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ARTICLE

Incidence and associated risk factors of venous thromboembolism after open and laparoscopic partial nephrectomy in patients administered short-period thromboprophylaxis: a Danish nationwide population-based cohort study

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ABSTRACT

Objective: To report the risk of venous thromboembolism (VTE) after partial nephrectomy in Denmark.

Materials and methods: A nationwide population-based registry was used to conduct a retrospective cohort study. All partial nephrectomies from January 2010 to August 2018 were assessed for postoperative VTE events. Univariable and multivariable analyses were used to evaluate the odds of postoperative VTE within 4 weeks and 4 months after partial nephrectomy in patients who received standard-of-care thromboprophylaxis.

Results: Among 2355 patients, postoperative VTE risk was 0.6% and 0.9%, at 4 weeks and 4 months, respectively. In multivariate analysis, prior VTE (OR = 24.9, $p < 0.001$) and length of hospital stay (OR = 0.89, $p < 0.001$) were predictors of postoperative VTE within 4 months after partial nephrectomy. Limitations included the retrospective and registry-based study design and the absence of BMI data.

Conclusion: Incidence of postoperative VTE is rare, but patients with prior VTE and those with a greater length of hospital stay are at greater long-term risk and should be evaluated when considering thromboprophylaxis.

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Introduction

Postoperative deep vein thrombosis, pulmonary embolism, and venous thromboembolism (VTE), carry significant morbidity following surgery. Costly treatments, lengthy hospital stays, and irreversible loss of health, quality of life, or death, complicate postoperative care and clinical outcomes. Several risk factors predisposing patients to postoperative VTE have been identified in renal patients. VTE incidence is higher in women compared to men until the age of 60 years [1,2]. The risk of recurrent VTE while on anticoagulant treatment is about 1% [1]. Patients with cancer have an increased risk of VTE of 14% annually and patients with temporary risk factors (surgery, immobilization, and trauma) have an annual risk of 3% [1]. Mortality due to postoperative VTE depends on the presence of multiple risk factors. For example, patients with cancer face an increased mortality rate following VTE of 19% within the first month of VTE diagnosis, compared to 3.6%—12.6% in patients without cancer [2].

There is a dearth of evidence regarding VTE prophylaxis in patients undergoing urological procedures [3], and the European Association of Urology (EAU) Guidelines are informed from systematic reviews, which only included retrospective studies [4,5]. Based on these recommendations, the risk of VTE is as high in the fourth-week post-surgery as in the first week; therefore, the optimal duration of pharmacological postoperative VTE prophylaxis is approximately four weeks [1,2]. In Denmark, the standard of care VTE prophylaxis strategy has a shorter duration of seven days or less, starting on the first day prior to surgery and ceasing at the day of discharge [6,7].

The aim of this present study was to understand postoperative VTE incidence and its associated predictive risk factors in patients who underwent partial nephrectomy in Denmark while receiving the above-mentioned standard of care short-period VTE prophylaxis strategy.

Methods

Evidence acquisition

A retrospective population-based nationwide registry was used. We included data from the National Patient Registry (NPR), which contains information on all hospitalizations [8], including surgical procedures coded according to the Nordic Classification of Surgical Procedures and diagnoses coded according to the International Classification of Diseases, Tenth Revision (ICD-10). Since 1968, all Danish citizens are registered with a unique personal identification number (Central Personal Registration number, CPR), which allows linkage between all national registries at the individual level.

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All procedures in this study followed the principles outlined by the Declaration of Helsinki. The study was approved by the Danish Data Protection Agency (FABID-00000152).

Study cohort and variables

Patients with partial nephrectomy performed either laparoscopically (LN) or open (ON) between January 2010 and August 2018 were included. Registry information on known risk factors of VTE was retrieved and included previous VTE at any time prior to surgery and a history of previous or current hypertension or cardiovascular disease. Any new cases of VTE within four weeks or four months after surgery and demographic data (age and gender) were available for all patients. Data on postoperative length of stay (LOS), defined as hospital stay after surgery and any re-admission within the first 30 days after surgery, along with reoperation within the first 30 days, was also retrieved. Registry-based data on the history of inflammatory diseases prior to surgery and body mass index (BMI) at the time of surgery was only available for some patients and were therefore not included in the current analyses. Indication of surgery being benign was defined as the patients having no cancer diagnosis at the final histological report.

