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Procedure-specific Risks of Thrombosis and Bleeding in Urological Cancer Surgery: Systematic Review and Meta-analysis

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Abstract

Context: Pharmacological thromboprophylaxis involves balancing a lower risk of venous thromboembolism (VTE) against a higher risk of bleeding, a trade-off that critically depends on the risks of VTE and bleeding in the absence of prophylaxis (baseline risk). **Objective:** To provide estimates of the baseline risk of symptomatic VTE and bleeding requiring reoperation in urological cancer surgery. **Evidence acquisition:** We identified contemporary observational studies reporting symptomatic VTE or bleeding after urological procedures. We used studies with the lowest risk of bias and accounted for use of thromboprophylaxis and length of follow-up to derive best estimates of the baseline risks within 4 wk of surgery. We used the GRADE approach to assess the quality of the evidence. **Evidence synthesis:** We included 71 studies reporting on 14 urological cancer procedures. The quality of the evidence was generally moderate for prostatectomy and cystectomy, and low or very low for other procedures. The duration of thromboprophylaxis was highly variable. The risk of VTE in cystectomies was high (2.6–11.6% across risk groups) whereas the risk of bleeding was low (0.3%). The risk of VTE in prostatectomies varied by procedure, from 0.2–0.9% in robotic prostatectomy without pelvic lymph node dissection (PLND) to 3.9–15.7% in open prostatectomy with extended PLND. The risk of bleeding was 0.1–1.0%. The risk of VTE following renal procedures was 0.7–2.9% for low-risk patients and 2.6–11.6% for high-risk patients; the risk of bleeding was 0.1–2.0%. **Conclusions:** Extended thromboprophylaxis is warranted in some procedures (eg, open and robotic cystectomy) but not others (eg, robotic prostatectomy without PLND in

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low-risk patients). For “close call” procedures, decisions will depend on values and preferences with regard to VTE and bleeding.

Patient summary: Clinicians often give blood thinners to patients to prevent blood clots after surgery for urological cancer. Unfortunately, blood thinners also increase bleeding. This study provides information on the risk of clots and bleeding that is crucial in deciding for or against giving blood thinners.

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1. Introduction

The volume of urological cancer surgery is large: more than 90 000 urological malignancies are treated and more than 200 000 urological planned operations are conducted annually in the UK alone [1]. Although safety has increased substantially, surgical complications remain a major challenge [2,3]. Serious complications of urological surgery include deep vein thrombosis (DVT) and pulmonary embolism (PE)—together referred to as venous thromboembolism (VTE)—and major bleeding.

Because pharmacological prophylaxis decreases the risk of VTE, but increases the risk of major bleeding [4], the decision to use prophylaxis involves a trade-off between a reduction in VTE and an increase in bleeding. The risk of VTE and bleeding in those not receiving thromboprophylaxis, which we will refer to as *baseline risk*, is the crucial issue in making the decision. When the baseline risk of VTE is high and the risk of bleeding is low, prophylaxis will be warranted; with low VTE risk and high bleeding risk, it will not. At intermediate risk, the relative patient aversion to VTE and bleeding is likely to determine the optimal practice.

Baseline risks for VTE and bleeding in the absence of prophylaxis vary widely between urological procedures [5–7] but their magnitude is uncertain. Given the imperfect knowledge regarding these risks [6,8,9], the substantial practice variation in the use of thromboprophylaxis in urology, both within and between countries, is not surprising [7,10–14]. To provide risk estimates of VTE and bleeding requiring reoperation for procedures for malignant diseases of the urinary tract and male genital system, and thus to address this gap in knowledge, we conducted a systematic review.

2. Evidence acquisition

Our study protocol, prospectively registered (PROSPERO: CRD42014010342) and previously published [4], followed Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidance [15].

2.1. Eligibility

We included observational studies published in English that enrolled a minimum of 50 adult patients undergoing procedures for malignant diseases of the urinary tract or male genital system and that reported an absolute estimate of risk for at least one of the patient-important outcomes of interest: fatal PE, symptomatic PE, symptomatic DVT,

symptomatic VTE, fatal bleeding, and bleeding requiring reoperation.

2.2. Data sources and searches

We developed search strategies in collaboration with experienced research librarians (N.B. and L.B.). For the baseline risk of VTE and bleeding, we searched the MEDLINE database for potentially eligible articles published from January 1, 2000 until January 1, 2016. A combination of keyword and medical subject headings search included the “urological procedures” term family combined with the “thrombosis” term family, and the “urological procedures” term family combined with the “bleeding” term family and the prognosis sensitivity filter. We asked content experts to provide potentially relevant articles and searched the reference lists of systematic reviews captured in our search. Details of the searches are presented in the Supplementary material (pages 73–78) [4]. We performed additional searches (Supplementary material, pages 79–83): (1) for patient-related risk factors for VTE and bleeding after surgery; (2) to inform modeling of outcomes for studies with varying follow-up, we searched for cohort studies addressing timing of VTE and bleeding after surgery; and (3) to model baseline risk for patients who were receiving prophylaxis, we searched for randomized trials addressing the effects of pharmacological and mechanical thromboprophylaxis on VTE and bleeding risk after surgery [4].

