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Original article

Effectiveness and safety of extended-duration prophylaxis for venous thromboembolism in major urologic oncology surgery

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Abstract

Purpose: To examine the association between extended-duration prophylaxis (EDP), low-molecular-weight heparin prophylaxis for 28 days after surgery for urologic cancer in patients at high risk of developing a venous thromboembolism (VTE), the risk of VTE, and the complications resulting from VTE prophylaxis.

Materials and methods: The cohort included 332 patients at high risk for VTE who were surgically treated for urologic cancer from June 2011 to June 2014. Adherence to VTE prophylaxis protocol, VTEs, and complications within 365 days from surgery were tracked. Patients were grouped as follows: (1) per protocol in-hospital prophylaxis with EDP ($n = 107$), (2) per protocol in-hospital prophylaxis without EDP ($n = 42$), (3) not per protocol in-hospital prophylaxis with EDP ($n = 83$), and (4) not per protocol in-hospital prophylaxis without EDP ($n = 100$). The risk of VTE was compared between the 4 groups using the Cox model, with adjustment for baseline risk factors.

Results: The rates of VTEs and median times to VTE were 7% and 58 days in group 1, 17% and 44 days in group 2, 17% and 46 days in group 3, and 21% and 15 days in group 4, respectively. Adjusted hazard ratios (HR) for VTE were HR = 0.27 (95% CI: 0.11–0.70) for groups 1 vs. 4; HR = 0.66 (95% CI: 0.25–1.60) for groups 2 vs. 4; and HR = 0.66 (95% CI: 0.29–1.26) for groups 3 vs. 4 with a trend of $P = 0.002$. The incidence of complications from VTE prophylaxis was not significantly different between the groups, with a rate of 8% in group 1, 17% in group 2, 6% in group 3, and 12% in group 4 ($P = 0.33$).

Conclusions: In high-risk urologic cancer surgery patients, a clinical protocol, with perioperative and EDP, is safe and effective in reducing VTE events.

Keywords: Venous thrombosis; Prevention and control; Pulmonary embolism; Neoplasms; Surgery

1. Introduction

Venous thromboembolism (VTE) remains a common cause of morbidity and mortality following urologic cancer surgery. VTEs, including deep vein thromboses and pulmonary embolisms (PEs), remain the most common non-surgical complication [1,2]. Given that postoperative VTE is the third most common adverse safety event in hospitalized patients, it is likely that VTE prevention initiatives will increase over time. As the need to reduce hospital-acquired VTE becomes more prominent, the concept of extended-duration prophylaxis (EDP) also is becoming more important [3,4].

Despite major reductions in VTE after surgery for urologic malignancy owing to the systematic application of some preventative recommendations, the occurrence of VTEs remains high [1]. Contemporary reports following

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specific urologic surgeries demonstrate that VTE rates vary, and similarly, so do VTE prophylaxis strategies. In the absence of VTE prophylaxis for major urologic surgeries, deep vein thrombosis incidence was estimated somewhere between 10% and 30%. The PE incidence was approximately 10%, 5% of which were reportedly fatal [5,6]. Specifically, VTE risk associated with radical cystectomy was found to be between 0.8% and 24% [6–12], nephrectomy 0.24% and 22.6% [6,9], and prostatectomy 1% and 11% [6,9,12,13].

Recently, several studies have been published reporting a reduction in VTE incidence in high-risk surgical patients with EDP and the safety associated with its use. It is estimated that after oncologic surgery, the incidence of VTE diagnosed after discharge but within 30 days is between 30.6% and 37.8% [1,14,15]. Several randomized studies have shown EDP to be more effective than limited duration prophylaxis (in-hospital only) in VTE incidence reduction after surgery for cancer [16,17]. Furthermore, a systematic review by the Cochrane group concluded that the administration of low-molecular-weight heparin (LMWH) for 4 weeks after major abdominal or pelvic surgery reduces VTE incidence without increased bleeding complications [18]. Given that the risk of VTEs remains elevated after surgery beyond discharge, there have been calls from many organizations to prescribe EDP in high-risk patients. Currently, the National Comprehensive Cancer Network (NCCN), American Society of Clinical Oncology (ASCO), and the American Academy of Chest Physicians (ACCP) have set forth guidelines recommending EDP in high-risk patients with LMWH for 4 weeks (Refer to Fig. 1 for exact recommendations) [19–21].

Despite these recommendations and evidence of EDP benefit, EDP employment has been suboptimal [2]. Barriers to EDP implementation have been the perceived increased complications (i.e., lymphoceles and bleeding), patients' aversions toward method of administration, and patients' costs to buy LMWH. Multiple publications refute increased bleeding and low acceptance among patients' as reasons to withhold EDP exist [1,16,22–24]. To date, there are few urology-specific recommendations for EDP. Our main objective was to evaluate a protocol instituted to achieve a reduction in VTE events and to assess the safety of its administration in high-risk urologic oncology patients undergoing major surgery.

