BJU Int 2024 doi:10.1111/bju.16444

BJUI
BJU International

Original Article

Thromboprophylaxis during neoadjuvant chemotherapy for bladder cancer reduces thromboembolism and bleeding

Luca Antonelli[1,6], Pedro David Wendel-Garcia[2,4], Manja Deforth[2], Luca Afferi[1], Costantino Leonardo[6], Francesco Esperto[7], Marco Borghesi[10,11], Alessandro Antonelli[12], Karl Tully[20], Paolo Umari[24], Simone Albisinni[8,25], Andrea Mari[13], Renate Pichler[26], Francesco Claps[16], Jeremy Yuen-Chun Teoh[27], Mathieu Roumiguié[28], Gerald Bastian Schulz[21], Luca Orecchia[9], Francesco Soria[17], Morgan Roupret[29], Gautier Marcq[30,31], Cedric Poyet[5], Majed Alrumayyan[32], Michael Rink[22], Stefania Zamboni[18], Maria Riaza Montes[34], Steven Okoye[23], Riccardo Campi[14,15], Wojciech Krajewski[35], Laura Mertens[36], Meftun Culpan[37], Luke T. Lavallée[33], Marco Moschini[19], Ulrike Held[2], Christian Daniel Fankhauser[1,3] and In collaboration with the EAU YAU urothelial carcinoma working group

[1]Department of Urology, Luzerner Kantonsspital, University of Lucerne, Lucerne, [2]Department of Biostatistics at the Epidemiology, Biostatistics and Prevention Institute, [3]University of Zurich, [4]Institute of Intensive Care Medicine, University Hospital Zurich, Zurich, [5]Department of Urology, University Hospital Zürich, Zürich, Switzerland, [6]Department of Urology, Sapienza University of Rome, [7]Department of Urology, Campus Bio-Medico University, [8]Urology Unit, Department of Surgical Sciences, Tor Vergata University Hospital, University of Rome Tor Vergata, [9]Urology Unit, Policlinico Tor Vergata Foundation, Rome, [10]IRCCS Ospedale Policlinico S. Martino, [11]Department of Surgical and Diagnostic Integrated Sciences, University of Genoa, Genoa, [12]Department of Urology, Azienda Ospedaliera Universitaria Integrata Verona, Verona, [13]Unit of Oncologic Minimally-Invasive Urology and Andrology - Careggi Hospital, Department of Clinical and Experimental Medicine, [14]Unit of Urological Robotic Surgery and Renal Transplantation, Careggi Hospital, [15]Department of Experimental and Clinical Medicine, University of Florence, Florence, [16]Department of Medicine, Surgery and Health Sciences, Urological Clinic, University of Trieste, Trieste, [17]Division of Urology, Department of Surgical Sciences, Torino School of Medicine, AOU città della Salute e della Scienza di Torino, Torino, [18]Unit of Urology, Department of Medical and Surgical Specialities, Radiological Science and Public Health, ASST Spedali Civili di Brescia, University of Brescia, Brescia, [19]Department of Urology and Division of Experimental Oncology, Urological Research Institute, Vita-Salute San Raffaele, Milan, Italy, [20]Departement of Urology and Neurourology, Marien Hospital Herne, Ruhr University Bochum, Bochum, [21]Department of Urology, LMU Munich, Munich, [22]Department of Urology, Marienkrankenhaus Hamburg, Hamburg, [23]Department of Urology, Charité-Universitätsmedizin Berlin, Berlin, Germany, [24]St. George's University Hospital, London, UK, [25]Service d'Urologie, Hôpital Universitaire de Bruxelles, Université Libre de Bruxelles, Bruxells, Belgium, [26]Department of Urology, Medical University of Innsbruck, Innsbruck, Austria, [27]Department of Surgery, S.H. Ho Urology Centre, The Chinese University of Hong Kong, Hong Kong, China, [28]Department of Urology, CHU-IUCT Toulouse, Toulouse, [29]GRC 5 Predictive Onco-Uro, AP-HP, Urology, Pitie-Salpetriere Hospital, Sorbonne University, Paris, [30]Urology Department, Claude Huriez Hospital, CHU Lille, [31]CNRS, Inserm, CHU Lille, Institut Pasteur de Lille, UMR9020-U1277 - CANTHER - Cancer Heterogeneity Plasticity and Resistance to Therapies, University Lille, Lille, France, [32]Division of Urology, Department of Surgery, Princess Margaret Cancer Centre, University Health Network, Toronto, Ontario, [33]Division of Urology, Department of Surgery, University of Ottawa and Ottawa Hospital Research Institute, Ottawa, Canada, [34]Galdakao-Usansolo Hospital, Vizcaya, Spain, [35]Department of Minimally Invasive and Robotic Urology, Wrocław Medical University, Wrocław, Poland, [36]Department of Urology, Netherlands Cancer Institute, Amsterdam, Netherlands, and [37]Department of Urology, Faculty of Medicine, Istanbul Medeniyet University, Istanbul, Turkey

L.A. and P.D.W-G. contributed equally to this work.

