology		
Urothelial	104/1559 (6.7)	ref
Non-urothelial	28/166 (16.9)	<0.001
Primary Tumor Location		
Other/Unknown	8/183 (4.4)	ref
Bladder	124/1549 (8.0)	0.08
Clinical T Stage		
T2	90/1145 (7.9)	ref
T3	27/403 (6.7)	0.45
T4	15/184 (8.2)	0.89
Clinical N Stage		
N0	62/1084 (5.7)	ref
N1	13/175 (7.4)	0.38
Nx	57/473 (12.1)	<0.001
Cardiovascular disease		
No	88/1332 (6.6)	ref
Yes	44/400 (11.0)	0.004
Renal Dysfunction		
No	112/1569 (5.1)	ref
Yes	20/163 (10.3)	0.02
Primary Treatment		
Surgery	32/582 (5.5)	ref
Surgery/Chemotherapy	54/640 (8.4)	0.05
Radiation	15/145 (10.3)	0.04
Radiation/Chemotherapy	14/114 (12.3)	0.01
None/Unknown	17/251 (6.8)	0.47

* No statistical difference in VTE based on age, gender, or race
** Other baseline co-morbidities assessed that were not statistically significant (defined as P≤0.05) on univariate analysis include chronic obstruction pulmonary disease, congestive heart failure, and presence of cardiovascular risk factors (i.e., diabetes mellitus, hypertension, or hyperlipidemia)

Table 3: Multivariate analysis of association of VTE and baseline characteristics and primary treatment modality

Characteristic	OR	95% CI	p-value
Histology			
Urothelial	1.0	ref	ref
Non-urothelial	2.62	(1.64,4.17)	<0.001
Clinical N Stage			
N0	1.0	ref	ref
N1	1.31	(0.69,2.47)	0.41
Nx	2.17	(1.47,3.20)	<0.001
Cardiovascular Disease			
No	1.0	ref	ref
Yes	1.74	(1.16,2.62)	0.01
Renal Dysfunction			
No	1.0	ref	ref
Yes	1.74	(1.02,2.98)	0.04
Primary Treatment			
Surgery	1.0	ref	ref
Surgery/Chemotherapy	1.65	(1.03,2.64)	0.04
Radiation	1.76	(0.91,3.40)	0.10
Radiation/Chemotherapy	2.03	(1.02,4.03)	0.04

* OR = odds ratio, CI= confidence interval
** Four baseline clinical characteristics were significantly different across treatment modalities and thus controlled for in the multivariate analysis. The four characteristics were presence of cardiovascular disease, presence of renal dysfunction, clinical T-stage at diagnosis, and clinical N-stage at diagnosis.
*** Histology and age were controlled for in this analysis but were not statistically different across the treatment groups. There was no statistical difference in VTE based on age.

Table 4: Multivariate analysis of association of VTE based on chemotherapy in patients with clinical locoregional disease

Chemotherapy Regimen	VTE/N	VTE rate	OR	95% CI	p-value
Gemcitabine and Cisplatin	30/365	8.2%	1.0	ref	ref
Gemcitabine and Carboplatin	6/82	7.3%	0.55	(0.21,1.47)	0.23
MVAC/CMV	7/125	5.6%	0.78	(0.33,1.88)	0.58

* OR = odds ratio, CI= confidence interval
** Logistic regression model includes age, presence of cardiovascular disease, presence of renal dysfunction, histology, clinical T-stage at diagnosis, and clinical N-stage at diagnosis