2.3. Study selection and data abstraction

Two reviewers independently evaluated titles and abstracts, then full-text articles of all potentially eligible studies, and finally for articles that proved eligible abstracted data including outcomes, study characteristics, and risk of bias. A clinician-methodologist adjudicator resolved disagreements on judgments at each stage. We contacted the authors of all the original articles to confirm the accuracy of the data extracted and, when needed, asked the authors to clarify missing or unclear information. When investigators published more than one report addressing the same population, we included the most comprehensive report.

2.4. Risk of bias

Criteria for risk of bias and for overall certainty in estimates are less well established for studies of baseline risk than for issues of therapy [16]. Therefore, through iterative discussion and consensus-building, and informed by the literature [17], we developed a novel instrument to categorize studies

with regard to the likelihood of producing biased estimates of VTE or bleeding (high or low risk of bias) [4]. Items included the representativeness of the patient population, thromboprophylaxis documentation, data source, whether a majority of patient recruitment years were earlier or later than 2000, clear specification of duration of follow-up, and study type (Supplementary material, page 27) [4].

2.5. Analysis

2.5.1. Outcomes

Outcomes included the absolute risks of symptomatic VTE and bleeding requiring reoperation (including exploration and angioembolization) at 4 wk, and the absolute risks of fatal PE and fatal bleeding. We analyzed outcomes separately for each procedure.

Although it is a patient-important outcome and may be associated with appreciable morbidity, we did not address blood transfusions because (1) studies often did not report transfusions and (2) criteria for transfusion vary widely between studies, and use of transfusion may follow protocols that have limited relation to underlying bleeding. Furthermore, we did not combine bleeding with operations as a morbidity outcome because transfusions are much less important to patients than are reoperations. We acknowledge that bleeding requiring reoperation is also based on the surgeon's decision and is therefore prone to variation. It is likely, however, that this variation is substantially less than variation in decisions to transfuse blood.

2.5.2. Calculating the risk of VTE and bleeding for individual studies

We adjusted the reported risk of VTE and bleeding for the use of thromboprophylaxis. For patients who received prophylaxis, we multiplied the reported risk by the relative risk of thromboprophylaxis (Supplementary material, pages 41–42). Our meta-analyses informed relative risk estimates of thromboprophylaxis (for forest plots see the Supplementary material, pages 54–72), with the exception of an earlier meta-analysis that informed risk estimates for direct oral anticoagulants [18] and, for aspirin, two large pragmatic trials [19,20]. We had high certainty in estimates of the effects of pharmacological prophylaxis but low certainty for mechanical prophylaxis (surrogate outcomes, very few events, unblinded patients and assessors; Supplementary material, pages 54–72). We therefore did not consider combination therapy as offering more protection than pharmacological prophylaxis alone [4,21]. For renal surgery studies that did not report use of thromboprophylaxis (and when the authors did not provide this information when requested), we estimated that patients in Europe and Asia received 1 wk of low-molecular-weight heparin, and those in the USA and Canada received 4 d of low-molecular-weight heparin (Supplementary material, page 43).

2.5.3. Modeling the risk of VTE and bleeding over time

Because 1 wk and 4 wk are feasible and frequently chosen as the duration of prophylaxis after surgery [7,10,11], we

estimated the risks of VTE and bleeding requiring reoperation for these durations [4,22,23]. For studies that did not report VTE and bleeding estimates at 1 wk and 4 wk, we modeled estimates using a previously published approach [4] that demonstrates an approximately constant hazard of VTE up to 4 wk (Supplementary material, pages 50–51). Bleeding risk, by contrast, is concentrated in the first 4 d (Supplementary material, page 51). For studies that provided the number of DVT and/or PE events, but not VTE, we modeled the number of VTE events using studies that had reported all DVT, PE, and VTE events (Supplementary material, page 44). We estimated the case fatality rates by dividing the number of fatal PE events by the number of symptomatic VTE events using studies that had provided both estimates (Supplementary material, pages 35–37). We used a similar approach to estimate the case fatality for bleeding requiring reoperation [4].

2.5.4. Choosing the best estimates

We used the median value of estimates from studies with the lowest risk of bias to estimate the baseline risk of VTE and bleeding requiring reoperation [4]. When the available studies with low risk of bias had fewer than 1000 patients, we included studies with a high risk of bias (Table 1). For radical prostatectomy (open, laparoscopic, robotic) and cystectomy (open, robotic) studies, but not for studies of kidney surgery, radical penectomy with inguinal lymphadenectomy, or primary nerve-sparing retroperitoneal lymph node dissection (too few studies), we excluded studies in which the majority of patient recruitment years were earlier than 2000 and studies that did not explicitly define the time period for follow-up. As a true baseline bleeding rate of zero is implausible in urological cancer surgery, if the median bleeding estimate was zero, and there was a study that represented a credible alternative because of study design (eg, multinational) and sample size (large), we used the bleeding risk from that study. If there were no studies reporting on risk of bleeding for a particular procedure, we estimated the bleeding risk using the estimate from the most similar procedure.

2.5.5. Risk stratification

After assessing the baseline risk of VTE for each procedure, we estimated risk for groups of patients according to patient risk factors (Table 2) [4]. Eligible studies and prior literature provided estimates of the proportion of patients having each risk factor, allowing estimates of the extent of overlap and thus calculation of estimates for each risk stratum (Supplementary material, pages 47–49, 52–53). Our search did not reveal studies demonstrating convincing and replicable risk factors for bleeding [4]. Therefore, we did not stratify bleeding risk by patient-specific factors.