Manual cohort validation through chart review was performed on 369 patients (16% of the entire cohort) to provide population estimates on the percentage of patients receiving standard-of-care short-period VTE-prophylaxis. Patients were randomly selected (in a central registry) from five Danish urological centers performing renal surgery. Data on type, dosage, and duration of VTE prophylaxis were obtained together with patient demographics and the number of reoperations.

Data analysis and statistics

Univariable and multivariable analyses were performed to evaluate clinical variables. Postoperative mortality was not considered for this study since its rate after renal surgery, according to the Danish Renal Cancer Database, is low (1%) [7]. A forward stepwise regression model for a final predictive adjusted model was performed, beginning with an empty model and then successively adding significantly correlated variables. SAS Software (version 7.1, SAS Institute, Cary, NC, USA) was used. All two-sided p-values <0.05 were considered statistically significant.

Results

A total of 2355 patients underwent partial nephrectomy during the study period. The median age at a time point of the surgery was 62 years (IQR 51–69) with 1446 (61.5%) male patients. Thirty (1.3%) patients underwent reoperations within the first 30 days of partial nephrectomy. Surgery for benign indications was performed in 849 patients (36.1%). LN was performed in 1373 patients (58.3%). Median LOS was three days (IQR 2–4) for both LN and OPN.

Postoperative VTE within four weeks

The incidence of postoperative VTE within four weeks was 15/2355 (0.6%). As shown in Table 1, univariable analyses revealed two significant factors: gender and previous history of VTE. Female patients saw a significantly lower OR of postoperative VTE at 0.11 (95%CI: 0.01–0.85, $p = 0.04$) compared to male patients. The previous history of VTE was associated with a very high OR of 26.4 (95%CI: 9.4–74.36, $p < 0.001$) compared to having no such history. Only previous history of VTE remained statistically significant in multivariable analyses and no additional risk factors were identified (Table 1).

Postoperative VTE within four months

The incidence of postoperative VTE within four months was 21/2355 (0.9%). As shown in Table 2, univariable analyses indicated three significant factors affecting the risk of postoperative VTE: previous history of VTE, previous history of hypertension, and length of hospital stay (LOS). Previous history of VTE was associated with a very high OR of 26.4 (95%CI: 9.4–74.36, $p < 0.001$) compared to no such history. Previous history of hypertension was associated with a very high OR of 24.6 (95%CI: 3.06–151.10, $p = 0.003$) compared to no such history. Regarding LOS, for each day less in the hospital, the odds ratio for developing postoperative VTE was reduced by 0.09. Multivariable analyses (Table 2) confirmed the history of VTE (yes vs. no) and LOS as significant factors affecting the risk of developing postoperative VTE by four months.

Associations identified in the VTE assessment at four months following surgery (previous history of VTE and LOS) were included in a forward stepwise regression model for a more robust evaluation of the overall effect and strength of these variables (Table 3).

Manual cohort validation of VTE prophylaxis use and VTE incidence

Compared to the entire cohort, the validation cohort demographics showed a median age of 63 years (IQR 59–73) compared to 62 years (IQR 51–69), 68% being male compared to 61.5% in the entire cohort, and LPN being performed in 73% vs. 58.3% in the entire cohort. In total, 3 (0.8%) out of 369 patients experienced a VTE episode, which was slightly lower when compared with the entire cohort (0.9%) four months after surgery. Type and dosage of VTE prophylaxis used were Tinzaparin anti-Xa 4500IE once daily, administered to 271/369 patients (73.4%), and 98/369 patients (26.6%) receiving Dalteparin anti-Xa 5000IE once daily.