2. Subjects and methods

2.1. VTE prevention protocol implementation

After institutional review board approval, a protocol for VTE prevention based on the ACCP, NCCN, and ASCO recommendations was implemented [21]. The protocol consisted of administration of preoperative heparin prophylaxis (within 8 h preoperatively) and postoperative pharmacologic prophylaxis (within 8 h after wound closure) in addition to intermittent pneumatic compression devices already in use. Because there has been little difference found between low-dose unfractionated heparin and LMWH in preventing VTE, low-dose unfractionated heparin as initial postoperative prophylaxis was considered per protocol if given at appropriate dose and intervals. The LMWHs, dalteparin 5,000 units or enoxaparin 40 mg, were administered subcutaneously and, if needed, doses were adjusted per manufacturer recommendations for weight and renal function. Patients were given formal self-administration training of the prophylactic medications by registered nurses at discharge.

2.2. Risk assessment

All patients undergoing major surgery for urologic cancer were evaluated using the Caprini risk assessment score (CRS) (Fig. 2) [6,22–25]. This model has been previously validated in urology patients and, retrospectively, in assigning risk scores. All elements of the CRS were evaluated at admission for surgery starting in July 2012. Retrospective risk assessment was used for patients undergoing urologic cancer surgery between June 2011 and June 2012, the charts were reviewed continuously, and those qualifying as high risk (CRS $\geq$ 8) were included for comparison analysis. A CRS $\geq$ 5 is often considered high risk; however, the version of CRS used for this study (Fig. 2) is more comprehensive,

ACCP, NCCN, ASCO Summary of Recommended VTE Prophylaxis for High-risk Patients Undergoing General and Abdominal-Pelvic Surgery

(General, Bariatric, GI, Gynecologic, Vascular, Urologic, Plastic and Reconstructive Surgery)

1. All patients undergoing major surgical intervention for malignant disease should be considered for thromboprophylaxis.
2. Patients undergoing laparotomy, laparoscopy, or thoracotomy lasting >30 minutes should receive pharmacologic thromboprophylaxis with either low-dose unfractionated heparin or low molecular weight heparin unless contraindicated because of a high-risk of bleeding or active bleeding.
3. Prophylaxis should be started preoperatively.
4. Mechanical methods should be used in addition to pharmacologic prophylaxis
5. Prolonged prophylaxis for up to 4 weeks should be considered in patients undergoing major abdominal or pelvic surgery for cancer with high-risk features.

Fig. 1. Summary of multiple organization's recommendations for VTE prophylaxis in the setting of general and abdominal-pelvic surgery in high-risk patients.

Caprini Risk Assessment Score

1 Point Each	*2 Points Each*	*3 Points Each*	*5 Points Each*
Age 41-60	Age 60-74	Age >75	Elective major lower extremity arthroplasty, hip, pelvis or leg fracture <1month
Minor surgery planned	Major surgery >60 minutes*	Major surgery 2-3 hours*	
History of prior major surgery	Laparoscopic surgery >60 minutes*	BMI >50	CVA < 1 month
Varicose Veins	Athroscopic surgery (>60 minutes)	History of superficial VT, DVT/PE	Major surgery >3 hours*
History of IBD	Previous malignancy	Family history of DVT/PE	Acute spinal cord injury (paralysis) (<1 month)
BMI >30	BMI >40	Present cancer or chemotherapy	Multiple trauma (<1 month)
Swollen legs (current)	Central venous access	Positive Factor V Leiden	
CHF <1 month		Positive Prothrombin 20210A	
AMI <1 month		Elevated serum homocysteine	
Serious lung disease (pneumonia)		Positive Lupus anticoagulant	
Abnormal pulmonary function (COPD)		Elevated anti-cardiolipin antibodies	
Bed rest		HIT	
Blood transfusion <1month		Other thrombophilia	
Women Only (1 point each)			
Oral contraceptive or hormone replacement therapy			
Pregnancy or postpartum (<1 month)			High-risk ≥8 Points Total
History of unexplained stillborn infant, >3 spontaneous abortions			

*Include only on surgical risk factor in the score. BMI-Body mass index, IBD-Inflammatory bowel disease, AMI-Acute myocardial infarction. CHF-Congestive Heart Failure, COPD-Chronic obstructive pulmonary disease, HIT-heparin induced thrombocytopenia, VT-venous thrombosis, DVT-Deep venous thrombosis, PE-Pulmonary embolism, CVA-Cerebrovascular accident.

