available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Platinum Priority – Review – Kidney Cancer
*Editorial by XXX on pp. x–y of this issue*

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

*Kari A.O. Tikkinen [a,*], Samantha Craigie [b,c], Arnav Agarwal [b,d], Philippe D. Violette [e,f], Giacomo Novara [g], Rufus Cartwright [h,i], Richard Naspro [j], Reed A.C. Siemieniuk [b,k], Bassel Ali [b], Leyla Eryuzlu [b,d], Johanna Geraci [b], Judi Winkup [b], Daniel Yoo [b,d], Michael K. Gould [l], Per Morten Sandset [m,n], Gordon H. Guyatt [b,o]*

[a] *Departments of Urology and Public Health, University of Helsinki and Helsinki University Hospital, Helsinki, Finland;* [b] *Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, ON, Canada;* [c] *Michael G. DeGroote National Pain Centre, McMaster University, Hamilton, ON, Canada;* [d] *School of Medicine, University of Toronto, Toronto, ON, Canada;* [e] *Department of Surgery, Division of Urology, Woodstock General Hospital, Woodstock, ON, Canada;* [f] *McMaster Department of Surgery Division of Urology, Hamilton, ON, Canada;* [g] *Department of Surgical, Oncological, and Gastroenterological Sciences, Urology Clinic, University of Padua, Padua, Italy;* [h] *Department of Epidemiology and Biostatistics, Imperial College London, London, UK;* [i] *Department of Urogynaecology, St Mary's Hospital, London, UK;* [j] *Department of Urology, ASST Papa Giovanni XXIII, Bergamo, Italy;* [k] *Department of Medicine, University of Toronto, Toronto, ON, Canada;* [l] *Department of Research and Evaluation, Kaiser Permanente Southern California, Pasadena, CA, USA;* [m] *Institute of Clinical Medicine, University of Oslo, Oslo, Norway;* [n] *Department of Haematology, Oslo University Hospital, Oslo, Norway;* [o] *Department of Medicine, McMaster University, Hamilton, ON, Canada*

**Article info**

***Article history:***
Accepted March 3, 2017

***Associate Editor:***
Christian Gratzke

***Keywords:***
Baseline risk
Bleeding
Modeling
Reporting
Risk of bias
Thromboprophylaxis
Urology
Venous thromboembolism

**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 low-

DOI of original article: http://dx.doi.org/10.1016/j.eururo.2017.02.025.
* Corresponding author. Department of Urology, University of Helsinki and Helsinki University Hospital, Haartmaninkatu 4, Helsinki 00029, Finland. Tel. +358 50 5393222.
E-mail address: kari.tikkinen@gmail.com (Kari A.O. Tikkinen).

http://dx.doi.org/10.1016/j.eururo.2017.03.008


Please cite this article in press as: Tikkinen KAO, et al. Procedure-specific Risks of Thrombosis and Bleeding in Urological Cancer Surgery: Systematic Review and Meta-analysis. Eur Urol (2017), http://dx.doi.org/10.1016/j.eururo.2017.03.008

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.



## 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

Please cite this article in press as: Tikkinen KAO, et al. Procedure-specific Risks of Thrombosis and Bleeding in Urological Cancer Surgery: Systematic Review and Meta-analysis. Eur Urol (2017), http://dx.doi.org/10.1016/j.eururo.2017.03.008