Objectives

To assess the risk of venous thromboembolic events (VTEs) and bleeding with or without thromboprophylaxis during neoadjuvant chemotherapy in bladder cancer patients scheduled for radical cystectomy.

Materials and Methods

We conducted a retrospective cohort study in 4886 patients with non-metastatic bladder cancer undergoing cystectomy across 28 centres in 13 countries between 1990 and 2021. Inverse probability weighting analyses were performed to estimate the effect of thromboprophylaxis on VTE and bleeding.

Results

In 147 patients (3%) VTEs were recorded within the first year. These occurred a median (interquartile range [IQR]) of 127 (82–198) days after bladder cancer diagnosis. Bleeding events occurred in 131 patients (3%) within the first year. These occurred a median (IQR) of 101 (83–171) days after cancer diagnosis. In inverse probability weighting analyses, compared to patients without thromboprophylaxis during chemotherapy, patients with thromboprophylaxis had not only a lower risk of VTE (hazard ratio [HR] 0.32, 95% confidence interval [CI] 0.12–0.81; $P = 0.016$) but also a lower bleeding risk (HR 0.03, 95% CI 0.09–0.12; $P < 0.0001$). The retrospective nature of the study was its main limitation.

Conclusions

In this retrospective analysis, the benefit of thromboprophylaxis during neoadjuvant chemotherapy before cystectomy is in line with data from randomised trials in other malignancies. Our data suggest thromboprophylaxis is protective against VTEs and should be the standard of care during neoadjuvant chemotherapy.

Keywords

bladder cancer, neoadjuvant chemotherapy, radical cystectomy, venous thromboembolic events, bleeding

Introduction

Venous thromboembolic events (VTEs) are common in patients with urinary bladder cancer scheduled for radical cystectomy, with an incidence ranging from 5% to 32%. [1,2]. As VTEs can negatively impact oncological outcomes by causing delays in surgery or by complicating peri-operative management as well as causing long-term complications, it is important to reduce their incidence before and after cystectomy. While thromboprophylaxis has been shown to reduce the risk of VTEs in ambulatory cancer patients receiving chemotherapy by 30%–60%, its use can also lead to an increased risk of bleeding [3–6]. Therefore, the current American Society of Clinical Oncology (ASCO) guidelines recommend a risk–benefit analysis and only to prescribe thromboprophylaxis during chemotherapy in patients with a high VTE and low bleeding risk [7]. Since no randomised trial studying patients during neoadjuvant chemotherapy before radical cystectomy is expected to be performed in the near future, we conducted a large retrospective study to explore the risk of VTE, risk of bleeding and the benefits of thromboprophylaxis. We therefore investigated if thromboprophylaxis is protective against VTEs during neoadjuvant chemotherapy in bladder cancer patients planned for radical cystectomy.

Methods

This retrospective observational cohort study used data from the Venous Thromboembolism Bladder Cancer Consortium, which comprises 28 institutions in 13 countries across Europe, North America and Asia. The study was conducted in compliance with the Declaration of Helsinki, the Guidelines on Good Clinical Practice issued by the European Medicines Agency, Swiss law and regulatory authority requirements, and the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines. Ethical approval was obtained from the local committee of the leading site (BASEC ID 2022-00538), and all collaborating centres adhered to local legal and ethical requirements outlined in the written data-sharing agreement. To ensure the protection of subjects' identities, all data have been anonymised. Prior to participation in this study, informed consent was obtained from each participant or their respective guardian or waived by the local ethics committee.

We retrospectively collected a standardised dataset for bladder cancer patients who received treatment at the participating centres between 1990 and 2021. The data were centrally aggregated, normalised, cleaned, and harmonised. Patients with localised or locally advanced bladder cancer who underwent radical cystectomy were included in the study. Data were collected at various time points, including at bladder cancer diagnosis, initiation of neoadjuvant chemotherapy, radical cystectomy, initiation of adjuvant therapy, and long-term follow-up. The collected data included patient characteristics, baseline variables such as age, gender, comorbidities, and performance status, histological and cancer staging information obtained during transurethral resection of the bladder tumour (TURBT), largest pelvic lymph node size

based on preoperative CT scans, laboratory values, risk factors for bleeding and VTE, neoadjuvant treatment regimes, characteristics of the radical cystectomy, adjuvant and systemic treatment regimes, survival outcomes, and VTEs and bleeding events.