Fig. 2. How the Caprini Risk Assessment Score is calculated. Each item in the column is tabulated for each risk factor the patient has. The sum of all the points is added and if the patient has greater than 8 points they are considered high-risk for VTE postoperatively.

including more operative characteristics. Patients requiring therapeutic anticoagulation, those with allergies to the medication, and those with a history of heparin-induced thrombocytopenia were excluded.

2.3. Treatment group assignment

Patients were grouped as follows: (1) per protocol in-hospital prophylaxis with EDP ($n = 107$), (2) per protocol in-hospital prophylaxis without EDP ($n = 42$), (3) not per protocol in-hospital prophylaxis with EDP ($n = 83$), and (4) not per protocol in-hospital prophylaxis without EDP ($n = 100$). (See Fig. 3 for a detailed diagram of patient group division.) The risk of VTE was compared between the 4 groups using the Cox model, with adjustment for baseline risk factors.

2.4. Event recording

Major bleeding events were defined in accordance with previous studies and a priori as postoperative fatal bleeding, clinically overt bleeding with a fall in hemoglobin level of 2 g/dL, clinically overt bleeding leading to transfusion of ≥ 2 units of packed red cells, intracranial bleeding, epidural hematoma, or clinically overt bleeding warranting treatment cessation. Small injection site ecchymoses (≤ 5-cm diameter) were not counted as bleeding events. The incidences of lymphoceles, thrombocytopenia, and serious adverse events were also recorded. Events were listed in an intention-to-treat manner, if VTE prophylaxis was withheld for bleeding concerns after the patient had already received their first dose, then the patient remained in the original intent-to-treat group such that complications reported are representative of the prophylaxis administration.

2.5. Program evaluation and statistical analysis

At the initiation of the protocol, patients were educated on VTE signs and symptoms and were instructed to notify their urologist if any of these became apparent after discharge. If a patient presented with postoperative VTE symptoms, depending on the presenting symptoms, they were evaluated according to the standard of care for their diagnosis. If they did not have follow-up at 30, 90, and 365 days, subjects were contacted with phone interviews to inquire if they had VTE events or complications of EDP.

Essential components of the protocol and outcomes were tracked with reviews of electronic medical records and

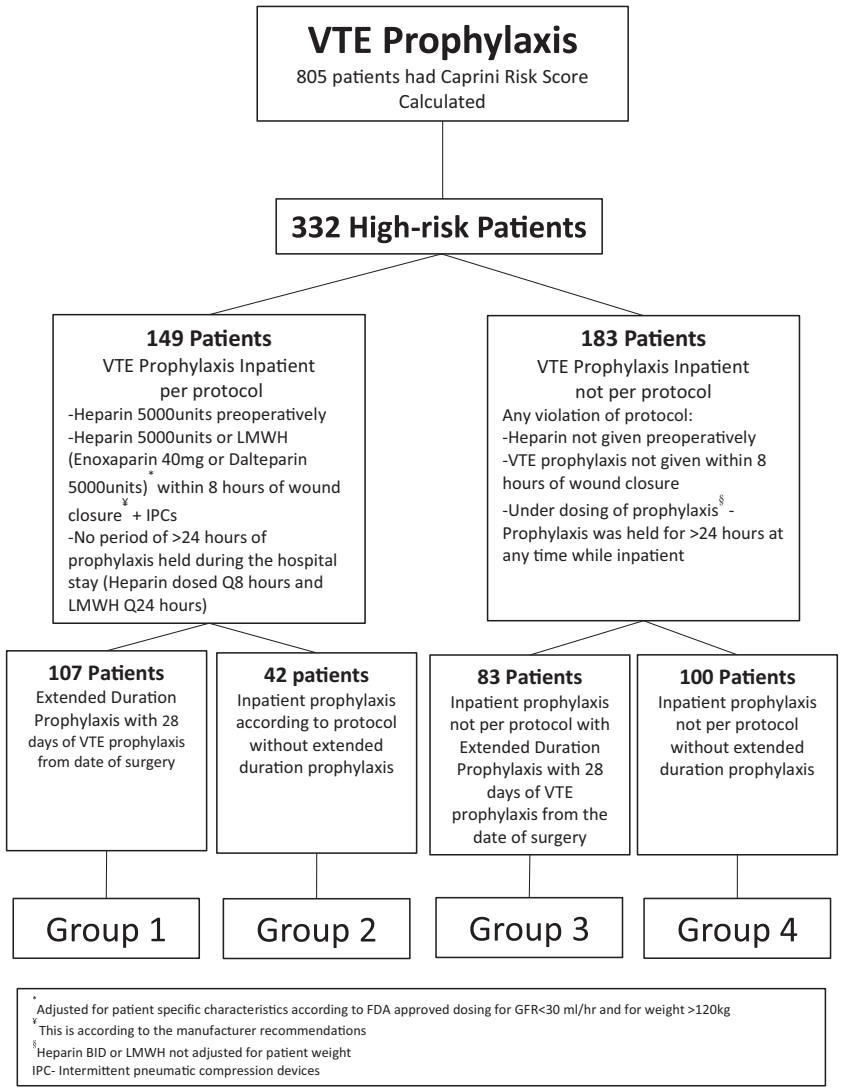

Fig. 3. This diagram explains the assignment of the patients into the VTE prophylaxis groupings.