Standard of care short-period VTE prophylaxis (see definition in study objectives above) was administered to 356 (96.5%) patients in the validation cohort. In comparison, the remaining 13 patients (3.5%) received extended VTE prophylaxis (starting one day before the surgery and lasting for more than 7 days but less than 28 days total). Of those with extended VTE prophylaxis, all patients had early postoperative complications, including one patient who experienced a

Table 1. Risk factors of venous thromboembolisms 4 weeks postoperatively after partial nephrectomy reported in the Danish National Register between January 2010 and August 2018.

Risk category	Variable	n with postop VTE/N total (%)	Univariable OR	Univariable 95% CI	Univariable *p*-value	Multivariable OR	Multivariable 95% CI	Multivariable *p*-value
Demographics	Age							
	≥70	6/576 (1.0%)	Ref.					
	<50	2/494 (0.4%)	0.38	0.07–1.91	0.24	0.88	0.30–2.54	0.6
	50–69	7/1285 (0.5%)	0.52	0.17–1.55	0.23	1.19	0.49–2.84	0.5
	Gender							
	Male	14/1446 (0.9%)	Ref.					
	Female	1/909 (0.1%)	0.11	0.01–0.85	0.04	0.49	0.39–7.63	0.3
History	Previous VTE	8/105 (7.6%)	26.4	9.4–74.36	<0.001	25.96	8.69–77.59	<0.001
	Previous CVD	2/99 (2.0%)	3.56	0.79–15.98	0.09	1.7	0.32–9.27	0.5
	Previous HT	7/648 (1.0%)	2.32	0.84–6.42	0.1	1.5	0.46–4.57	0.5
Surgery	Indication							
	Malignant	10/1506 (0.7%)	Ref.					
	Benign	5/849 (0.6%)	0.88	0.30–2.60	0.8	0.79	0.24–2.53	0.6
	Type							
	ON	6/982 (0.6%)	1.07	0.38–3.04	0.9	1.25	0.75–1.64	0.6
	LN	9/1373 (0.7%)	Ref.			Ref.		
Postoperative	LOS[a] (days)	N/A	0.94	0.88–1.01	0.09	0.93	0.86–1.01	0.07

List of abbreviations: CVD: cardiovascular disease; HT: Hypertension; LN: Laparoscopic partial nephrectomy; LOS: Length of hospital stay (days); N/A: not applicable; ON: Open partial nephrectomy; VTE: venous thromboembolism. [a]LOS odds ratio interpretation; For each day less in hospital stay the odds ratio for developing postoperative VTE is reduced by 0.06 (univariable) and increased by 0.07 (multivariable), respectively, both non-significant.

Table 2. Risk factors of venous thromboembolisms 4 months postoperatively after partial nephrectomy reported in the Danish National Register between January 2010 and August 2018.

Risk category	Variable	n with postop VTE/N total (%)	Univariable OR	Univariable 95% CI	Univariable *p*-value	Multivariable OR	Multivariable 95% CI	Multivariable *p*-value
Demographics	Age							
	≥70	8/576 (1.3%)	Ref.					
	<50	3/494 (0.6%)	0.43	0.11–1.64	0.2	0.88	0.33–2.54	0.6
	50–69	10/1285 (0.8%)	0.56	0.21–1.42	0.2	1.19	0.50–2.84	0.5
	Gender							
	Male	17/1446 (1.2%)	Ref.					
	Female	4/909 (0.5%)	0.37	0.12–1.10	0.07	0.25	0.13–1.28	0.08
History	Previous VTE	10/105 (15.5%)	26.43	9.39–74.36	<0.0001	24.91	9.55–64.97	<0.001
	Previous CVD	2/99 (1.1%)	2.43	0.55–10.57	0.2	1.21	0.23–6.43	0.8
	Previous HT	8/648 (2.3%)	24.55	3.06–151.10	0.003	1.08	0.39–2.96	0.8
Surgery	Indication							
	Malignant	16/1506 (1.1%)	Ref.			Ref.		
	Benign	5/849 (0.6%)	0.55	0.20–1.51	0.2	0.67	0.44–1.28	0.3
	Type							
	LN	12/1373 (0.9%)	Ref.			Ref.		
	ON	9/982 (0.9%)	1.05	0.44–2.49	0.9	1.28	0.28–1.87	0.5
Postoperative	LOS[a] (days)	N/A	0.91	0.87–0.95	<0.001	0.89	0.85–0.93	<0.0001
	Re-operation	1/30 (3.3%)	5.7	0.72–44.73	0.09	3.76	0.38–37.18	0.2