Clinical performance was defined based on the Eastern Cooperative Oncology Group (ECOG) performance status [8] and American Society of Anesthesiologists score [9]. Comorbidities were quantified using the Charlson Comorbidity Index [10]. Cancer staging was performed according to the 1973 [11] and 2004 [12] WHO grading scheme and the TNM 2017 staging system defined by the American Joint Committee on Cancer [13]. Largest pelvic lymph node size was assessed radiologically by measurement of the short axial diameter on CT. Renal disease was defined as a serum creatinine level of >200 μmoL/L or 2.26 mg/dL, dialysis requirement or renal transplant. Conversely, liver disease diagnosis was based on the presence of total bilirubin levels elevated twofold above normal in combination with elevated serum alanine aminotransferase, aspartate aminotransferase or alkaline phosphatase levels three times above the cutoff of normality or the presence of cirrhosis. Alcohol abuse was defined as alcohol beverage consumption of more than eight drinks per week.

Outcomes

A VTE was defined as: (i) a deep vein thrombosis diagnosed by new non-compressibility or intraluminal filling defect of lower or upper extremity deep venous segments through compression ultrasonography or venogram, and/ or (ii) pulmonary embolism, diagnosed as intraluminal defects in two or more pulmonary angiography views, sudden contrast cutoff of one or more vessels >2.5 mm in diameter in pulmonary angiography, highly indicative ventilation-perfusion lung scan or filling defect in a subsegmental or larger vessel in CT pulmonary angiography [3].

Bleeding was classified according to the European Society of Cardiology [14] as: (1) trivial bleeding: any bleeding not requiring medical intervention or further evaluation; (2) mild bleeding: any bleeding that requires medical attention without requiring hospitalisation; (3) moderate bleeding: any bleeding associated with blood loss (>3 g/dL haemoglobin) and/or requiring hospitalisation, which is haemodynamically stable and not rapidly evolving; (4) severe bleeding: any bleeding requiring hospitalisation associated with a severe blood loss (>5 g/dL haemoglobin), which is haemodynamically stable and not rapidly evolving; (5) life-threatening bleeding: any severe active bleeding putting patient's life immediately at risk; and (6) fatal bleeding: death because of bleeding.

Methods to Account for Missing Data

To account for missing data, multiple imputations with chained equations by fully conditional specification with predictive mean matching, or logistic regression for binary variables, under the missing at random assumption were performed [15,16]. One-hundred parallel imputation models with 100 iterations each were run. All independent baseline variables recorded in the dataset were included, including outcomes, although these were not imputed and only served as covariates for the imputation models. For each variable, a linear regression model, when continuous, or a logistic regression, when dichotomous, accounting for all other variables, as well as a centre-clustering factor, was specified. Multiple imputations were assessed for plausibility by means of visual inspection of convergence plots, distribution plots and first and higher moment order comparison of the imputation against the original dataset stratified by variable and imputation set.

Statistical Methods

Individual variable distributions were visually investigated via histograms and quantile–quantile plots. Descriptive statistics include medians and interquartile ranges (IQRs) for continuous variables and counts and percentages for categorical and ordinal variables.

To enable inference of the average treatment effect associated with the use of anticoagulation we employed inverse probability weighting based on a propensity score calculated with all relevant confounders at bladder cancer diagnosis (Table S1). Inverse probability weighting refers to a statistical method used to enable exchangeability of exposed and unexposed subjects to one or multiple treatments to minimise confounding. Applying a weight to each individual subject generates a standardised pseudo-population, in which causal treatment effect inference is possible. Inverse probability weighting was applied independently to every imputation and the modelled results pooled together by means of Rubin's rule in a final step.

Time-to-event analyses were performed by means of a proportional hazards model considering VTE, or bleeding, as the dependent variable, and adjusting for all variables considered for the inverse probability weighting propensity score. Furthermore, and to evaluate the robustness of the analyses, we performed time-to-event analyses adjusting for two different sets of confounders as predefined by the investigators (Tables S2 and S3) in a multiple Cox proportional hazards regression model.

Additionally, and to account for the variability in duration of neoadjuvant chemotherapy, anticoagulation and the varying time-to-cystectomy, an additional proportional hazards model considering these three variables as time-varying was defined.