patient phone interviews screening for occurrences of VTEs. The primary efficacy outcome was defined as the incidence of total documented clinically symptomatic VTEs. Routine imaging was not performed specifically to detect VTE in asymptomatic patients. Secondary outcomes were complications, VTE-related mortality, and all-cause mortality at 30, 90, and 365 days after surgery. Follow-up ended at 365 days postoperatively. Other analysis variables included demographics, type of surgery (i.e., cystectomy or nephrectomy), CRS and its individual components (i.e., operating room time and body mass index), pathological tumor category (grouped as $\leq$pT2 vs. $\geq$ pT3), nodal status (N0/Nx vs. N1–N3), and use of neoadjuvant or adjuvant chemotherapy. Data were extracted from charts by 2 independent reviewers. The costs for LMWH were obtained from the outpatient pharmacy at our institution. The prices were for the patients' direct costs.

Distributions of continuous covariates were summarized with medians, first quartiles and third quartiles and were compared between the 4 VTE prophylaxis groups using the Kruskal-Wallis test [26]. Distributions of categorical covariates were summarized with counts and percentages and compared between the 4 prophylaxis groups using the Fisher exact test. A test for trend was performed in univariable and multivariable analyses [26]. In each of the 4 comparison groups, incidence of VTE events was examined by using the Kaplan-Meier curves in univariable analysis and using the Cox model in univariable and multivariable analyses [27,28].

For the purpose of point and interval estimation, the 4 comparison groups were entered into the Cox model using the standard method of reference cell coding with group 4 as the reference. Other covariates were entered into the multivariable model for covariate adjustment only if they were unequally distributed between the 4 comparison groups in univariable analysis with a $P < 0.05$, except for the CRS, which was forced into the model based on biological considerations (CRS is known as a strong VTE predictor).

Table 1
Baseline characteristics

Variable	Group 1 (n = 107)	Group 2 (n = 42)	Group 3 (n = 83)	Group 4 (n = 100)	P value
Age, median (Q1–Q3), y	66 (61–74)	65 (58–76)	66 (60–76)	69 (60–76)	0.87
Sex, men, n (%)	73 (68)	29 (69)	59 (72)	71 (71)	0.97
Caprini Risk Score, median (Q1–Q3)	12 (11–13)	12 (10–13)	12 (11–14)	12 (11–13)	0.19
Surgery					0.01
Cystectomy, n (%)	63 (59)	22 (52)	35 (42)	37 (37)	
Nephrectomy, n (%)	19 (18)	11 (26)	17 (20)	25 (25)	
Nephroureterectomy, n (%)	10 (9)	3 (7)	6 (7)	9 (9)	
Other, n (%)	8 (7)	1 (2)	5 (6)	2 (2)	
Partial cystectomy, n (%)	3 (3)	3 (7)	8 (10)	4 (4)	
Partial nephrectomy, n (%)	0 (0)	0 (0)	6 (7)	10 (10)	
Prostatectomy, n (%)	3 (3)	2 (5)	2 (2)	6 (6)	
RPLND, n (%)	1 (1)	0 (0)	4 (5)	7 (7)	
Hospital days, median (Q1–Q3)	6 (4–8)	6 (5–8)	6 (4–10)	6 (4–9.5)	0.83
Neoadjuvant chemotherapy, n (%)	20 (19)	2 (5)	12 (14)	10 (10)	0.10
Adjuvant chemotherapy, n (%)	13 (12)	6 (14)	9 (11)	10 (10)	0.89
pT Category $\leq$T2, n (%)	64 (60)	25 (60)	54 (65)	73 (73)	0.20
pN Category N0/Nx, n (%)	84 (79)	35 (83)	68 (82)	88 (88)	0.34
pM Category M0/Mx, n (%)	92 (86)	39 (93)	74 (89)	90 (90)	0.74
BMI > 30, n (%)	33 (31)	15 (36)	29 (35)	32 (32)	0.91
Sepsis, n (%)	27 (25)	10 (24)	31 (37)	22 (22)	0.10
AMI, CHF, n (%)	8 (7)	0 (0)	3 (4)	6 (6)	0.26
COPD, n (%)	19 (18)	4 (10)	15 (18)	17 (17)	0.62
Transfusion, n (%)	37 (35)	14 (33)	25 (30)	27 (27)	0.67

AMI = acute myocardial infarction; BMI = body mass index; CHF = congestive heart failure; COPD = chronic-obstructive pulmonary disease; Q1 = first quartile; Q3 = third quartile; RPLND = retroperitoneal lymph node dissection.