List of abbreviations: CVD: cardiovascular disease; HT: Hypertension; LN: Laparoscopic partial nephrectomy; LOS: Length of hospital stay (days); N/A: not applicable, ON: Open partial nephrectomy; VTE: venous thromboembolism. [a]LOS odds ratio interpretation; For each day less in hospital stay the odds ratio for developing postoperative VTE is reduced by 0.09 (univariable) and 0.11 (multivariable), respectively 12/1373 (0.9%).

Table 3. Forward stepwise multivariable regression model to predict venous thromboembolisms four months postoperatively after partial nephrectomy reported in the Danish National Register between January 2010 and August 2018.

Risk category	Variable	OR	95% CI	*p*-value
History	Previous VTE	25.64	10.16–64.69	<0.0001
Postoperative	LOS[a] (days)	0.89	0.85–0.94	<0.0001

List of abbreviations: VTE: venous thromboembolism; LOS: Length of hospital stay (days). [a]LOS odds ratio interpretation; For each day less in hospital stay the odds ratio for developing postoperative VTE is reduced by 0.11.

VTE within four months of surgery. The complication in these 13 patients included bleeding in nine patients, infection in two patients, and the need for reoperation (Clavien-Dindo IIIb) in three patients. Based on the validation cohort, 14 patients receiving extended VTE prophylaxis are needed in order to prevent one patient receiving short-period VTE prophylaxis from developing VTE within four months (OR = 14).

Comment

In a large cohort of Danish patients undergoing renal resection, our study found that in contrast to EAU Guidelines recommendations, patients with a high risk of VTE may see benefits from thromboprophylaxis beyond 4 weeks after surgery, using Tinzaparin anti-Xa 4500 IE or Dalteparin anti-Xa 5000 IE once daily. Our results showed that postoperative VTE events after partial nephrectomy are relatively low (0.6% at four weeks and 0.9% at four months), provided patients receive the above-described VTE prophylaxis regimen. To our knowledge, this is to date the largest nationwide patient cohort investigating postoperative VTE incidence in patients undergoing partial nephrectomy.

One reason for this discrepancy may be that our cohort only included patients who underwent partial nephrectomy, averting the issue of procedure-specific differences in VTE risk estimates seen in other studies. Tikkinen et al. performed

a systematic review of patients who underwent various urological procedures for diseases of the urinary tract and male genital system. He found that VTE risk increases until the 4-week mark, from which it plateaus. Our results demonstrate elevated VTE risk in some patients beyond the 4-week mark [4].

Patients at higher risk of VTE may benefit the most from thromboprophylaxis, as seen in a systematic review and meta-analysis of VTE risk 4 weeks after renal surgery, underpinning the EAU recommendations on VTE prophylaxis [5]. Risk groups were stratified as follows: low (no risk factors), medium (one of the following factors: age $\geq$75 years, body mass index $\geq$35 kg/m^2, or history of VTE in any first-degree relative), and high (prior history of VTE or more than one of the medium risk factors). All groups saw greater VTE risk (0.7–2.9% for low, 1.3–5.8% for medium, and 2.6–11.6% for high-risk patients). These results were based on only nine studies (three studies on LN with 196 patients and six studies evaluating ON in 5,632 patients), with overall certainty of risk estimates ranging from low to very low. Further, patients did not receive thromboprophylaxis when pooled VTE risk estimates were calculated.

