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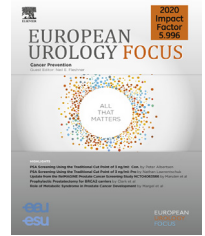
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Epidemiology

An International Survey on the Use of Thromboprophylaxis in Urological Surgery

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Abstract

Background: The use of perioperative thromboprophylaxis in urological surgery is common but not standardized.

Objective: To characterize international practice variation in thromboprophylaxis use in urological surgery.

Design, setting, and participants: We conducted a scenario-based survey addressing the use of mechanical and pharmacological thromboprophylaxis in urological cancer procedures (radical cystectomy [RC], radical prostatectomy [RP], and radical nephrectomy [RN]) among practicing urologists in Canada, Finland, and Japan. The survey presented patient profiles reflecting a spectrum of risk for venous thromboembolism; the respondents described their clinical practice.

Outcome measurements and statistical analysis: The proportion of respondents who routinely used (1) mechanical, (2) pharmacological, and (3) extended pharmacological prophylaxis was stratified by procedure. A logistic regression identified characteristics associated with thromboprophylaxis use.

Results and limitations: Of 1051 urologists contacted, 570 (54%) participated in the survey. Japanese urologists were less likely to prescribe pharmacological prophylaxis than Canadian or Finnish urologists ($p < 0.001$ for all procedures). Canadian and Finnish urologists exhibited large variation for extended pharmacological prophylaxis for RP and RN. Finnish urologists were most likely to prescribe extended prophylaxis versus Canadian and Japanese urologists (RC 98%, 84%, and 26%; Open RP 25%, 8%, and 3%; robotic RP 11%, 9%, and 0%; and RN 43%, 7%, and 1%, respectively; $p < 0.001$ for each procedure). Less variation was found regarding the prescription of mechanical prophylaxis, which was most commonly used until ambulation or discharge. The length of hospital stay was longer in Japan and may bias estimates of extended prophylaxis in Japan.

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Conclusions: We found large variation in clinical practice regarding pharmacological thromboprophylaxis within and between countries. Knowledge translation of evidence-based guidelines may reduce problematic international variation in practice.

Patient summary: Use of medications to decrease blood clots after urological cancer surgery differs within and between countries. Closer adherence to urology guidelines addressing the prevention of blood clots may decrease this variation and improve patient outcomes.

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1. Introduction

Venous thromboembolism (VTE), including deep vein thrombosis and pulmonary embolism, represents a serious and sometimes fatal complication of surgery [1]. Pharmacological prophylaxis decreases the relative risk of VTE in surgical patients by approximately 50%, but with an increase in the relative risk of postoperative major bleeding of 50% [2]. Therefore, the decision to use pharmacological prophylaxis presents a tradeoff between a reduction in VTE and an increase in bleeding [3].

An additional challenge regarding the use of thromboprophylaxis in urology is international clinical practice variation [4–6]. A lack of knowledge of evidence regarding the procedure- and patient-specific baseline risks of thrombosis and bleeding, critical in making an informed decision on the use of thromboprophylaxis, may, at least in part, explain this variation [1,2,7]. Conflicting recommendations from different guidelines and previous lack of guidelines specific to the different urological surgeries may also contribute [3,8]. To further understand international variation in thromboprophylaxis use in urological surgery, we conducted an international survey (International Survey on Use of Thromboprophylaxis in Urological Surgery [ISTHMUS]). Our goal was to characterize the within- and between-country variation in thromboprophylaxis use for common urological procedures.

2. Patients and methods

2.1. Survey

We designed a questionnaire that consisted of three scenarios intended to elicit practice in prescribing both pharmacological and mechanical thromboprophylaxis for radical cystectomy (RC), open and robotic radical prostatectomy (RP), and radical nephrectomy (RN; Table 1). Using the patient risk factor model used in the European Association of Urology (EAU) guideline on thromboprophylaxis in urological surgery [3], the survey presented brief patient profiles that reflected a spectrum of VTE risks (Table 1). Table 2 presents the degree of VTE risk, based on systematic reviews [2], associated with each scenario. This information was not included in the survey and thus was unavailable to participants. Participants indicated their usual practice for each patient profile using response options consisting of single-answer multiple choices (Table 1). Respondents also provided their age, gender, and urologist profile (resident/consultant). A group of clinicians and methodologists generated the items in the questionnaire, which was then pilot tested and reviewed with a group of 20 board-certified urological surgeons from Canada, Finland, and Japan who assessed its face validity.

