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

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Abstract

Context: Pharmacological thromboprophylaxis involves a trade-off between a reduction in venous thromboembolism (VTE) and increased bleeding. No guidance specific for procedure and patient factors exists in urology.
Objective: To inform estimates of absolute risk of symptomatic VTE and bleeding requiring reoperation in urological non-cancer surgery.
Evidence acquisition: We searched for contemporary observational studies and estimated the risk of symptomatic VTE or bleeding requiring reoperation in the 4 wk after urological surgery. We used the GRADE approach to assess the quality of the evidence.
Evidence synthesis: The 37 eligible studies reported on 11 urological non-cancer procedures. The duration of prophylaxis varied widely both within and between procedures; for example, the median was 12.3 d (interquartile range [IQR] 3.1–55) for open recipient nephrectomy (kidney transplantation) studies and 1 d (IQR 0–1.3) for percutaneous nephrolithotomy, open prolapse surgery, and reconstructive pelvic surgery studies. Studies of open recipient nephrectomy reported the highest risks of VTE and bleeding (1.8–7.4% depending on patient characteristics and 2.4% for bleeding). The risk of VTE was low for 8/11 procedures (0.2–0.7% for patients with low/medium risk; 0.8–1.4% for high risk) and the risk of bleeding was low for 6/7 procedures ($\leq$0.5%; no bleeding estimates for 4 procedures). The quality of the evidence supporting these estimates was low or very low.
Conclusions: Although inferences are limited owing to low-quality evidence, our results suggest that extended prophylaxis is warranted for some procedures (eg, kidney transplantation procedures in high-risk patients) but not others (transurethral resection of the prostate and reconstructive female pelvic surgery in low-risk patients).

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Patient summary: The best evidence suggests that the benefits of blood-thinning drugs to prevent clots after surgery outweigh the risks of bleeding in some procedures (such as kidney transplantation procedures in patients at high risk of clots) but not others (such as prostate surgery in patients at low risk of clots).

1. Introduction

The volume of urological non-cancer surgery worldwide is large. In the UK alone, urologists plan more than 200 000 urological operations yearly [1]. Almost all patients undergoing such surgical procedures are at risk of deep vein thrombosis (DVT) and pulmonary embolism (PE)—together referred to as venous thromboembolism (VTE)—and major bleeding.

Whether to use thromboprophylaxis depends on the trade-off between a reduction in VTE and an increase in bleeding [2]. The benefits and harms of thromboprophylaxis critically depend on the risk of VTE and bleeding in those not receiving thromboprophylaxis, which we refer to as *baseline risk*. Prophylaxis is warranted when the baseline risk of VTE is high and the risk of bleeding is low, but not in those with low VTE risk and high bleeding risk.

Although the baseline risks of VTE and bleeding in the absence of prophylaxis vary widely between urological procedures [3,4], their specific magnitude has not been established. This uncertainty is, at least in part [4,5], responsible for substantial practice variation in the use of thromboprophylaxis in urology, both within and between countries [6–9]. In an accompanying paper, we provide baseline risk estimates of VTE and bleeding for surgery in malignant diseases of the urinary tract and male genital system [7]. Here, we summarize the evidence regarding risks of VTE and bleeding in urological non-cancer surgery.

2. Evidence acquisition

Our study protocol, which was prospectively registered (PROSPERO: CRD42014010342) and previously published [2], followed PRISMA guidance [10]. Our methods follow those presented in detail previously [2,7]; here, we summarize in brief.

2.1. Eligibility

We included observational studies published in English in which investigators enrolled at least 50 adult patients undergoing procedures for non-malignant diseases of the urinary tract or male genital system. Eligible studies reported absolute estimates of risk for one or more of the outcomes of interest: fatal PE, symptomatic PE, symptomatic DVT, symptomatic VTE, fatal bleeding, and bleeding requiring reoperation.