For radical prostatectomies (open, laparoscopic, and robotic), evidence suggests that limited/standard pelvic lymph node dissection (PLND) approximately doubles the risk of VTE compared to no PLND, and extended PLND increases the risk of VTE compared to no PLND by a factor of approximately four [24–27]. For bleeding risk, we

Table 1 – Principles for the use of GRADE for assessment of evidence of risk of complications, and examples of GRADE use for estimating evidence of the risk of VTE bleeding requiring reoperation after urological cancer surgery

	General principles in GRADE	Criteria for judgment in our study	Examples
Risk of bias	The risk of misleading results is higher if studies are flawed in their design or conduct	When the available studies with low RoB ^a had fewer than 1000 patients, we also used studies with a high RoB for estimates of risk. We rated down for RoB if most patients (>50%) came from studies at high RoB	For VTE, open PN had 1 low RoB study with 110 patients, and 5 high RoB studies with 3504 patients. We used all studies. For bleeding, open PN had 2 low RoB studies with 1139 patients, and 2 high RoB studies. We used only low RoB studies in our analysis. We rated down for RoB for VTE but not for bleeding
Inconsistency	Widely differing estimates (heterogeneity or variability in results) across studies is called inconsistency. If point estimates vary substantially across studies, or confidence intervals show little or no overlap, certainty is likely to be rated down for inconsistency. Variability may arise from differences in populations, or methodology	We rated down for inconsistency if there was at least a 3% difference between the median value and the study with either the highest or lowest rate of VTE, and a 1.5% difference for bleeding requiring reoperation	Open PN had median VTE of 1.5%; the highest incidence was 4.9% and the lowest was 0.9%. As the study with the highest differs by >3% from the median value, we rated down for inconsistency
Indirectness	Evidence can be indirect in several ways. Indirectness may arise from differences in the population or outcome of interest between included studies and the population of interest	We did not usually rate down for indirectness, as the eligible studies measured relevant outcomes in representative populations. We rated down for indirectness when there was little evidence with questionable applicability	Open RN had only 1 study that reported bleeding requiring reoperation, with zero events recorded. We considered a risk of bleeding of 0 in this procedure to be implausible. We therefore estimated the risk of bleeding to be half that for open PN. We rated down two levels for indirectness
Imprecision	When studies have wide confidence intervals, typically because of relatively few patients or events, imprecision occurs	We rated down by one level if studies included <1000 patients, and by two if they included <200 patients	Laparoscopic RN had 3 studies with 196 patients for risk of VTE. We rated down two levels for imprecision
Quality of evidence/CiE	In studies of the risk of complications, a body of observational evidence begins as high quality. The five GRADE domains consider in rating down CiE of treatment effect—that is, RoB, imprecision, inconsistency, indirectness, and publication bias (no rating down for publication bias here)—as well as GRADE criteria for rating up quality, also apply to estimates of the risks of complications. CiE options include high, moderate, low and very low.	Although certainty in a body of evidence from observational studies addressing a question of prognosis begins as high quality, we rated down to moderate in all cases owing to uncertainties in our models of risk of VTE and bleeding over time (Supplementary material, p. 3–22) and in our model of patient risk strata (Table 1). We then further rated down as described for the other four categories	For open PN, for VTE risk we rated down for each uncertainty in our models, RoB and inconsistency, resulting in very low certainty in estimates. For bleeding, we rated down for uncertainty in our models, resulting in moderate quality of evidence

GRADE = Grades of Recommendation, Assessment, Development, and Evaluation; CiE = certainty in estimates; VTE = venous thromboembolism; PN = partial nephrectomy; RN = radical nephrectomy; RoB = risk of bias.

^a RoB criteria included the representativeness of the patient population, thromboprophylaxis documentation, data source, whether a majority of patient recruitment years were earlier or later than 2000, clear specification of the duration of follow-up, and study type (Supplementary material, page 27).

Table 2 – Model for risk of venous thromboembolism according to patient risk factors

	Risk	
Low risk	No risk factors	1×
Medium risk	Any one of the following: - Age ≥75 yr - Body mass index ≥35 kg/m ² - VTE in first-degree relative (parent, full sibling, or child)	2×
High risk	Prior VTE Patients with any combination of two or more risk factors	4×

VTE = venous thromboembolism.

We developed a very simple model for VTE risk based on studies reporting the most relevant and compelling evidence [4] identified in a literature search addressing VTE risk factors in the context of urology, general surgery, gynecology, and gastrointestinal surgery. To calculate estimates of absolute risks for these groups, we estimated the proportion of patients having each of the risk factors using eligible studies for each procedure. The calculation principles and model figures are presented in the Supplementary material (pages 47–49, 52–53).

considered limited/standard PLND to have 1.5 times the risk of bleeding requiring reoperation compared to no PLND, and extended PLND to have twice the risk of bleeding. These estimates were based on advice from two leading authorities in urological surgery (Supplementary material, pages 38–40 and 45–46).