We performed this survey before the first procedure- and patient-specific thromboprophylaxis guideline in urology—the EAU guideline—was published [3]. We invited actively practicing urologists from Canada, Finland, and Japan to complete the survey. In Canada, we invited Canadian urologists attending the annual meeting of the Canadian Urological Association (CUA), held in Ottawa in June 2015. In Finland and Japan, we identified urologists from the registers of the Finnish Urological Association and the Japanese Urological Association. In Canada, urologists completed the survey at the conclusion of the plenary sessions and at break periods throughout the conference. We collected surveys immediately upon completion and used the number of urologists attending the meeting as the denominator for calculating the response rate (the use of the number of urologists attending the meeting as the denominator likely underestimates the response rate). All urologists in Finland received an invitation to participate by a postal letter. In Japan, a sample of 500 urologists (of whom 487 proved to be eligible) were randomly identified from the national membership directory and invited, by mail, to participate. We mailed the questionnaires between August and September 2015 (first round), and mailed two rounds of reminders in October (second round) and December 2015 (third round). Furthermore,

Table 1 – Scenarios tested in the survey with response options.

<i>Scenario 1 (cystectomy):</i> A 65-yr-old woman who has a BMI of 36 and a personal history of VTE but is otherwise healthy is undergoing an open radical cystectomy. If you were prescribing thromboprophylaxis for this patient, what regimen would you choose most commonly?
<i>Scenario 2 (prostatectomy):</i> A 58-yr-old man with a BMI of 23 and no personal or family history of VTE is undergoing a radical prostatectomy without lymphadenectomy (respondents were asked to select an open or a robotic approach). If you were prescribing thromboprophylaxis for this patient, what regimen would you choose most commonly?
<i>Scenario 3 (nephrectomy):</i> An 80-yr-old man who has a BMI of 24 and no personal or family history of VTE is undergoing an open radical nephrectomy. If you were prescribing thromboprophylaxis for this patient, what regimen would you choose most commonly?
<i>Response options:</i>
Pharmacological prophylaxis:
1. No pharmacological thromboprophylaxis
2. Pharmacological thromboprophylaxis until the patient is ambulating
3. Pharmacological thromboprophylaxis for the duration of hospital stay
4. Pharmacological thromboprophylaxis for the duration of hospital stay and ≤2 wk after discharge
5. Pharmacological thromboprophylaxis for the duration of hospital stay and >2 wk after discharge
Mechanical prophylaxis:
1. No mechanical thromboprophylaxis
2. Mechanical thromboprophylaxis until the patient is ambulating
3. Mechanical thromboprophylaxis for the duration of hospital stay
4. Mechanical thromboprophylaxis for the duration of hospital stay and ≤2 wk after discharge
5. Mechanical thromboprophylaxis for the duration of hospital stay and >2 wk after discharge

BMI = body mass index; VTE = venous thromboembolism.

Table 2 – VTE and major bleeding risk estimates of the presented patient profiles.

Scenario	Operation	Patient risk strata ^a	Risk of VTE (%) ^b	Risk of major bleeding (%) ^c
1	Open radical cystectomy	High risk	11.6	0.3
2	Open radical prostatectomy without lymphadenectomy	Low risk	1.0	0.1
2	Robotic radical prostatectomy without lymphadenectomy	Low risk	0.2	0.4
3	Open radical nephrectomy	Medium risk	2.2	0.1

VTE = venous thromboembolism.
^a Patient risk stratification according to the European Association of Urology guideline on thromboprophylaxis in urological surgery [3].
^b VTE defined as symptomatic pulmonary embolus or deep vein thrombosis within 30 d of surgery [2].
^c Major bleeding defined as bleeding requiring reoperation within 30 d of surgery [2].

we sent an e-mail before each round to inform urologists about the upcoming mail survey.

In Canada, the CUA board of directors, who are independent of study investigators, reviewed the proposal and approved the administration of survey at the CUA annual meeting without requirement for further ethics review. In Finland, the ethics committee of the Helsinki and Uusimaa Hospital District granted exemption from ethical review (R11110). In Japan, the ethics committee of the University of Fukui (Fukui, Japan; #20150067) approved the protocol. The reporting of the study conforms to the STROBE statement [9].