To account for centre variability, a cluster effect based on the grouped jackknife method was implemented. Proportional hazard assumptions were assessed through inspection of Schoenfeld residuals. Cumulative incidence functions were generated by implementing the Kaplan–Meier estimator. Standard errors for the estimated effects were pooled across imputations by means of Rubin's rule and 95% CIs were computed using Wald's method. All analyses were performed in the R programming language (R Core Team, 2022).

Results

From January 1990 until December 2021, 4886 patients were included in 28 centres across 13 countries in the VTE bladder cancer consortium (Tables 1 and 2; Fig. S1). Of those, 1077 (22%) were treated with neoadjuvant chemotherapy before radical cystectomy. The most commonly employed chemotherapy regimens were cisplatin (83%) and gemcitabine (86%). The median (IQR) duration of neoadjuvant chemotherapy was 63 (61–83) days, which corresponded to a median of 4 (3–4) cycles. The median (IQR) time from TURBT to cystectomy was 90 (49–153) days. At TURBT performance, 3018 patients (64%) had a primary tumour stage of T2, 1285 (27%) of T1, 31 (<1%) of Ta and 352 (7%) of Tis. The regional lymph node stage was cN0 in 3401 patients (81%), with the largest pelvic lymph node being a median (IQR) of 9 (6–4) mm in diameter. High-grade tumours were diagnosed in 92% and G3 in 85% of patients.

No thromboprophylaxis or anticoagulation was given in 4631 patients (95%). Anticoagulation was prescribed already before bladder cancer treatment in 104 patients (2%) for the following reasons: atrial fibrillation (46%); previous stroke or acute coronary event (34%); and a previous VTE (12%). Thromboprophylaxis during neoadjuvant chemotherapy was prescribed in 151 patients (3%), with enoxaparin used in 80% for a median (range) duration of 94 (38–104) days.

Within the first year, VTEs were recorded in 147 patients (3%). These occurred a median (IQR) of 127 (82–198) days after bladder cancer diagnosis. Deep vein thromboses accounted for 80 (56%) VTEs, whereas 63 (44%) included pulmonary embolism. In 105 patients (71%) the VTE had a symptomatic clinical presentation, whereas 41 VTEs (28%) were asymptomatic and discovered on staging imaging. VTEs were associated with a hospital admission in 59 patients (40%).

Bleeding events occurred in 131 patients (3%) within the first year at a median (IQR) of 101 (83–171) days after cancer diagnosis. Trivial or mild bleeding events occurred in 41 patients (33%), whereas moderate-to-severe bleeding events occurred in 85 patients (67%). Only one patient experienced a life-threatening bleeding event and none experienced a fatal bleeding event. Overall, 42 of 131 patients (33%) required radiological, endoscopic or surgical intervention in order to treat the bleeding.

In inverse probability weighting analyses, patients with thromboprophylaxis compared to patients without thromboprophylaxis during chemotherapy had not only a lower VTE (hazard ratio [HR] 0.32 [95% CI 0.12–0.81]; $P = 0.016$) but also a lower bleeding risk (HR 0.03 [95% CI 0.09–0.12]; $P < 0.0001$ [Fig. 1]).

The inverse probability weighting-inferred effects of both thromboprophylaxis and full anticoagulation on VTE and bleeding events remained robust in a variety of sensitivity analyses including proportional hazard models with two different adjustment specifications (Tables S4–S7) and in time-varying proportional hazard models (Tables S8 and S9).

Discussion

In a large multi-institutional retrospective cohort study, we observed a low incidence of VTE and bleeding events, along with infrequent use of thromboprophylaxis during neoadjuvant chemotherapy before cystectomy. After adjusting for potential confounders, our data suggest that thromboprophylaxis is protective against VTEs.

Venous thromboembolic events are a hallmark of cancer and represent a common complication during chemotherapy [17]. Recent studies using Doppler ultrasound screening on the day of admission have reported that 14% of patients may already have asymptomatic VTEs the day before surgery. This suggests that asymptomatic VTEs may develop during neoadjuvant chemotherapy and become symptomatic after surgery [18,19]. Short-term consequences of VTEs include delays in treatment and, in cases of pulmonary embolism, a fatality rate of up to 44% [20]. Further, full anticoagulation for treatment of VTEs can increase the risk of clinically relevant bleeding in up to 10% of patients [21,22]. As well as those life-threatening short-term complications, several long-term complications may arise subsequently. These include post-thrombotic syndromes that lead to recurring venous leg ulcers, resulting in chronic pain, decreased mobility, and ongoing medical resource utilisation. Pulmonary embolism can also impair right ventricular function and pulmonary arterial pressure, which may not recover in 10%–30% of patients, and up to 4% may develop chronic thromboembolic pulmonary hypertension [23]. These complications can significantly reduce quality of life and increase lifetime healthcare costs [24]. Therefore, prevention of VTEs before and after cystectomy is important.