2.5.6. Quality of evidence

We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to rate the quality of evidence (also known as certainty or confidence in evidence; Table 1) [28,29]. The quality of a body of evidence from observational studies addressing a question of prognosis begins as high quality; in all cases, we rated down to moderate owing to uncertainties in our model of risk of VTE and bleeding over time and in our model of patient risk strata [4]. When identified, we further rated down for risk of bias, inconsistency of results, indirectness of evidence, or imprecision (Table 1).

Table 3 – Summary of the studies included by procedure

Procedure	Studies (patients)		Recruitment period	Median patient age (yr)	Women (%)	Studies reporting PX, n (%) ^a
	Found	Included				
Cystectomy, open	15 (4130)	9 (3036)	1993–2010	69	25	9 (100)
Cystectomy, robotic	5 (1320)	5 (1320)	2002–2013	69	18	4 (80)
Partial nephrectomy, laparoscopic	10 (4036)	10 (4036)	1998–2011	60	38	4 (40)
Partial nephrectomy, open	8 (4794)	8 (4794)	1995–2012	61	32	3 (38)
Partial nephrectomy, robotic	5 (1935)	2 (1331)	2006–2014	60	41	2 (100)
Radical nephrectomy, laparoscopic	3 (196)	3 (196)	1999–2006	61	33	2 (67)
Radical nephrectomy, open	3 (5334)	3 (5334)	1995–2012	63	NR	0 (0)
Radical nephrectomy with thrombectomy	3 (298)	3 (298)	1995–2012	63	35	2 (67)
Nephroureterectomy, open	1 (293)	1 (293)	2005–2012	NR	NR	0 (0)
Radical penectomy with inguinal LAD	1 (1435)	1 (1435)	2005–2011	NR	0	0 (0)
Primary nerve-sparing RPLND	3 (872)	3 (872)	1995–2011	30	0	1 (50)
Prostatectomy, laparoscopic	4 (7116)	2 (1051)	1998–2005	62	0	2 (100)
Prostatectomy, open	13 (23 036)	5 (4001)	1993–2009	63	0	5 (100)
Prostatectomy, robotic	14 (11 355)	7 (6362)	1999–2011	61	0	7 (100)

PX = prophylaxis; LAD = lymphadenectomy; RPLND = retroperitoneal lymph node dissection.
 If the same patients (same time frame and same institute[s]) were included in more than one study, we included the most comprehensive study. Where possible, we used only studies with a low risk of bias (Table 2; Supplementary material, pages 23–31, 91–93). Age is the median of the means or medians reported in the individual studies (Supplementary material, pages 23–26). The median proportion of women is reported (Supplementary material, pages 23–26).
^a Studies included that reported prophylaxis, including type, number of patients, and duration (Supplementary material, pages 32–34).

3. Evidence synthesis

3.1. Literature search

For baseline risk estimation, of 1153 potentially relevant titles and abstracts identified by the search and 89 articles provided by the content experts, we judged 311 as warranting full-text review; of these, 71 reports addressing 14 urological cancer procedures proved eligible (some articles reported on multiple procedures; a flow chart is provided in the Supplementary material, page 84): cystectomy (open and robotic), partial nephrectomy (laparoscopic, open, and robotic), radical nephrectomy (laparoscopic and open), radical nephrectomy with thrombectomy, open nephroureterectomy, radical penectomy with inguinal lymphadenectomy, primary nerve-sparing retroperitoneal lymph node dissection, and prostatectomy (laparoscopic, open and robotic; Table 3). On the basis of these studies, we created 20 evidence profiles of risk of VTE and bleeding after urological cancer surgery procedures (for each prostatectomy approach, we further stratified by no PLND or limited/standard PLND [Supplementary material, pages 38–40], resulting in a total of 9 prostatectomy procedures; for penectomy, we were able to create estimates for VTE but not for bleeding), as presented in the Supplementary material (pages 3–22). Of the 71 studies, the authors of 64 (90%) confirmed the accuracy of our data extraction, corrected errors, and/or provided the additional information requested (Supplementary material, page 88).

3.2. Study characteristics and quality of evidence

Table 3 presents the characteristics of the studies for each procedure (more details are available in the Supplementary material, pages 23–26). For the baseline risk of VTE and

bleeding, the median of the mean/median ages was 69 yr for cystectomy, 62 yr for prostatectomies, 61 yr for renal procedures, and 30 yr for primary nerve-sparing retroperitoneal lymph node dissection (Table 3). Among the eligible studies, seven had high and 11 had low risk of bias for cystectomies, 16 had high and 14 had low risk of bias for prostatectomies, and 21 had high and five had low risk of bias for renal procedures (Supplementary material, pages 27–31). Overall, the quality of evidence was generally moderate for prostatectomy and cystectomy, and low or very low for renal/other procedures (Tables 4–6; Supplementary material, pages 3–22).

3.3. Thromboprophylaxis use

All prostatectomy (open, laparoscopic, and robotic) and open cystectomy studies, as well as four of five (80%) robotic cystectomy studies reported on use of thromboprophylaxis; rates varied widely for renal procedures (median 40%, interquartile range [IQR] 19–675; Table 3). Among the studies providing this information, the duration of thromboprophylaxis was longest for cystectomies (median 21.1 d, IQR 15.0–28.0); shorter for prostatectomies (median 6 d, IQR 1.4–13.6), and shortest for renal procedures (median 2.9 d, IQR 1.9–4.0), and was highly variable (Supplementary material, pages 32–34).