Given the relatively small number of events and because information contained in this variable was already incorporated into the model with CRS, adjustment for individual components of the CRS was not performed to avoid overfitting the models. Tests for trend in the Cox models were performed by entering the 4 comparison groups in the model as ordinal variables. An additional analysis was performed with the same methods for cystectomy patients only.

3. Results

Of the 805 patients undergoing major urologic oncology surgery at our institution, 332 qualified as high risk. There were 142 patients included who had surgery before the protocol's implementation in July 2012 and 190 who had it after that. Distributions of the main baseline characteristics are summarized in Table 1, with stratification according to group (1, 2, 3, or 4) based on parameters of VTE prophylaxis. Differences in distributions of individual components of the CRS did not reach statistical significance. There was no significant difference in complication frequencies between groups (Table 2).

The frequency of thromboembolic events is summarized in Table 3. A total of 50 events occurred in the 4 comparison groups, with the highest frequency being seen in group 4 and the lowest in group 1. However, these relative frequencies are not directly comparable between the groups because of differences in follow-up time (Table 3). Table 4 shows no difference in VTE events between the open and laparoscopic surgical modalities. The incidence of any VTE event with adjustment for follow-up time is depicted in Fig. 4, and univariable and multivariable Cox models for this end point are shown in Table 5.

Table 2
Summary of complications of prophylactic anticoagulation

	Group 1 (n = 107)	Group 2 (n = 42)	Group 3 (n = 83)	Group 4 (n = 100)	Total	P value
Required $\geq$2 units of PRBCs, n (%)	9 (8)	3 (7)	7 (9)	12 (12)	31	0.75
Total prophylaxis complications, n (%)	9 (8)	7 (17)	6 (7)	12 (12)	34	0.33
Hematoma, n (%)	3 (3)	1 (2)	3 (4)	5 (5)	12	0.82
Lymphocele, n (%)	3 (3)	4 (10)	1 (1)	4 (4)	12	0.14
Epidural hematoma, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0	N/A
GI bleed, n (%)	3 (3)	1 (2)	3 (4)	2 (2)	9	0.93

GI = gastrointestinal; N/A = not applicable; PRBC = packed red blood cell.

Table 3
Summary of VTE events and Follow-up

Variable	Group 1 (n = 107)	Group 2 (n = 42)	Group 3 (n = 83)	Group 4 (n = 100)	Total (n = 332)
VTE events					
Any VTE, n (%)	8 (7)	7 (17)	14 (17)	21 (21)	50
DVT, n (%)	5 (5)	6 (14)	10 (12)	15 (15)	36
Any PE, n (%)	3 (3)	2 (5)	6 (7)	7 (7)	18
Fatal PE, n (%)	0 (0)	1 (2)	1 (1)	2 (2)	4
All deaths from any cause, n (%)	18 (17)	10 (24)	16 (19)	22 (22)	66
Time to VTE, median (Q1–Q3), d	58 (41–85)	44 (21–149)	46 (30–113)	15 (5–30)	
VTE in <30 d	1 (1)	3 (7)	3 (4)	14 (14)	21
Follow-up, d					
Mean	260	306	257	261	265
Median (Q1–Q3)	295 (160–365)	365 (362–365)	291 (176–365)	365 (64–365)	365 (158–365)
Total number with 365 d of follow-up, n (%)	46 (43)	31 (74)	37 (45)	63 (63)	177 (53)
Follow up >90 d, n (%)	98 (92)	38 (90)	71 (86)	73 (73)	280 (84)

DVT = deep venous thrombosis; Q1 = first quartile; Q3 = third quartile.

In univariable analysis, there was an appearance of a dose-response relationship between the group variable and the risk of VTE events, with lowest risk being observed in group 1 and highest risk in group 4 (P = 0.006; Fig. 4 and Table 5). This was also seen in multivariable analysis (P = 0.002) after adjustment for the type of surgery and the CRS (Table 5). In these analyses, prophylaxis group was the most significant predictor of VTE (P = 0.002). It should be noted that, because patients were left in the intention-to-treat groupings, if they had a VTE event before prophylaxis was initiated, or it was held for several days and then prophylaxis initiated, followed by a VTE event before discharge, their data remained in group 3.

Additionally due to the high-risk nature of cystectomy patients for developing VTE, a subanalysis was preformed, the results of which can be seen in Table 6. The cystectomy analysis revealed the CRS was the biggest predictor of VTE development.

Lastly, prophylaxis averaged $5.00 (interquartile range: $3–$10) as total cost to the patient for the remaining days of prophylaxis (in 2014 US dollars).