2.2. Statistical analysis

For every patient profile, we calculated the proportion of use of (1) mechanical prophylaxis, (2) pharmacological prophylaxis, and (3) extended pharmacological prophylaxis of ≥ 2 wk and tested for statistical significance using chi-square analysis. As the length of hospital stay varies substantially between countries (considerably longer in Japan than in Canada or Finland; Supplementary Tables 1 and 2), and therefore the implication of prophylaxis during hospital stay differs across jurisdictions (Supplementary material), definitions of extended prophylaxis corresponded to duration of hospital stay in the three countries (Table 1 and Supplementary Table 3). We used multivariable logistic regression adjusted for the included countries to determine whether the urologist profile (resident/consultant) was associated with any mechanical prophylaxis, any pharmacological prophylaxis, or extended prophylaxis. We report the odds ratio and 95% confidence interval for the multivariable logistic regression using a threshold p value of <0.05 . All analyses were performed in SPSS version 20 (IBM Corp., Armonk, NY, USA).

3. Results

The 570 urologists who participated in this survey (Table 3) represent an overall response rate of 54% (Canada: 216 of 385, 57%; Finland: 110 of 179, 61%; and Japan: 244 of 487, 50%). Of the 570 eligible individuals who responded to the survey, 566 (99%) responded to at least five out of six

scenario questions. Most participants were men (89.6% [511/570]); the median age of the participants was 43.0 yr (interquartile range: 35–54) with a majority being consultants (82.5% [470/570]).

Almost all respondents used mechanical prophylaxis for patients undergoing RC (Canada: 92% [199/216], Finland: 96% [106/110], Japan: 96% [234/244], $p = 0.13$; Table 4). More respondents reported using mechanical prophylaxis after an open RP in Japan (98% [239/244]) than in Finland (88% [158/179]) and Canada (79% [171/216], $p < 0.001$). Similarly, after a robotic RP, the Japanese urologists reported a higher rate of mechanical prophylaxis (100%) than the Canadian (81% [175/216]) and Finnish urologists (75% [83/110]; $p < 0.001$). Japanese urologists also reported more use of mechanical prophylaxis after an RN (95% [232/244]) compared with Canadian (84% [181/216]) and Finnish (80% [88/110], $p < 0.001$).

Use of pharmacological prophylaxis of any duration after RC was more common in Canada and Finland (both 99% [208/210, 109/110]) than in Japan (70% [171/244], $p < 0.001$; Table 4). Fewer Japanese respondents indicated that they would use pharmacological prophylaxis after an RP (open RP: 14% [34/244], robotic RP: 33% [81/244]) compared with Canadian (open RP: 93% [201/216], robotic RP: 90% [194/216]) and Finnish (open RP: 88% [97/110], robotic RP: 94% [103/110]) respondents ($p < 0.0001$ for both open and robotic RP). Similarly, more respondents reported using pharmacological prophylaxis after an RN in Finland (95% [105/110]) and Canada (92% [199/216]) than in Japan (20% [49/244], $p < 0.001$).

Finnish and Canadian respondents were more likely to use extended pharmacological prophylaxis after RC (Finland: 98% [108/110], Canada: 84% [181/216]) than Japanese respondents (26% [63/244], $p < 0.001$). It was uncommon for respondents in any country to use extended

Table 3 – Baseline characteristics of the respondents.

	Canada	Finland	Japan	Total
Response (%)	216/385 (57)	110/179 (61)	244/487 (50)	570 (54)
Male (%)	194 (89.8)	91 (82.7)	226 (92.6)	511 (89.6)
Female (%)	19 (8.8) ^a	19 (17.3)	18 (7.4)	56 (9.8)
Age (yr), median (IQR)	38.0 (33–50)	48.0 (30–57.5)	45.0 (38–55)	43.0 (35–54)
Consultant (%)	152 (70.4)	97 (88.2)	221 (90.6)	470 (82.5)
Resident (%)	62 (28.7)	13 (11.8)	22 (9.0)	97 (17.0)

IQR = interquartile range.
^a Three missing values regarding gender in the Canadian sample.

Table 4 – Proportion (in percentages) of those with any duration of mechanical prophylaxis, any duration of pharmacological prophylaxis, and pharmacological prophylaxis of at least 2 wk by procedure and country.