3.4. The 4-wk postoperative risk of symptomatic VTE and bleeding requiring reoperation

The 4-wk risk of VTE varied widely among procedures, and between approaches for the same procedure (Tables 4–6; Supplementary material, pages 35–37). Patients undergoing cystectomy (both open and robotic) were at high risk of VTE (2.6–11.6% across risk groups) but at low risk of

Table 4 – The 4-wk postoperative risk of symptomatic nonfatal venous thromboembolism and bleeding requiring reoperation after radical cystectomy

Procedure	Outcome	Studies (patients)	Estimate by patient risk strata (%)	Certainty in estimate
Open radical cystectomy	Venous thromboembolism	9 (3036)	Low risk: 2.9	Moderate
			Medium risk: 5.8	Moderate
			High risk: 11.6	Moderate
Robotic radical cystectomy	Venous thromboembolism	5 (1320)	Low risk: 2.6	Low
			Medium risk: 5.2	Low
			High risk: 10.3	Low
	Bleeding requiring reoperation	3 (1185)	0.3	Low

For more details, see the Supplementary material, pages 3–4.

Table 5 – The 4-wk postoperative risk of symptomatic nonfatal venous thromboembolism and bleeding requiring reoperation after radical prostatectomy (RP)

Procedure	Outcome	Studies (patients)	Estimate by patient risk strata (%)	Certainty in estimate
Laparoscopic RP without PLND	Venous thromboembolism	2 (1051)	Low risk: 0.4	Moderate
			Medium risk: 0.8	Moderate
			High risk: 1.5	Moderate
Laparoscopic RP with standard PLND	Venous thromboembolism	2 (1051)	Low risk: 0.8	Moderate
			Medium risk: 1.5	Moderate
			High risk: 3.0	Moderate
Laparoscopic RP with extended PLND	Venous thromboembolism	2 (1051)	Low risk: 1.5	Moderate
			Medium risk: 3.0	Moderate
			High risk: 6.0	Moderate
Open RP without PLND	Venous thromboembolism	5 (4001)	Low risk: 1.0	Moderate
			Medium risk: 2.0	Moderate
			High risk: 3.9	Moderate
Open RP with standard PLND	Venous thromboembolism	5 (4001)	Low risk: 2.0	Moderate
			Medium risk: 3.9	Moderate
			High risk: 7.9	Moderate
Open RP with extended PLND	Venous thromboembolism	5 (4001)	Low risk: 3.9	Moderate
			Medium risk: 7.9	Moderate
			High risk: 15.7	Moderate
Robotic RP without PLND	Venous thromboembolism	7 (6362)	Low risk: 0.2	Moderate
			Medium risk: 0.5	Moderate
			High risk: 0.9	Moderate
Robotic RP with standard PLND	Venous thromboembolism	7 (6362)	Low risk: 0.5	Moderate
			Medium risk: 0.9	Moderate
			High risk: 1.9	Moderate
Robotic RP with extended PLND	Venous thromboembolism	7 (6362)	Low risk: 0.9	Moderate
			Medium risk: 1.9	Moderate
			High risk: 3.7	Moderate
	Bleeding requiring reoperation	6 (6055)	0.8	Moderate

PLND = pelvic lymph node dissection.
For more details, see the Supplementary material, pages 14–22.

bleeding requiring reoperation (0.3%; Table 4). Depending on the patient risk group, the incidence of VTE in prostatectomies varied from 0.2–0.9% in robotic prostatectomy without PLND (0.4% for bleeding risk) to 3.9–15.7% for open prostatectomy with extended PLND (0.2% bleeding

risk). The risk of VTE was highest after open prostatectomy, followed by laparoscopic and robotic (lowest) prostatectomies, while the risk of bleeding was highest after laparoscopic prostatectomy, followed by robotic and open approaches (Table 5). The risk of VTE in renal procedures

Table 6 – The 4-wk postoperative risk of symptomatic nonfatal venous thromboembolism and bleeding requiring reoperation after kidney surgery, radical penectomy with inguinal lymphadenectomy, and primary nerve-sparing retroperitoneal lymph node dissection

Procedure	Outcome	Studies (patients)	Estimate by patient risk strata (%)	Certainty in estimate
Laparoscopic partial nephrectomy	Venous thromboembolism	7 (2848)	Low risk: 1.1 Medium risk: 2.1 High risk: 4.2	Low Low Low
	Bleeding requiring reoperation	7 (2087)	1.7	Low
Open partial nephrectomy	Venous thromboembolism	6 (3614)	Low risk: 1.0 Medium risk: 2.0 High risk: 3.9	Very low Very low Very low
	Bleeding requiring reoperation	2 (1139)	0.1	Moderate
Robotic partial nephrectomy	Venous thromboembolism	2 (1331)	Low risk: 1.0 Medium risk: 1.9 High risk: 3.9	Moderate Moderate Moderate
	Bleeding requiring reoperation	2 (1331)	0.5	Moderate
Laparoscopic radical nephrectomy	Venous thromboembolism	3 (196)	Low risk: 0.7 Medium risk: 1.3 High risk: 2.6	Very low Very low Very low
	Bleeding requiring reoperation	2 (130)	0.5	Very low
Open radical nephrectomy	Venous thromboembolism	3 (5334)	Low risk: 1.1 Medium risk: 2.2 High risk: 4.4	Low Low Low
	Bleeding requiring reoperation	2 (1139)	0.05	Very low
Radical nephrectomy with thrombectomy	Venous thromboembolism	3 (298)	Low risk: 2.9 Medium risk: 5.8 High risk: 11.6	Very low Very low Very low
	Bleeding requiring reoperation	3 (298)	2.0	Very low
Open nephroureterectomy	Venous thromboembolism	293 (1)	Low risk: 1.6 Medium risk: 3.1 High risk: 6.2	Very low Very low Very low
	Bleeding requiring reoperation	1139 (2)	0.05	Very low
Radical penectomy with inguinal LAD	Venous thromboembolism	1435 (1)	Low risk: 0.8 Medium risk: 1.6 High risk: 3.1	Very low Very low Very low
	Bleeding requiring reoperation	2898 (3)	0.2	Very low
Primary nerve-sparing RPLND	Venous thromboembolism	724 (2)	Low risk: 2.3 Medium risk: 4.5 High risk: 9.1	Very low Very low Very low
	Bleeding requiring reoperation	2898 (3)	0.2	Very low