Figure 1: Patient Inclusion/Exclusion Criteria

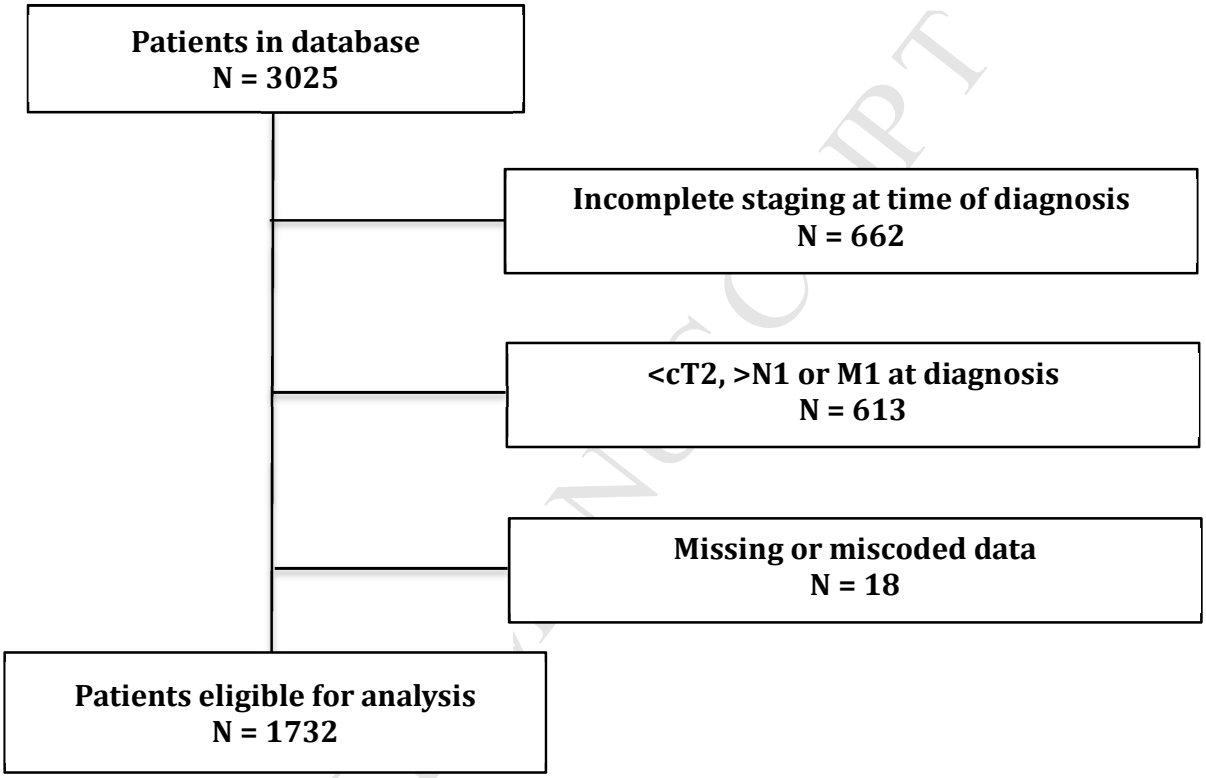

Figure 2: Cumulative incidence of VTE of study cohort.

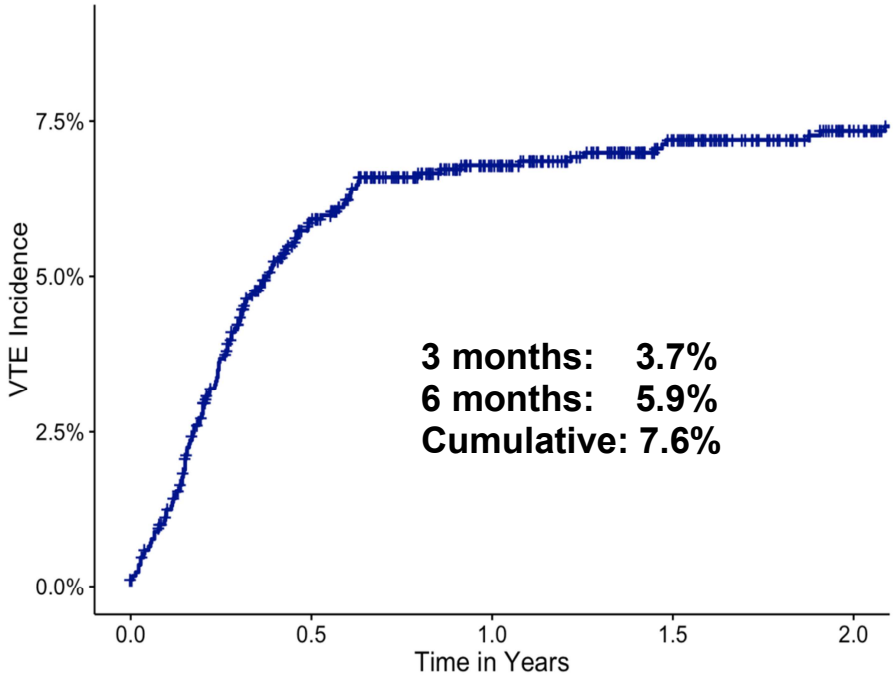

Figure 3: Overall survival stratified by VTE