	Open radical cystectomy			Open radical prostatectomy		
	Mechanical, any % (95% CI)	Pharmacological		Mechanical, any % (95% CI)	Pharmacological	
		Any % (95% CI)	Extended % (95% CI)		Any % (95% CI)	Extended % (95% CI)
Canada	92 (87–95)	99 (96–100)	84 (78–88)	79 (70–86)	93 (86–97)	8 (4–15)
Finland	96 (89–98)	99 (94–100)	98 (93–100)	88 (67–97)	88 (67–97)	25 (11–47)
Japan	96 (93–98)	70 (61–73)	26 (21–32)	98 (92–99)	14 (9–22)	3 (1–8)
	Robotic radical prostatectomy			Open radical nephrectomy		
	Mechanical, any % (95% CI)	Pharmacological		Mechanical, any % (95% CI)	Pharmacological	
		Any % (95% CI)	Extended % (95% CI)		Any % (95% CI)	Extended % (95% CI)
Canada	81 (72–88)	90 (82–95)	9 (4–17)	80 (74–85)	92 (87–95)	7 (4–12)
Finland	75 (62–84)	94 (84–98)	11 (5–21)	84 (76–90)	95 (89–98)	43 (34–53)
Japan	100 (98–100)	33 (23–46)	0 (0–2)	95 (91–97)	20 (15–25)	1 (0–3)

CI = confidence interval.

pharmacological prophylaxis after open RP (Japan: 3% [7/244], Canada: 8% [17/216], Finland: 25% [28/110]; $p < 0.001$) and robotic RP (Japan: 0% [0/244], Canada: 9% [19/216], Finland: 11% [12/110]; $p = 0.02$). Finnish respondents (43% [47/110]) were more likely to use extended pharmacological prophylaxis after RN than Canadian (7% [15/216]) or Japanese (1% [2/244]) respondents ($p < 0.001$).

Multivariable analysis, adjusted for the country, demonstrated no difference in resident versus consultant urologists' use of mechanical, pharmacological, or extended pharmacological prophylaxis (Supplementary Table 4).

4. Discussion

This is the first study in urology to examine international variability in the use of thromboprophylaxis between countries in different continents. This large-scale multinational survey identified large variation in the use of pharmacological VTE prophylaxis during hospital stay and in the use of extended prophylaxis after discharge within and between countries. Canadian and Finnish urologists reported similar frequent use of pharmacological prophylaxis, but Japanese respondents reported far less use. Reported use of mechanical prophylaxis for urological procedures had much less variation, both within and between countries. Finally, we found no differences between resident and consultant urologists in the use of mechanical, pharmacological, or extended pharmacological prophylaxis.

4.1. Strengths and limitations

The strengths of the current study include a population representative of the target populations of Canadian, Finnish, and Japanese urologists, in age and gender distribution [10–12]. Our study's strengths also include a satisfactory participation rate and very high completeness

of questionnaire responses. We assessed the use of thromboprophylaxis by clinical case scenarios relevant to current clinical practice.

Our study has limitations. First, as this survey was intended to capture an overview of practice pattern, we are not able to draw conclusion about the causes of the practice variation. We did not ask respondents about their perception of the incidence of VTE—perception of a lower risk in Japan could be responsible for a lower use of pharmacological, but not mechanical, prophylaxis. Whether such differences in incidence actually exist has not been established [2]. Second, how urologists actually practice in a hospital setting might differ from their responses to the scenarios presented in our study. In addition, as thromboprophylaxis is often prescribed by more junior doctors rather than by the operating surgeon, we did not collect data on the specialization of respondents. It is uncertain whether this approach biased estimates. Third, we have used different sampling strategies for Canada from those used for Finland and Japan. This pragmatic decision was based on our goal of including a representative sample in each country. Fourth, many of the respondents do not perform some of the procedures presented. They may, however, still participate in the prescription of thromboprophylaxis. Fifth, we assessed only a limited range of surgeries and scenarios. Fifth, the length of hospital stay was longer in Japan, which may influence the use of extended prophylaxis. Finally, generalization to jurisdictions beyond the three that we included in this survey remains uncertain.

4.2. Comparison with other studies

There are few earlier surveys examining the use of perioperative VTE prophylaxis. A British survey [5], on a mixed population of respondents including 29 consultant

urologists, 30 residents, and 35 urology clinical nurse specialists practicing in 64 UK pelvic cancer centers, found that all units used low-molecular-weight heparin (LMWH) prophylaxis routinely for the inpatient period after RC and 98% used perioperative prophylaxis after RP. Routine use of LMWH for all patients after discharge following RC was reported in 67% and after RP in 61% of units (investigators did not differentiate between approaches, such as open or robotic) [5].

A US database study of 94 709 men who underwent RP (72% open and 28% robotic) found that 52% of men after open RP received mechanical only, 7% pharmacological only, and 11% both mechanical and pharmacological prophylaxis, and 30% received no prophylaxis [6]. Discharge prophylaxis was not included in the scope of this study. Another US study [4] surveyed the members of the American Urological Association in 2011. Only 11% of those invited responded (1210 respondents), of whom approximately 70% for RC and <60% for RP reported the use of any thromboprophylaxis “frequently” or “always” [4]. The authors did not address postdischarge prophylaxis. Although small sample size [5], retrospective database design [6], and low response rate [4] limit the strength of inference from these studies, consistent with our finding, there remains little doubt of considerable variation in practice of thromboprophylaxis in urological procedures both within and between countries.