Two randomised trials assessed the risks and benefits of rivaroxaban or apixaban in ambulatory patients selected for increased risk of VTE and receiving chemotherapy [3,4]. Both trials demonstrated a 30%–60% risk reduction in VTE but increased risk of bleeding (2–3.5%). Earlier studies of low-molecular-weight heparin showed a similar reduction, but those earlier trials did not preselect patients and had a lower cumulative VTE incidence [5,6]. Based on the results of these

Table 1 Baseline characteristics of the included patients undergoing radical cystectomy, stratified by use of thromboprophylaxis or full anticoagulation.

	Overall	No anticoagulation	Thromboprophylaxis during chemotherapy	Full anticoagulation	SMD	Missing value, %
n	4886	4631	151	104		
Age, years	70 (63, 77)	71 (63, 77)	65 (58, 69)	74 (67, 79)	0.646	3.5
Sex: Female, *n* (%)	1131 (23.2)	1063 (23.0)	46 (30.5)	22 (21.2)	0.143	0
BMI, kg/m^2	25.96 (23.44, 29.04)	25.95 (23.44, 29.02)	26.02 (23.14, 29.40)	25.96 (22.77, 28.73)	0.024	18.7
ECOG performance score	0 (0, 1)	0 (0, 1)	0 (0, 0)	1 (0, 1)	0.484	21.1
ASA classification	3 (2, 3)	3 (2, 3)	1 (1, 2)	3 (2, 3)	1.045	6.5
Charlson Comorbidity Index	2 (2, 4)	2 (2, 4)	3 (2, 5)	2 (1, 4)	0.016	19.6
T stage, *n* (%)						
0	386 (8.2)	381 (8.6)	3 (2.0)	2 (1.9)	0.561	4.0
1	1285 (27.4)	1269 (28.6)	6 (4.0)	10 (9.6)		
2	3018 (64.3)	2784 (62.8)	142 (94.0)	92 (88.5)		
3	1 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)		
WHO grade 1973, *n* (%)						
1	193 (5.2)	186 (5.4)	7 (4.7)	0 (0.0)	0.275	24.1
2	345 (9.3)	325 (9.4)	10 (6.7)	10 (11.2)		
3	3140 (84.7)	2931 (84.5)	130 (87.2)	79 (88.8)		
High grade according to WHO 2004, *n* (%)	4036 (92.0)	3796 (91.8)	138 (91.4)	102 (99.0)	0.243	10.2
Clinical N stage, *n* (%)						
cN0	3401 (81.4)	3191 (81.3)	128 (84.8)	82 (78.8)	0.194	14.5
cN2	392 (9.4)	362 (9.2)	14 (9.3)	16 (15.4)		
cN3	260 (6.2)	251 (6.4)	5 (3.3)	4 (3.8)		
cN3	126 (3.0)	120 (3.1)	4 (2.6)	2 (1.9)		
Largest pelvic lymphnode diameter, cm	9 (6, 14)	9 (6, 14)	15 (11, 16)	9 (8, 10)	0.130	68.8
Khorana score	1 (1, 2)	1 (1, 2)	1 (1, 2)	1 (1, 2)	0.269	0
Preexisting comorbidities, *n* (%)						
Arterial hypertension	2583 (53.2)	2423 (52.6)	96 (63.6)	64 (61.5)	0.147	0.6
Chronic heart failure	426 (8.7)	395 (8.6)	1 (0.7)	30 (28.8)	0.596	0.3
Diabetes mellitus	998 (20.5)	931 (20.2)	40 (26.5)	27 (26.0)	0.099	0.4
Liver disease	70 (1.6)	69 (1.7)	0 (0.0)	1 (1.0)	0.125	12.2
Renal disease	253 (5.9)	243 (6.0)	0 (0.0)	10 (9.6)	0.318	12.2
Stroke	318 (7)	285 (6)	6 (4)	27 (26)	0.436	0.0
Vascular disease	1090 (22.4)	1041 (22.6)	32 (21.2)	17 (16.3)	0.104	0.3
Alcohol abuse	217 (5.6)	202 (5.6)	15 (9.9)	0 (0.0)	0.327	21.0
Smoking history, *n* (%)						
Never	1530 (32.5)	1476 (33.2)	25 (16.6)	29 (27.9)	0.351	3.7
Past	1478 (31.4)	1355 (30.5)	82 (54.3)	41 (39.4)		
Present	1695 (36.0)	1617 (36.4)	44 (29.1)	34 (32.7)		
Preoperative laboratory values						19.2
Creatinine, mg/dL	99 (80, 129)	98 (80, 129)	106 (80, 128)	106 (89, 148)	0.099	19.2
Haemoglobin, g/L	128 (111, 142)	129 (112, 142)	120 (110, 140)	111 (95.75, 124.25)	0.527	9.0
Leucocytes, G/L	7.40 (6.00, 9.20)	7.40 (6.00, 9.20)	8.95 (6.52, 11.91)	6.76 (5.08, 8.14)	0.183	13.2
Platelets, G/L	246 (199, 307)	245 (198, 305)	287 (219, 365)	235 (183, 315)	0.203	9.2
Concomitant antiplatelet therapy	1127 (23)	1045 (23)	41 (27)	41 (39)	0.247	0.0
Neoadjuvant chemotherapy	1077 (22.0)	871 (18.8)	151 (100.0)	55 (52.9)	1.678	0
Cisplatin	898 (18.4)	704 (15.2)	150 (99.3)	44 (42.3)	1.824	
Gemcitabine	928 (19.0)	732 (15.8)	149 (98.7)	47 (45.2)	1.740	
Days of neoadjuvant chemotherapy	63 (61, 83)	62 (60, 81)	78 (62, 84)	78 (68, 89)	0.017	16.4
Days of thromboprophylaxis before cystectomy		–	95 (48, 104)	92 (21, 103)	–	6.6
Days from TURBT to cystectomy	90 (49, 153)	90 (49, 156)	111 (97, 121)	104 (58, 166)	0.089	3.5