The median days of home prophylaxis were 22 (interquartile range: 15–24). Only 4 of 172 admitted to nonadherence with EDP, of which 2 were advised to stop by their primary care physicians.

4. Discussion

Our results confirm LMWH EDP as both safe and effective. Additionally, the results of the present study validate the CRS as a tool for identifying patients at high risk for VTE following urologic cancer surgery.

It should be noted, in all groups, that more than half of the VTE events occurred after discharge. Those performing major surgery for urologic malignancy should consider LMWH EDP for high-risk patients. Our results are similar to those of previous evaluations, demonstrating that EDP is beneficial at preventing clinically significant VTE events in high-risk patients [16–18]. Additionally, these results are consistent with the recommendations of the ACCP, ASCO, and NCCN [19–21].

In the era of complications as a marker of hospital and care quality, it may not be reasonable to consider VTE as a "never event." The national surgical quality improvement project goal of 95% compliance with VTE prophylaxis is a reasonable benchmark; however, even when given according to the ACCP recommendations, in this population which is at high risk for VTE, unfortunately, there postoperative VTE events are still likely [29,30]. However, there is a significant reduction in the overall incidence of VTE events when prophylaxis is administered

Table 4
Surgical modality, laparoscopic, and open

	Total	Group 1 (n = 107)	Group 2 (n = 42)	Group 3 (n = 83)	Group 4 (n = 100)
Surgical modalities					
Robot assisted					
Laparoscopy, n (%)	160 (48)	55 (51)	23 (55)	31 (37)	51 (51)
Open, n (%)	172 (52)	52 (49)	19 (45)	52 (66)	49 (49)
VTE events by modality					
Robot assisted Laparoscopy, n (%)		4 (7)	5 (22)	6 (19)	11 (22)
Open, n (%)		4 (8)	2 (11)	8 (15)	10 (20)

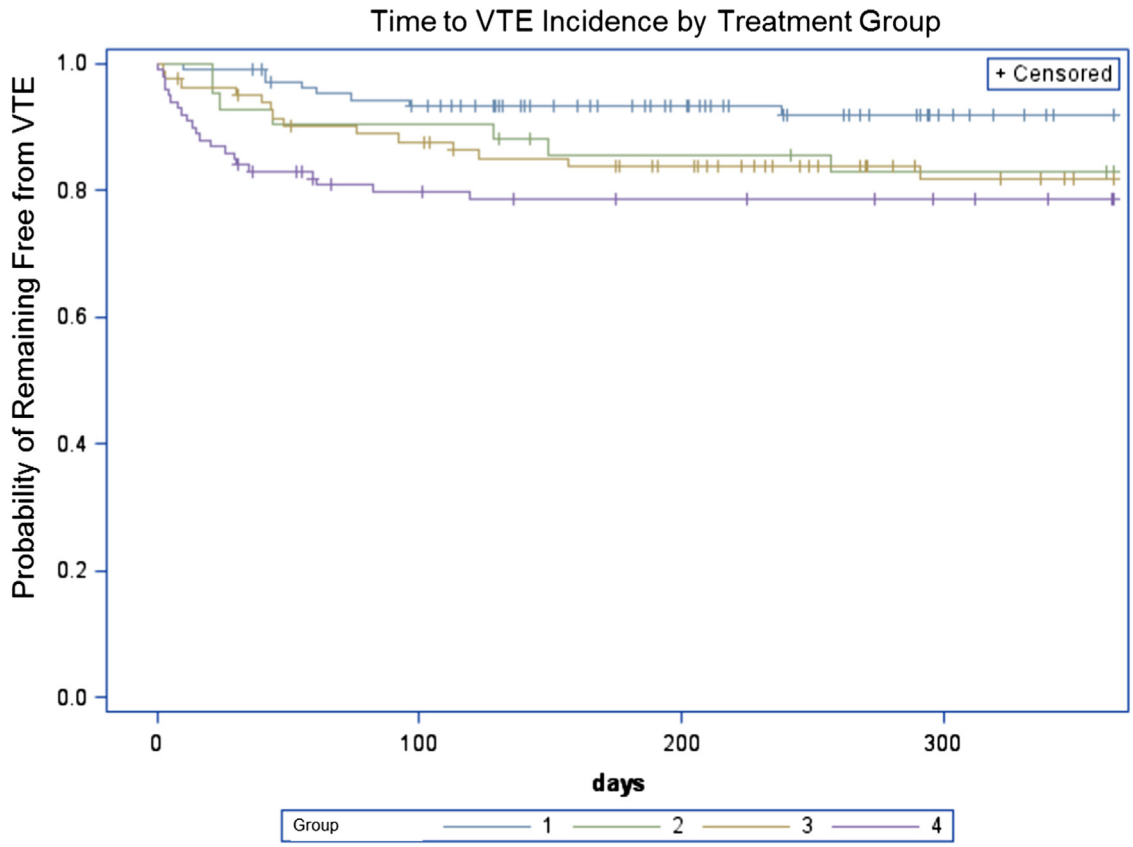

Fig. 4. These curves show the time to VTE event incidence adjusted for follow up time.

according to the recommendations of the ACCP, ASCO, and NCCN.