LAD = lymphadenectomy; RPLND = retroperitoneal lymph node dissection.
For more details, see the Supplementary material, pages 5–13.

varied from 0.7–2.9% for low-risk patients to 2.6–11.6% for high-risk patients, and the risk of bleeding ranged between 0.1% and 2.0% (Table 6). The risk of VTE was between 0.8% and 3.1% in radical penectomy with inguinal lymphadenectomy, and between 2.3% and 9.1% in primary nerve-sparing retroperitoneal lymph node dissection (Table 6).

3.5. Discussion

This systematic review provides the first available summary of the relevant literature from observational studies to generate the current best estimates of baseline risk of symptomatic VTE and serious bleeding for major cancer surgeries in urology. This essential step informs patients, clinicians, guideline panelists, and policy makers in making optimal treatment decisions regarding the use of thromboprophylaxis in urological surgery. Our study also provides novel approaches to improve systematic reviews of risks of prognosis and baseline risk.

Among urological cancer procedures we found high baseline risk of VTE at 4 wk for open (2.9–11.6%) and robotic

(2.6–10.3%) cystectomy, which varied by patient factors (age, body mass index, and personal or family history of VTE; Table 4). Open radical prostatectomy had a considerably higher risk of VTE (1.0–15.7%) compared to robotic (0.2–3.7%) and laparoscopic approaches (0.4–6.0%), which varied by patient risk factors and increased with the extent of lymph node dissection (Table 5). These findings may be due to differences between open and minimally invasive approaches, as well as to differences in patient populations and postoperative care. Certainty in estimates for these procedures proved typically moderate (Tables 4 and 5).

For renal and other procedures such as radical nephrectomy, partial nephrectomy, nephroureterectomy, and retroperitoneal lymph node dissection, we found that bleeding risk was typically low, although variable (0.1 to 2.0% across procedures); the range for VTE risk depended on patient risk factors and procedure (0.7–11.6% across procedures; Table 6). The quality of evidence regarding these estimates, in part as a consequence of the high risk of bias associated with the available studies, is low or very low.

3.6. Strengths and limitations

The strengths of our study include a contemporary and procedure-specific search, rigorous adherence to methodological standards that include duplicate assessment of eligibility and data abstraction, checking of abstracted data by a methodologist clinician, and systematic appraisal of the risk of bias. Our work also benefited from successful communication with the authors of the studies included, which provided much more complete data than the original publications alone. To optimize applicability to current practice, when adequate data were available we used only studies in which most of the patients underwent surgery in 2000 or thereafter. We developed novel methods to construct models for estimation that considered length of follow-up, use of thromboprophylaxis, and patient risk factors. We applied the GRADE approach in assessing the quality of evidence for each outcome.

The limitations of our review include the less established indexing for observational studies compared to RCTs, and therefore the possibility that our search failed to identify some otherwise eligible studies. Many studies that we did identify, despite reporting on bleeding, did not report patient-important outcomes of interest, but rather surrogates such as blood loss during surgery or perioperative changes in hemoglobin levels [30,31]. We also had to exclude many studies that failed to distinguish the type of procedure, such as whether prostatectomy or nephrectomy was open, laparoscopic, or robotic [32]. In addition, of the studies that distinguished the type of procedure and reported estimates of symptomatic VTE or bleeding, many did not provide information on the use of thromboprophylaxis or the precise length of follow-up [33–40]. For a number of estimates, we needed to use modeling approaches to deal with uncertainties, and assumptions for these models are open to question.

3.7. Implications of the findings

Our results have important implications for the practice of urological surgery worldwide. Anecdotally, and in the formal comparisons undertaken, post-discharge thromboprophylaxis practice varies widely both within and between countries. Our results are consistent with this evidence [10–14]: we found that there was very large variation in the use of thromboprophylaxis across studies.

Particularly when the trade-offs between VTE prevention and bleeding risk are clear, such variation is problematic. High VTE risk and low bleeding risk establish a net benefit of prophylaxis for all patient risk groups in open and robotic cystectomy, and in open prostatectomy with or without PLND. Low risk of VTE and higher bleeding risk establish a net benefit of withholding prophylaxis in patients undergoing laparoscopic or robotic prostatectomy without PLND who have clinical features placing them at low risk of VTE. Thus, our results facilitate rationalization of practice and a reduction in unwarranted practice variation.