Continuous variables are presented as median (interquartile range) and categorical variables as count (proportion). All baseline characteristics were collected at the time of TURBT performance.
ASA, American Society of Anesthesiologists; BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; SMD, standardised mean difference; TURBT, transurethral resection of bladder tumour.

Table 2 Baseline characteristics of the included patients undergoing radical cystectomy, stratified by use of thromboprophylaxis or full anticoagulation, after inverse probability weighting.

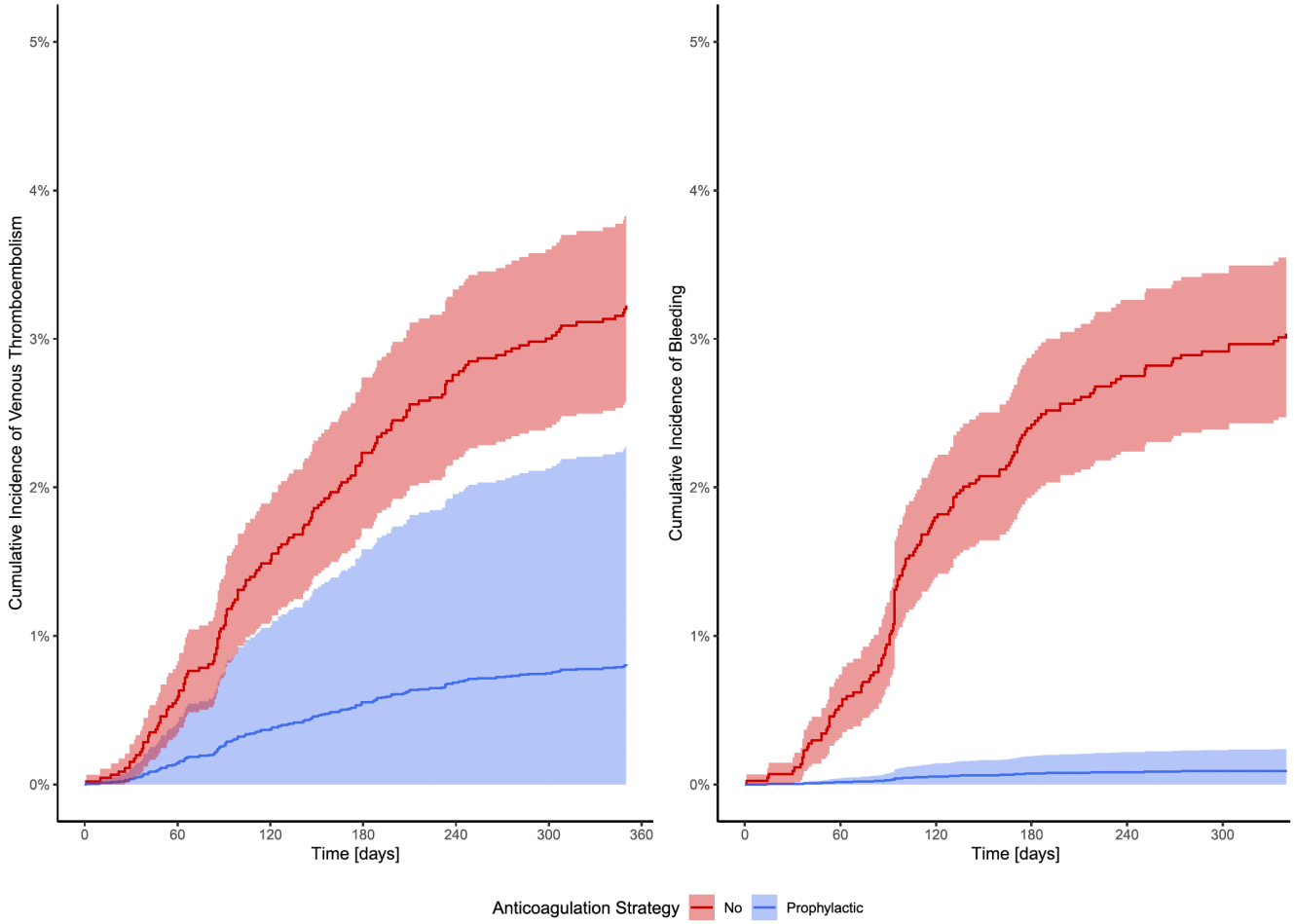
	Overall	No anticoagulation	Thromboprophylaxis during chemotherapy	Full anticoagulation	SMD
n	4710	4591	44	75	
Age, years	71 (63, 77)	71 (63, 77)	71 (66, 74)	69 (66, 76)	0.071
Sex: Female	1083 (23)	1056 (23)	14 (32)	13 (17)	
BMI, kg/m^2	25.95 (23.25, 29.22)	25.96 (23.32, 29.24)	25.39 (23.00, 27.75)	23.45 (22.04, 28.80)	0.063
ECOG performance	0 (0, 1)	0 (0, 1)	0 (0, 1)	0 (0, 1)	0.237
ASA classification	3 (2, 3)	3 (2, 3)	2 (2, 3)	2 (1, 3)	0.273
Charlson Comorbidity Index	2 (2, 4)	2 (2, 4)	4 (2, 6)	2 (1, 4)	0.436
T stage, *n* (%)					
0	384 (8)	381 (8)	0 (0)	3 (4)	0.525
1	1294 (27)	1269 (28)	6 (14)	19 (25)	
2	3031 (64)	2940 (64)	38 (86)	53 (71)	
3	1 (0)	1 (0)	0 (0)	0 (0)	
WHO Grade 1973, *n* (%)					
1	257 (5)	248 (5)	9 (20)	0 (0)	1.227
2	436 (9)	414 (9)	16 (36)	6 (8)	
3	3977 (84)	3889 (85)	19 (43)	69 (92)	
High grade according to WHO 2004, *n* (%)	4331 (91)	4226 (92)	30 (68)	75 (100)	0.970