Tikkinen's results also found age to be associated with prior VTE, with an approximately 10% cumulative risk of having had a VTE by 80 years of age [5]. In our multivariable analysis however, when comparing patients $\geq$70 years old with patients between 51–69 or $\leq$50-years old, all of whom 96.5% (according to our manual validation) receiving short-term VTE prophylaxis, no significant association was demonstrated between age and VTE history at either 4 weeks or 4 months. Prior VTE in our study was the most strongly associated risk factor for developing postoperative VTE, with an OR of 26 at four weeks and OR of 25 at four months. Our study, therefore, finds that patient age may not be a significant risk factor in those undergoing partial nephrectomy, but rather, maybe a confounding factor to prior history of VTE, as supported by our multivariable predictive model.

ON is more invasive than LN, and our previous results [8], as well as the systematic review by Tikkinen et al., showed a higher risk of VTE in patients undergoing ON compared to LN, whereas our results here did not replicate this finding. In Tikkinen's paper, details on VTE prophylaxis strategies were reported in only 40% of the included studies with a pooled estimate of VTE prophylaxis use for 2.9 days (IQR 1.9–4.0) [5]. We previously showed that those undergoing ON had an OR of 3.3 at four weeks and 2.5 at four months, with similar VTE prophylaxis duration, but this study found no significant difference between the type of nephrectomy and VTE risk at either four weeks or four months. Compared to other urological procedures, the risk of VTE in partial nephrectomy patients is generally lower [9].

Length of hospital stay was significantly associated with greater VTE risk post partial nephrectomy at four months, but not at four weeks. Our forward multivariate regression model predicts that for each day less of hospital stay, the odds ratio for developing postoperative VTE is reduced by 0.11 (95%CI 0.85–0.93, $p < 0.0001$). However, this result must be interpreted with caution as the estimated protective effect of shorter LOS is minimal.

Lastly, female patients had a non-significant lower risk of postoperative VTE ($p = 0.075$) at four months after surgery in our forward stepwise multivariable regression model, and a non-significantly lower risk at 4 weeks (OR = 0.49, 95%CI 0.39—7.63, $p = 0.3$).

This study is the first to the best of our knowledge to highlight the potential need for extended VTE for partial nephrectomy patients at high risk of VTE. We have highlighted two risk factors for postoperative VTE in patients undergoing partial nephrectomy (history of VTE and LOS) and therefore believe a personalized VTE prophylaxis strategy may reduce the incidence of postoperative VTE in patients undergoing renal resection. Future studies are needed to identify high-risk patients benefiting from either short- or long-term VTE prophylaxis, and to strengthen better pinpointing of the specific risks. Li et al. for example recently developed a prediction model based on five risk factors (previous VTE, blood-thinning agents before admission, D-dimer, lower extremity swelling, and chest symptoms) to predict VTE in non-oncological urological surgery patients [10]. A pilot study by Emani et al. in pediatric patients undergoing cardiac surgery found that guiding aspirin doses based on platelet testing led to significantly lower rates of thrombosis [11].

One strength of our study was using a robust nationwide population-based registry to identify partial nephrectomy patients. Compared to survey-based or single-center studies, reporting and selection biases are lower with nationwide registries. We also were able to follow up with patients long-term at four months, improving our understanding of risk factors associated with postoperative VTE risk. Limitations include the retrospective registry-based study design and not including BMI data, which was unavailable for most patients in this study. Our manual validation review of 16% of the cohort helped to somewhat ameliorate the retrospective design limitation by providing estimates of patients receiving standard-of-care short-period VTE, reducing the potential of confounding results by VTE prophylaxis type, dosage, and duration. Furthermore, a manual validation review showed that patients showed a high adherence rate to the VTE prophylaxis regimen.

Standard of care short-period VTE prophylaxis, starting at the first preoperative day and ceasing up until seven days or at discharge, reduces the incidence of postoperative VTE in the short term. The previous history of VTE and length of hospital stay increase the probability of postoperative VTE in partial nephrectomy patients and may be considered in an extended VTE treatment strategy. A high level of evidence intervention studies is needed to further evaluate these predictive risk factors.

Disclosure statement

- Conflict of interest: None of the contributing authors have any conflict of interest.
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