2.2. Data sources and searches

For the baseline risk of VTE and bleeding [2], we conducted a comprehensive systematic search, developed together with experienced research librarians (N.B. and L.B.), of MEDLINE from January 1, 2000 to January 1, 2016 (Supplementary material, pages 58–63). We performed additional searches: (1) for patient-related risk factors for VTE and bleeding after surgery; (2) for cohort studies addressing timing of VTE and bleeding after surgery to inform modeling of outcomes for studies with varying follow-up; and (3) for randomized trials addressing the effects of pharmacological and mechanical thromboprophylaxis on VTE and bleeding risk after surgery to calculate baseline risks in patients not receiving prophylaxis (Supplementary material, pages 64–68).

2.3. Study selection and data abstraction

We used standard methods for systematic reviews for independent duplicate screening and data extraction [2,7]. To confirm the accuracy of the data extracted, and if necessary to clarify missing or unclear information, we contacted the authors of all the original articles.

2.4. Risk of bias

Through iterative discussion and consensus-building, and informed by the prior literature [11,12], we developed a novel instrument to categorize studies as either at low or high risk of bias (RoB) in their estimates of VTE or bleeding risk [2,7]. Items included the representativeness of the patient population, thromboprophylaxis documentation, data sources, 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 17).

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, as well as fatal PE and fatal bleeding. We analyzed all outcomes separately for each type of procedure.

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

In calculating VTE and bleeding risk, we adjusted analyses for the extent of thromboprophylaxis use (Supplementary material, pages 27–28, 30, 34–57), as described in an accompanying paper. For studies that did not report on use of thromboprophylaxis, we estimated thromboprophylaxis use (Supplementary material, page 29).

2.5.3. Choosing the best estimates

We used the median value of estimates from eligible studies to estimate baseline risk of VTE and bleeding requiring reoperation [2].

Table 1 – Model for risk of venous thromboembolism (VTE) 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×

We developed a very simple model for VTE risk based on studies reporting the most relevant and compelling evidence [2] 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 for each procedure, we estimated the proportion of patients having each of the risk factors using eligible studies. The calculation principles and model figures are presented in the Supplementary material, pages 31–33 and 36–37.

2.5.4. 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 1; Supplementary material, pages 31–33, 36–37) [2,7].

2.5.5. Quality of evidence

We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) to rate the quality of evidence (also known as certainty or confidence in evidence) [7,13,14]. The quality of a body of evidence drawn from observational studies addressing a question of prognosis begins as "high quality"; in all cases, we rated down to "moderate quality" because of uncertainties in our modeling of the risks of VTE and bleeding over time (Supplementary material, pages 34–35) and in our model of patient risk strata (Table 1) [2,7]. Whenever identified, we further rated down for RoB, inconsistency of results, indirectness of evidence, or imprecision [7].

3. Evidence synthesis

3.1. Literature search

For baseline risk estimation, of the 1153 potentially relevant titles and abstracts identified by the search and 88 articles provided by the content experts, we judged 311 as warranting full-text review. Of these, 38 reports addressing 11 urological non-cancer procedures proved eligible (some articles reported on multiple procedures; further details, including a flow chart, are provided in the Supplementary material, pages 69–71): laparoscopic donor nephrectomy (11 studies), open donor nephrectomy (3 studies), open recipient nephrectomy (5 studies), percutaneous nephrolithotomy (PCNL; 4 studies), transurethral resection of the prostate (TURP) or equivalent (8 studies), open prolapse surgery (3 studies), and reconstructive pelvic surgery (addressing vaginal prolapse and sling surgery; 6 studies) reporting on both VTE and bleeding, and artificial urinary sphincter procedure (1 study), open simple prostatectomy (1 study), sling surgery for male stress urinary incontinence (1 study), and urethroplasty (1 study) reported only on VTE (Table 2). On the basis of these studies, we created seven evidence profiles of the risks of VTE and bleeding and four evidence profiles without information on bleeding (Supplementary material, pages 3–13). Of the 38 primary study authors contacted, 22 (58%) confirmed the accuracy of our data extraction, corrected errors, and/or provided additional information (Supplementary material, page 72).