When trade-offs are closer (including robotic partial nephrectomy in low-risk patients and robotic prostatectomy with standard PLND in patients with low or medium risk) or estimates are very uncertain (including many renal cancer surgery procedures), optimal prophylaxis practice may reasonably vary. Our work has identified areas in which the evidence is of low or very low quality. These should constitute research priorities. Furthermore, we have identified methodological standards for such research, including comprehensive characterization of patient populations and follow-up times, documentation of prophylaxis used, and documentation of DVT, PE, and reproducible bleeding assessments.

Meanwhile, for procedures for which the evidence is of low quality, or for which VTE and bleeding are closely balanced, practice should be based on patients' values and preferences, which may or may not differ between countries. Additional study of patient preferences for those procedures for which we identified close or uncertain trade-offs could further rationalize the practice of thromboprophylaxis in urologic surgery.

4. Conclusions

We performed a series of systematic reviews to provide estimates of absolute risk of symptomatic VTE and bleeding requiring reoperation in urologic cancer surgery. Our results demonstrate that in some procedures, extended thromboprophylaxis, for instance pharmacological prophylaxis 4 wk post surgery, results in substantial reduction in VTE with only modest or minimal increases in bleeding. For such procedures, which include open and robotic cystectomy and open prostatectomy, prophylaxis is warranted. For other procedures (laparoscopic or robotic prostatectomy in low-risk patients), prophylaxis is associated with a minimal reduction in VTE but appreciable bleeding, and is not warranted. Variation in practice in such procedures is problematic. For other procedures with a closer trade-off and greater uncertainty, variation in practice is anticipated and acceptable.

Author contributions: Kari A.O. Tikkinen had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Tikkinen, Guyatt.

Acquisition of data: Tikkinen, Craigie, Agarwal, Violette, Novara, Cartwright, Naspro, Siemieniuk, Ali, Eryuzlu, Geraci, Winkup, Yoo.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.eururo.2017.02.025>.

References

- [1] National Health Service. What HES data are available? www.hscic.gov.uk/hesdata. Accessed May 16 2016.
- [2] Pearse RM, Moreno RP, Bauer P, et al. Mortality after surgery in Europe: a 7 day cohort study. *Lancet* 2012;380:1059–65.
- [3] Noordzij PG, Poldermans D, Schouten O, Bax JJ, Schreiner FA, Boersma E. Postoperative mortality in The Netherlands: a population-based analysis of surgery-specific risk in adults. *Anesthesiology* 2010;112:1105–15.
- [4] Tikkinen KA, Agarwal A, Craigie S, et al. Systematic reviews of observational studies of risk of thrombosis and bleeding in urological surgery (ROTBUS): introduction and methodology. *Syst Rev* 2014;3:150.
- [5] National Institute for Health and Care Excellence. NICE clinical guideline (CG92). Venous thromboembolism: reducing the risk for patients in hospital. www.nice.org.uk/guidance/cg92.
- [6] Forrest JB, Clemens JQ, Finamore P, et al. AUA best practice statement for the prevention of deep vein thrombosis in patients undergoing urologic surgery. *J Urol* 2009;181:1170–7.
- [7] Tyson MD, Castle EP, Humphreys MR, Andrews PE. Venous thromboembolism after urological surgery. *J Urol* 2014;192:793–7.
- [8] Violette PD, Cartwright R, Briel M, Tikkinen KA, Guyatt GH. Guideline of guidelines: thromboprophylaxis for urologic surgery. *BJU Int* 2016;118:351–8.
- [9] Eberli D. Optimal thromboprophylaxis remains a challenge. *BJU Int* 2016;118:342.
- [10] Galvin DJ, Mulvin D, Quinlan DM. Thromboprophylaxis for radical prostatectomy: a comparative analysis of present practice between the USA, the UK, and Ireland. *Prostate* 2004;60:338–42.
- [11] Soloway MS. Thromboembolism prophylaxis and total prostatectomy: is pharmacologic therapy required? *Eur Urol* 2008;53:21–3.
- [12] Pridgeon S, Allchorne P, Turner B, Peters J, Green J. Venous thromboembolism (VTE) prophylaxis and urological pelvic cancer surgery: a UK national audit. *BJU Int* 2015;115:223–9.
- [13] Weinberg A, Wright J, Deibert C, et al. Nationwide practice patterns for the use of venous thromboembolism prophylaxis among men undergoing radical prostatectomy. *World J Urol* 2014;32:1313–21.
- [14] Benyo M, Harsfalvi J, Pfliegler G, et al. Present practice of thrombosis prophylaxis of radical prostatectomy in a European country: a Hungarian multicenter study. *Urol Int* 2014;92:289–93.
- [15] Moher D, Liberati A, Tetzlaff J, Altman DG. PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009;339:b2535.
- [16] Guyatt GH, Oxman AD, Vist G, et al. GRADE guidelines: 4. Rating the quality of evidence—study limitations (risk of bias). *J Clin Epidemiol* 2011;64:407–15.
- [17] Kim SY, Park JE, Lee YJ, et al. Testing a tool for assessing the risk of bias for nonrandomized studies showed moderate reliability and promising validity. *J Clin Epidemiol* 2013;66:408–14.
- [18] Neumann I, Rada G, Claro JC, et al. Oral direct factor Xa inhibitors versus low-molecular-weight heparin to prevent venous thromboembolism in patients undergoing total hip or knee replacement: a systematic review and meta-analysis. *Ann Intern Med* 2012;156:710–9.
- [19] Devereaux PJ, Mrkobra M, Sessler DI, et al. Aspirin in patients undergoing noncardiac surgery. *N Engl J Med* 2014;370:1494–503.
- [20] Pulmonary Embolism Prevention Trial Collaborative Group. Prevention of pulmonary embolism and deep vein thrombosis with low dose aspirin: Pulmonary Embolism Prevention (PEP) trial. *Lancet* 2000;355:1295–302.
- [21] O’Connell S, Bashir K, Broderick BJ, et al. The use of intermittent pneumatic compression in orthopedic and neurosurgical postoperative patients: a systematic review and meta-analysis. *Ann Surg* 2016;263:888–9.
- [22] Amin AN, Lenhart G, Princic N, Lin J, Thompson S, Johnston S. Retrospective administrative database study of the risk the time period of venous thromboembolism risk during and following hospitalization for major orthopedic or abdominal surgery in real-world US patients. *Hosp Pract* 2011;39:7–17.
- [23] Sweetland S, Green J, Liu B, et al. Duration and magnitude of the postoperative risk of venous thromboembolism in middle aged women: prospective cohort study. *BMJ* 2009;339:b4583.
- [24] Musch M, Klevecka V, Roggenbuck U, Kroepfl D. Complications of pelvic lymphadenectomy in 1,380 patients undergoing radical retropubic prostatectomy between 1993 and 2006. *J Urol* 2008;179:923–8.