The limitations of our study include its nonrandomized study design. The diagnoses of VTEs were done clinically and not with routine imaging, which may have made the diagnoses nonstandardized and possibly less reliable. The results found in this study cannot be extrapolated to nononcologic procedures or endoscopic techniques. The causes of death were not evaluated with autopsy but were defined based on clinical grounds used in previously published VTE analyses. The study was performed at a single-institution cancer referral center, which may exaggerate patient acuity compared with that seen in the general population with similar surgical requirements.

Table 5
Incidence of VTE events: univariable and multivariable Cox models

Model	Variable	HR	95% CI	*P* value
Univariable	Prophylaxis			0.006
	Group 3 vs. 4	0.75	0.38–1.48	
	Group 2 vs. 4	0.70	0.30–1.65	
	Group 1 vs. 4	0.32	0.14–0.72	
	Group 2 vs. 1	2.20	0.80–6.08	
	Group 3 vs. 1	2.35	0.99–5.61	
	Group 4 vs. 1	3.14	1.39–7.08	
Multivariable	Prophylaxis			0.002
	Group 3 vs. 4	0.55	0.28–1.11	
	Group 2 vs. 4	0.68	0.29–1.60	
	Group 1 vs. 4	0.25	0.11–0.58	
	Group 2 vs. 1	2.66	0.96–7.38	
	Group 3 vs. 1	2.18	0.91–5.26	
	Group 4 vs. 1	3.94	1.73–8.99	
	Surgery			0.29
	Neph. vs. Cyst.	0.64	0.30–1.33	
	Other vs. Cyst.	1.24	0.55–2.79	
	CRS			0.001
	Per 1 point increase	1.29	1.13–1.46	

Cyst. = cystectomy; Neph. = nephrectomy.

It should be noted that the primary outcome measure was VTE occurrence because PE and especially fatal PE are relatively rare events. Thus, PEs and fatal PEs could not be defined separately as primary end points because of insufficient power. Additionally, VTE events are relatively rare and subsequently wide CIs are in the analysis. Additionally, the median time of follow-up differed between the groups to some extent. However, all patients included in the analysis had at least 30 days of follow-up and use of the Cox proportional hazard model should control for the difference in follow-up, there could be residual confounding, although this is unlikely given the balanced follow-up between the groups.

The strengths of this study include the groups' heterogeneity, and most high-risk patients agreed to participate with good adherence to study protocol, thus limiting bias

Table 6
Cystectomy baseline characteristics

Variable	Group 1 ($n = 63$)	Group 2 ($n = 22$)	Group 3 ($n = 35$)	Group 4 ($n = 37$)	Total	*P* value
Age, median (Q1–Q3), y	67 (62–76)	73 (57–78)	69 (61–76)	72 (63–77)	157	0.96
Sex, men, *n* (%)	42 (67)	19 (86)	27 (77)	34 (92)	122	0.02
Caprini Risk Score, median (Q1–Q3)	14 (12–15)	12 (11–14)	13 (11–15)	12 (11–14)		0.17
Robot assisted laparoscopy, *n* (%)	36 (57)	12 (55)	12 (34)	22 (60)	82	0.11
Hospital days, median (Q1–Q3)	6 (4–10)	7 (6–9)	7 (6–14)	11 (6–21)		
Neoadjuvant chemotherapy, *n* (%)	18 (29)	2 (9)	9 (26)	5 (14)	34	0.14
Adjuvant chemotherapy, *n* (%)	8 (13)	3 (14)	4 (11)	5 (14)	20	0.99
pT Category ≤T2, *n* (%)	42 (67)	14 (64)	18 (51)	27 (73)	101	0.27
pN Category N0/Nx, *n* (%)	50 (79)	18 (82)	26 (74)	33 (90)	127	0.43
BMI > 30, *n* (%)	22 (33)	9 (41)	11 (31)	12 (32)	54	0.89
Sepsis,[a] *n* (%)	24 (38)	10 (45)	17 (49)	17 (46)	68	0.74
AMI, CHF, *n* (%)	7 (11)	1 (5)	2 (6)	3 (8)	13	0.71
COPD, *n* (%)	14 (22)	5 (23)	7 (20)	9 (24)	34	0.99
Transfusion, *n* (%)	30 (48)	8 (36)	18 (51)	18 (49)	74	0.72
VTE events for cystectomies						
Any VTE, *n* (%)	7 (11)	5 (23)	9 (26)	9 (24)	30	
DVT, *n* (%)	4 (6)	4 (18)	6 (17)	7 (19)	21	
Any PE, *n* (%)	3 (5)	1 (5)	4 (11)	2 (5)	10	
Fatal PE, *n* (%)	0 (0)	0 (0)	1 (3)	2 (5)	3	
All deaths from any cause, *n* (%)	14 (22)	6 (27)	10 (29)	15 (41)	45	
Time to VTE, median (Q1–Q3), d	55 (41–74)	128 (44–149)	48 (43–123)	30 (13–59)		
Follow-up for cystectomies, d						
Mean	250	293	238	238		
Median (Q1–Q3)	298 (130–365)	365 (242–365)	270 (113–365)	365 (59–365)		0.27
Summary of complications for cystectomies						
Required ≥2 units of PRBCs, *n* (%)	9 (10)	3 (7)	7 (9)	12 (12)	31	0.75
Complications of prophylaxis						
Total prophylaxis complications, *n* (%)	8 (13)	5 (23)	5 (14)	5 (14)	23	0.72
Hematoma, *n* (%)	3 (5)	0	2 (6)	3 (8)	8	
Lymphocele, *n* (%)	2 (3)	5 (23)	1 (3)	2 (5)	10	
Epidural hematoma, *n* (%)	0 (0)	0 (0)	0 (0)	0 (0)	0	
GI bleed, *n* (%)	3 (5)	1 (5)	3 (9)	1 (3)	8	0.72
VTE events by modality for cystectomies						
Laparoscopic, *n* (%)	4 (13)	3 (10)	3 (10)	4 (13)	14	0.85
Open, *n* (%)	3 (10)	2 (7)	6 (20)	5 (17)	16	