3.2. Study characteristics and quality of evidence

Table 2 presents the characteristics of the studies for each procedure (more details are available in the Supplementary material, pages 14–16). The median of the mean/median ages varied from 47 yr for donor and recipient nephrectomies to 71 yr for TURP or its equivalent (Table 2). Eligible studies included two low RoB and 17 high RoB studies for

Table 2 – Summary of studies included by procedure [a]

Procedure	Studies found, *n* (patients)	Patient recruitment years	Median patient age (yr)	Proportion of women (%)	Studies reporting prophylaxis, *n* (%)
Artificial urinary sphincter	1 (419)	2005–2011	NR	0	0 (0)
Prostatectomy, open simple	1 (232)	2005–2011	NR	0	0 (0)
Sling surgery for male stress urinary incontinence	1 (475)	2005–2011	NR	0	0 (0)
TURP or equivalent [b]	8 (13 644)	2002–2011	71	0	4 (67)
Urethroplasty	1 (358)	2005–2011	NR	0	0 (0)
Donor nephrectomy, laparoscopic	11 (1895)	1997–2014	48	58	5 (45)
Donor nephrectomy, open	3 (502)	1997–2010	46	50	0 (0)
Recipient nephrectomy, open	5 (1490)	1991–2011	47	39	4 (80)
Prolapse surgery, open	3 (150)	2002–2010	56	100	2 (67)
Reconstructive pelvic surgery [c]	6 (34 692)	1993–2012	63	100	2 (33)
Percutaneous nephrolithotomy	4 (2497)	1993–2011	53	52	2 (50)

[a] If the same patients (same time frame and same institute[s]) were included in more than one study, we included the most comprehensive study. Age is given as the median of the means or medians reported in the individual studies. The proportion of women is given as the median of the proportions of women reported in the individual studies. Reporting prophylaxis: studies reporting a type of prophylaxis, number of patients, and duration of prophylaxis. For more details, see the Supplementary material, pages 14–26.
[b] Included patients undergoing transurethral resection of the prostate (TURP), laser-TURP, and transurethral vaporization in saline.
[c] Included sling surgery for stress urinary incontinence and vaginal prolapse surgery.

donor and recipient nephrectomies, one low RoB and three high RoB studies for PCNL, three low RoB and five high RoB studies for TURP, two low RoB and one high RoB study for open prolapse surgery, and two low RoB and four high RoB studies for reconstructive pelvic surgery (Supplementary material, pages 18–20). The quality of evidence was low for risk of VTE and risk of bleeding for laparoscopic donor nephrectomy; low for risk of VTE and very low for risk of bleeding for TURP and open prolapse surgery; and very low for risk of both VTE and bleeding for all other procedures (Table 3 and Supplementary material, pages 3–13).

3.3. Thromboprophylaxis use

Most open recipient nephrectomy (80%), open prolapse surgery (67%), and TURP (67%) studies reported information on the use of thromboprophylaxis; rates of reporting of thromboprophylaxis use were lower for other procedures (median 0%, interquartile range [IQR] 0–40%; Table 2). Among the studies providing this information, short duration was reported for PCNL, open prolapse surgery, and reconstructive pelvic surgery (median 1.0 d, IQR 0–1.3), longer for laparoscopic donor nephrectomies (median 3.4 d, IQR 2.0–9.1), and longest for open recipient nephrectomy

Table 3 – The 4-wk postoperative risk of symptomatic nonfatal venous thromboembolism (VTE) and bleeding requiring reoperation (BRR) after urological non-cancer procedures [a]