4.3. Implications of findings

The practice variation that we identified is likely due to several factors. First, the quality of evidence supporting decisions regarding VTE prophylaxis is not of high quality and thus open to variable interpretation [2,13]. Second, the low-quality evidence may also explain the divergent recommendations from several major VTE guidelines in different countries [8]. For instance, prominent VTE guidelines from the American College of Chest Physicians and National Institute for Health and Care Excellence do not consider specific urological surgeries separately but would consider all scenarios in the survey as “abdominopelvic” [14,15]. Third, urologists in some regions may also prefer to defer decisions regarding the use of thromboprophylaxis to colleagues from other disciplines with a different weighing of trade-off between bleeding and VTE from a nonsurgeon point of view. Possibly, VTE risk may also vary by population, given differences in body mass index or age at surgery that may predominate in different regions [14], with choices of prophylaxis appropriately reflecting local risk.

We performed the survey prior to the publication of the systematic reviews addressing estimates of absolute risks of symptomatic VTE and major bleeding in urological surgery [2,13] and an EAU guideline addressing thromboprophylaxis [3], the first procedure and patient risk factor-specific guideline in urology. Therefore, respondents could not have been influenced by these guideline recommendations, and this survey can be used as a benchmark for tracking changes in practice pattern with further dissemination of urology-specific VTE guidelines. Healthcare professionals across

jurisdictions may consider, in their clinical decision making, this evidence-based, procedure-specific guideline [3], which has also been published as a freely available infographic [15]. Doing so would rationalize the practice and may decrease this substantial variation.

In patients at high risk of VTE, for some major surgeries, there is a clear net benefit to extended pharmacological thromboprophylaxis [2,3,16]. Our results suggest that for high-risk VTE and low bleeding risk (scenario 1: cystectomy for high-risk patients, Tables 1 and 2), practice in Canada and Finland follows the EAU guideline more closely [3].

In scenario 2 (RP without lymphadenectomy for low-risk patients; Tables 1 and 2), the EAU guideline suggests the use of extended pharmacological prophylaxis in the open approach but recommends against the use of prophylaxis in robotic prostatectomy without lymphadenectomy [3]. In our survey, participants from Canada and Finland typically reported the use of pharmacological prophylaxis in hospital but not after discharge irrespective of the approach (open vs robotic), whereas one in seven of Japanese urologists after an open approach and one in three after a robotic approach reported in-hospital use of pharmacological prophylaxis.

In scenario 3 (open RN for medium-risk patients; Tables 1 and 2), respondents’ practice in this situation proved to be less aligned with EAU guideline recommendations [3]: Canadian and Finnish respondents tended to report the use of in-hospital prophylaxis but not discharge prophylaxis, while Japanese respondents typically did not report any use of pharmacological prophylaxis.

4.4. Unanswered questions and future research

Variation in practice suggests limited adherence to clinical guidelines, which should represent the best practice for most patients. Therefore, efforts to increase familiarity with EAU guidelines [3]—rigorously evidence-based and the first procedure-specific guideline—may improve patient care. Perioperative VTE guidelines depend on a clear understanding of patient-important trade-offs and the quality of supporting evidence. Therefore, future efforts to improve the body of evidence, especially with the conduct of high-quality trials and observational studies, will result in improved clinical guidance and patient care [3,17,18]. In addition, future surveys are needed to monitor changes in practice regarding perioperative thromboprophylaxis resulting from publication of new guidance.

5. Conclusions

We performed a large-scale multinational survey and identified a large variation in the use of pharmacological VTE prophylaxis within and between countries. This variation existed in the use of both pharmacological prophylaxis during hospital stay and extended prophylaxis after discharge. The variation in the reported use of mechanical prophylaxis for urological procedures was much less, with uniformly high use over 75% across all scenarios. Knowledge translation of evidence-based guidelines may reduce

problematic variation in practice globally and thus may help optimize future patient care.

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: Violette, Agarwal, Cartwright, Taily, Novara, Craigie, Guyatt, Tikkinen.

Acquisition of data: Violette, Aoki, Agarwal, Arai, Breau, Tikkinen.

Analysis and interpretation of data: All authors.

Drafting of the manuscript: Violette, Vernooij, Guyatt, Tikkinen.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Vernooij.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.euf.2020.05.015>.

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