Cystectomy only Cox proportional hazard ratio

Model	Variable	HR	95% CI	*P* value	Model	Variable	HR	95% CI	*P* value
Univariable	Prophylaxis			0.05	Multivariable	Prophylaxis			0.03
	Group 3 vs. 4	0.40	0.15–1.08			Group 3 vs. 4	0.84	0.33–2.20	
	Group 2 vs. 4	0.79	0.26–2.35			Group 2 vs. 4	0.76	0.25–2.27	
	Group 1 vs. 4	1.00	0.040–2.52			Group 1 vs. 4	0.35	0.13–0.96	
	NAC	0.90	0.39–2.10	0.81		CRS (per 1 point increase)	1.17	1.00–1.37	0.06
	Sex female vs. male	0.70	0.27–1.82	0.46					

AMI = acute myocardial infarction; BMI = body mass index; CHF = congestive heart failure; COPD = chronic-obstructive pulmonary disease; DVT = deep vein thrombosis; GI = gastrointestinal; NAC = neoadjuvant chemotherapy; PRBC = packed red blood cell; Q1 = first quartile; Q3 = third quartile.

[a]Sepsis (defined by 2 of the following: fever >100.4°F or <96.8°, HR > 90 beats/min, respiratory rate >20 breaths/min, $PaCO_2$ < 32 mm Hg, white blood cells <4,000 of >10% immature [band] forms, anion gap acidosis >16 and a positive culture), within the first 90 days after cystectomy.

and confounding. With a comprehensive electronic medical record and the ability to quickly obtain outside hospital records, the chance of a prospectively followed patient having an unrecorded clinically significant VTE event is low. Additionally, chart review and patient interviews are more comprehensive than a database review limited to diagnosis coding and billing codes. Patient interviews for those alive both in the prospective and retrospective cohorts

were carried out if no follow-up data were available so as to minimize the chance of information bias. Finally, as all patients had undergone major surgery for urologic malignancy, the data were derived from a restricted patient population. Both inpatient VTE prophylaxis and EDP were safe and seemingly offered a favorable risk-to-benefit ratio profile.

This study is significant because, to our knowledge, it is the first urologic-only cancer-specific population undergoing major surgery to be studied to assess EDP safety and effectiveness. It further validates the CRS for classifying high-risk patients for postoperative VTE in those undergoing major surgery for urologic malignancy. Further studies should be considered with varying durations, cost-effectiveness, and possibly new oral anti-Xa inhibitors for VTE prophylaxis, as this has shown promise in the orthopedics patients with improved reduction of VTE events in high-risk patients.

5. Conclusions

Among patients treated with surgery for urologic cancer, the risk of VTE is inversely associated with adherence to the EDP protocol. The risk is lowest in patients who receive prophylaxis per protocol while hospitalized with continued prophylaxis following discharge and is highest in patients who do not receive per-protocol prophylaxis in the hospital and have no prophylaxis after discharge. We found that, in high-risk urological oncology surgery patients, a clinical protocol is effective and safe in reducing VTE events. All high-risk patients undergoing major urologic oncology surgery should be considered for in-hospital and extended-duration VTE prophylaxis.

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