Clinical N stage, *n* (%)					
cN0	3816 (81)	3745 (82)	24 (55)	47 (63)	0.639
cN2	464 (10)	425 (9)	15 (34)	24 (32)	
cN3	286 (6)	279 (6)	6 (14)	1 (1)	
cN3	147 (3)	142 (3)	2 (5)	3 (4)	
Largest pelvic lymphnode diameter, cm	9 (6, 14)	9 (6, 14)	13 (8, 16)	9 (6, 12)	0.288
Khorana score	1 (1, 2)	1 (1, 2)	1 (1, 1)	1 (1, 2)	0.235
Preexisting comorbidities, *n* (%)					
Arterial hypertension	2475 (53)	2423 (53)	18 (41)	34 (45)	0.242
Chronic heart failure	417 (9)	403 (9)	7 (16)	7 (9)	0.213
Diabetes mellitus	976 (21)	940 (20)	13 (30)	23 (31)	0.254
Liver disease	78 (2)	76 (2)	0 (0)	2 (3)	0.249
Renal disease	279 (6)	277 (6)	0 (0)	2 (3)	0.357
Stroke	314 (7)	304 (7)	7 (16)	3 (4)	0.408
Vascular disease	1063 (23)	1023 (22)	6 (14)	34 (45)	0.723
Alcohol abuse	284 (6)	280 (6)	4 (9)	0 (0)	0.445
Smoking history, *n* (%)					
Never	1549 (33)	1516 (33)	15 (34)	18 (24)	0.362
Past	1464 (31)	1428 (31)	9 (20)	27 (36)	
Present	1699 (36)	1648 (36)	20 (45)	31 (41)	
Preoperative laboratory values					
Creatinine, mg/dL	99 (80, 131)	99 (80, 130)	116 (101, 138)	92 (74, 108)	0.167
Haemoglobin, g/L	128 (111, 142)	128 (112, 142)	117 (107, 126)	122 (109, 132)	0.321
Leucocytes, G/L	7.40 (5.98, 9.20)	7.40 (6.00, 9.20)	5.90 (5.41, 7.80)	6.63 (5.31, 8.54)	0.094
Platelets, G/L	245 (197, 306)	246 (197, 306)	253 (203, 295)	225 (172, 316)	0.083
Concomitant antiplatelet therapy	1106 (23)	1057 (23)	15 (34)	34 (45)	0.477
Neoadjuvant chemotherapy	1080 (23)	987 (21)	44 (100)	49 (65)	2.743