Procedure	Outcome	Studies, *n* (participants)	Estimate by patient risk strata (%)		Certainty of estimate
Artificial urinary sphincter	VTE	1 (419)	Low risk:	0.3	Very low
			Medium risk:	0.5	Very low
			High risk:	1.0	Very low
	BRR		Not reported		
Prostatectomy, open simple	VTE	1 (232)	Low risk:	2.7	Very low
			Medium risk:	5.4	Very low
			High risk:	10.8	Very low
	BRR		Not reported		
Sling surgery for male stress urinary incontinence	VTE	1 (475)	Low risk:	0.4	Very low
			Medium risk:	0.8	Very low
			High risk:	1.6	Very low
	BRR		Not reported		
Transurethral resection of the prostate (TURP) or equivalent	VTE	4 (13 320)	Low risk:	0.2	Low
			Medium risk:	0.4	Low
			High risk:	0.8	Low
	BRR	4 (756)		0.2	Very low
Urethroplasty	VTE	1 (358)	Low risk:	0.3	Very low
			Medium risk:	0.6	Very low
			High risk:	1.1	Very low
	BRR		Not reported		
Donor nephrectomy, laparoscopic	VTE	8 (1576)	Low risk:	0.4	Low
			Medium risk:	0.7	Low
			High risk:	1.4	Low
	BRR	9 (1723)		0.1	Low
Donor nephrectomy, open	VTE	1 (383)	Low risk:	0.3	Very low
			Medium risk:	0.7	Very low
			High risk:	1.3	Very low
	BRR	9 (1723)		0.1	Very low
Recipient nephrectomy, open	VTE	4 (1350)	Low risk:	1.3	Very low
			Medium risk:	2.7	Very low
			High risk:	5.3	Very low
	BRR	2 (653)		2.3	Very low
Prolapse surgery (open)	VTE	3 (1783)	Low risk:	0.2	Low
			Medium risk:	0.3	Low
			High risk:	0.7	Low
	BRR	2 (150)		0.4	Very low
Reconstructive pelvic surgery [b]	VTE	4 (44 965)	Low risk:	0.1	Very low
			Medium risk:	0.3	Very low
			High risk:	0.5	Very low
	BRR	4 (982)		0.3	Very low
Percutaneous nephrolithotomy	VTE	2 (441)	Low risk:	0.2	Very low
			Medium risk:	0.4	Very low
			High risk:	0.7	Very low
	BRR	5 (2780)		0.9	Low

[a] For more details, see the Supplementary material, pages 3–13.
[b] Included sling surgery for female stress urinary incontinence and vaginal prolapse.

(median 12.3 d, IQR 3.1–55; Supplementary material, pages 21–23).

3.4. Postoperative (4 wk) risk of symptomatic VTE and bleeding requiring reoperation

Patients undergoing open recipient nephrectomy proved at high risk of VTE (range 1.3–5.3% across risk groups) and at appreciable risk of bleeding requiring reoperation (2.3%), whereas patients undergoing donor nephrectomy (both laparoscopic and open) were at lower risk of both VTE (range 0.4–1.4% for laparoscopic and 0.3–1.3% for open across risk groups) and bleeding requiring reoperation (0.1% for both; Table 3 and Supplementary material, pages 24–26). The risks of VTE and bleeding requiring reoperation were <1.0% for all risk groups after TURP, open prolapse surgery, reconstructive pelvic surgery, and PCNL. For a number of procedures, studies reported only VTE risk. For these, the incidence was lowest for artificial urinary sphincter (0.3–1.0%), slightly higher for urethroplasty (0.3–1.10%), somewhat higher for sling surgery for male stress incontinence (0.4–1.6%), and much higher for open simple prostatectomy (2.7–10.8%), with the quality of evidence very low in all cases.