- [25] Lindberg C, Davidsson T, Gudjónsson S, Hilmarsson R, Liedberg F, Bratt O. Extended pelvic lymphadenectomy for prostate cancer: will the previously reported benefits be reproduced in hospitals with lower surgical volumes? *Scand J Urol* 2009;43:437–41.
- [26] Eifler JB, Levinson AW, Hyndman ME, Trock BJ, Pavlovich CP. Pelvic lymph node dissection is associated with symptomatic venous thromboembolism risk during laparoscopic radical prostatectomy. *J Urol* 2011;185:1661–5.
- [27] Van Hemelrijck M, Garmo H, Holmberg L, et al. Thromboembolic events following surgery for prostate cancer. *Eur Urol* 2013;63:354–63.
- [28] Guyatt GH, Oxman AD, Kunz R, et al. What is 'quality of evidence' and why is it important to clinicians? *BMJ* 2008;336:995–8.
- [29] Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;336:924–6.
- [30] Patel T, Kirby W, Hruby G, Benson MC, McKiernan JM, Badani K. Heparin prophylaxis and the risk of venous thromboembolism after robotic-assisted laparoscopic prostatectomy. *BJU Int* 2011;108:729–32.
- [31] Ng CK, Kauffman EC, Lee MM, et al. A comparison of postoperative complications in open versus robotic cystectomy. *Eur Urol* 2010;57:274–81.
- [32] Trinh VQ, Karakiewicz PI, Sammon J, et al. Venous thromboembolism after major cancer surgery: temporal trends and patterns of care. *JAMA Surg.* 2014;149:43–9.
- [33] Maffezzini M, Campodonico F, Capponi G, Manuputty E, Gerbi G. Fast-track surgery and technical nuances to reduce complications after radical cystectomy and intestinal urinary diversion with the modified Indiana pouch. *Surg Oncol* 2012;21:191–5.
- [34] Arumainayagam N, McGrath J, Jefferson KP, Gillatt DA. Introduction of an enhanced recovery protocol for radical cystectomy. *BJU Int* 2008;101:698–701.
- [35] James AC, Holt SK, Wright JL, Porter MP, Gore JL. Burden and timing of venothrombotic events in patients younger than 65 years undergoing radical cystectomy for bladder cancer. *Urol Oncol* 2014;32:815–9.
- [36] VanDluc AA, Cowan NG, Chen Y, et al. Timing, incidence and risk factors for venous thromboembolism in patients undergoing radical cystectomy for malignancy: a case for extended duration pharmacological prophylaxis. *J Urol* 2014;191:943–7.
- [37] Desai MM, de Castro Abreu AL, Leslie S, et al. Robotic partial nephrectomy with superselective versus main artery clamping: a retrospective comparison. *Eur Urol* 2014;66:713–9.
- [38] Hu JC, Treat E, Filson CP, et al. Technique and outcomes of robot-assisted retroperitoneoscopic partial nephrectomy: a multicenter study. *Eur Urol* 2014;66:542–9.
- [39] Sun AJ, Djaladat H, Schuckman A, Miranda G, Cai J, Daneshmand S. Venous thromboembolism following radical cystectomy: significant predictors, comparison of different anticoagulants and timing of events. *J Urol* 2015;193:565–9.
- [40] Tyritzis SI, Wallerstedt A, Steineck G, et al. Thromboembolic complications in 3,544 patients undergoing radical prostatectomy with or without lymph node dissection. *J Urol* 2015;193:117–25.

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