Continuous variables are presented as median (interquartile range) and categorical variables as count (proportion). All baseline characteristics were collected at the time of TURBT performance.
ASA, American Society of Anesthesiologists; BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; SMD, standardised mean difference; TURBT, transurethral resection of bladder tumour.

randomised trials, the ASCO Clinical Practice Guideline Update 2023 now recommends offering VTE prophylaxis with apixaban, rivaroxaban, or low-molecular-weight heparin to selected high-risk outpatients during chemotherapy and after cancer surgery [7]. Since there is a lack of randomised trials studying the risk and benefits of thromboprophylaxis during neoadjuvant chemotherapy before radical cystectomy, we conducted a large retrospective study. Our data confirm an increased VTE risk and a benefit of thromboprophylaxis in patients undergoing neoadjuvant chemotherapy before radical cystectomy.

Our cohort study fills an important research gap and may influence guidelines to recommend thromboprophylaxis as a standard of care in patients undergoing neoadjuvant chemotherapy before radical cystectomy. Nevertheless, this was a retrospective cohort study and not a randomised prospective trial, thus potential biases represent inherit

Fig. 1 Inversed probability-weighted cumulative incidence curves for venous thromboembolism (left) and bleeding (right). Timepoint 0 corresponds to the day of transurethral resection of the bladder. The y-axis represents the percentage of events, with a truncated scale up to 5%.



limitations in our analysis. First, several potential unmeasured confounders might have affected the estimated effects. However, it is likely that patients with an increased risk of VTE received thromboprophylaxis, which may bias the results towards the null and therefore the VTE risk reduction might even be greater than that observed in our cohort. Second, the retrospective nature of the data collection might have led to biases in the inclusion of patients or the availability of the collected data, which is reflected in the moderate amount of missing data. Third, while the definition of VTE and bleeding was predefined in the protocol, events were identified retrospectively. Their frequency was lower compared to previously published cohort studies, suggesting underreporting, but this probably represents non-differential misclassification [20]. Finally, the regional and guideline variability among centres was large, and the time span of the cohort was over 30 years, thus there was inherent variability in the standard of care that may have affected the results.

In conclusion, in this retrospective analysis, the benefit of thromboprophylaxis during neoadjuvant chemotherapy before cystectomy is in line with data from randomised trials in other malignancies. Our data suggest thromboprophylaxis is protective against VTEs during neoadjuvant chemotherapy in bladder cancer patients planned for cystectomy. The ASCO guidelines recommending thromboprophylaxis during chemotherapy should therefore also be regarded as a standard of care in patients treated with neoadjuvant chemotherapy before cystectomy.

Acknowledgement

Open access funding provided by Universitat Luzern.

Disclosure of Interests

All authors declare there are no existing, relevant conflicts in respect to this article.

Funding Sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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Correspondence: Christian Daniel Fankhauser, Department of Urology, Luzerner Kantonsspital, University of Lucerne, Spitalstrasse, 6000 Luzern 16, Switzerland.

e-mail: cdfankhauser@gmail.com

Abbreviations: ASCO, American Society of Clinical Oncology; HR, hazard ratio; IQR, interquartile range; TURBT, transurethral resection of bladder tumour; VTE, venous thromboembolic event.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Fig. S1. Patient flow diagram detailing the inclusion of study participants.

Table S1. Weighting variables.

Table S2. Variable adjustment Set 1.

Table S3. Variable adjustment Set 2.

Table S4. Adjusted proportional hazards model – Model 1 - Venous thromboembolism.

Table S5. Adjusted proportional hazards model – Model 1 - Bleeding event.

Table S6. Adjusted proportional hazards model – Model 2 - Venous thromboembolism.

Table S7. Adjusted proportional hazards model – Model 2 – Bleeding event.

Table S8. Time-varying proportional hazards model - Venous thromboembolic event.

Table S9. Time-varying proportional hazards model - Bleeding event.