3.5. Discussion

This systematic review provides the first summary of best estimates of the baseline risk of symptomatic VTE and serious bleeding for major non-cancer surgeries in urology. Among urological non-cancer procedures for which we were able to estimate both VTE and bleeding risks, the highest baseline risk of VTE at 4 wk was observed for open recipient nephrectomy (1.3–5.3%), for which the risk varied with patient factors (age, BMI, and personal or family history of VTE; Table 3). Patients undergoing donor nephrectomy were at lower risk of VTE than those undergoing recipient nephrectomy (range 0.4–1.4% for laparoscopic and 0.3–1.3% for open surgery across risk groups). The risk of VTE was <1.0% for all risk groups after TURP, open prolapse surgery, reconstructive pelvic surgery, and PCNL (Table 3).

Among urological non-cancer procedures, studies on open recipient nephrectomy reported the highest baseline risk of bleeding requiring reoperation at 4 wk (2.4%), followed by studies on PCNL (0.9%). The risk of bleeding requiring reoperation was ≤0.5% for all other non-cancer procedures. Certainty for both VTE and bleeding estimates was either low or very low (Table 3).

3.6. Strengths and limitations

The strengths of our study include a contemporary and procedure-specific search; rigorous adherence to methodological standards, including duplicate assessment of eligibility and data abstraction, and checking of abstracted data by a methodologist clinician; systematic appraisal of RoB; and assessment of the quality of evidence using the GRADE system [13,14]. Successful communication with many of the authors of the studies included provided far more complete data than the original publications alone. To optimize the applicability to current practice, we used only studies in which all patients underwent surgery in 1990 or thereafter. We developed novel methods for constructing models for estimation that considered the length of follow-up, the use of thromboprophylaxis, and patient risk factors [2,7].

The limitations of our review are largely those of the original studies. Many studies did not provide information regarding the use of thromboprophylaxis or the precise length of follow-up [15–17]. Studies were generally at high risk of bias; the modeling approaches—including assumptions for thromboprophylaxis use—we needed to use are associated with unavoidable uncertainty, and estimates were often associated with substantial imprecision [7]. As a result, we categorized the evidence as low or very low in quality, reducing the strength of inferences that can be drawn from the evidence.

3.7. Clinical implications

These summaries should have important implications for the practice of urological surgery worldwide. Both anecdotally and in the formal comparisons undertaken, post-discharge thromboprophylaxis practice varies widely both within and between countries. Our results were consistent with this evidence: we found that there was very large variation in the use of thromboprophylaxis across studies [6–8].

When estimates clearly suggest that the benefits of VTE prevention outweigh over risks of bleeding (ie, for all types of kidney transplantation procedure in high-risk patients), or conversely when estimates clearly show that bleeding risks outweigh any benefit from thromboprophylaxis (ie, in TURP, PCNL and reconstructive female pelvic surgery in low-risk patients) such variation is problematic. When the trade-off is closer (for instance, open prolapse surgery in high-risk patients), evaluation of the benefits versus risks of thromboprophylaxis will differ across surgeons and patients, and one would expect practice to vary.

Our work highlights that in non-cancer urology the evidence is of low or very low quality, even for procedures with high volumes and non-negligible risks, including kidney transplantation and TURP. Therefore, the generation of higher-quality evidence should constitute a research priority. This research should adhere to methodological standards that have seldom been observed thus far, including comprehensive characterization of patient populations and follow-up times, documentation of prophylaxis use, and reproducible measurements of DVT, PE, and bleeding. Studies on the importance that patients place on avoiding VTE versus avoiding bleeding would further enhance optimal decision-making regarding thromboprophylaxis for urological procedures.

4. Conclusions

The current evidence suggests a net benefit of VTE prophylaxis for some procedures (kidney transplantation

procedures in high-risk patients) but that bleeding risks outweigh the benefits of thromboprophylaxis (net harm) for others (TURP and reconstructive female pelvic surgery in low-risk patients). The evidence regarding the baseline risk of VTE and bleeding in non-cancer urology is of low or very low quality; generating higher-quality evidence should constitute a research priority.

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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.2015.10.045.

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