Baseline Risks of Venous Thromboembolism and Major Bleeding are Crucial in Decision-making on Thromboprophylaxis

Tikkinen, Kari A. O.

2020-09

Tikkinen , K A O & Guyatt , G H 2020 , ' Baseline Risks of Venous Thromboembolism and Major Bleeding are Crucial in Decision-making on Thromboprophylaxis ' , European Urology , vol. 78 , no. 3 , pp. 369-370 . https://doi.org/10.1016/j.eururo.2020.05.032

http://hdl.handle.net/10138/333122
https://doi.org/10.1016/j.eururo.2020.05.032

Platinum Priority – Editorial

Baseline risks of venous thromboembolism and major bleeding are crucial in thromboprophylaxis decision-making

Kari A.O. Tikkinen[1,2*] and Gordon H. Guyatt[3,4]

1. Department of Urology, University of Helsinki and Helsinki University Hospital, Helsinki, Finland
2. Department of Public Health, University of Helsinki, Helsinki, Finland
3. Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, ON, Canada
4. Department of Medicine, McMaster University, Hamilton, ON, Canada

* Corresponding author. Department of Urology, Helsinki University Hospital, Haartmaninkatu 4, 00029 Helsinki, Finland. Tel. +358-50-5250971. E-mail address: kari.tikkinen@gmail.com.

Keywords: thromboprophylaxis, randomized trial, guidelines, urology, statistical power

Word count: 989

Patients undergoing urologic surgery incur risks of deep vein thrombosis and pulmonary embolism - together referred to as venous thromboembolism (VTE) - and major bleeding. Because pharmacologic prophylaxis decreases VTE, but increases bleeding, and because the magnitude of these risks remains uncertain, both clinical practice and guideline recommendations vary widely [1,2].

When balancing thrombosis and bleeding outcomes, one must understand their magnitude in both relative and absolute effects. To understand the issues, consider a hypothetical urologic VTE prevention trial in which 2,000 patients are randomized to anticoagulant and control arms. If one patient in anticoagulant arm and two patients in the placebo arm develop VTE, the relative risk reduction would be 50% ([0.2% - 0.1%] / 0.2%) and the absolute risk reduction would be 0.1% or 1 in 1,000 (0.2% - 0.1%).

How certain are we in the 50% relative and the 0.1% absolute estimates of risk reduction? Let us assume that this study was otherwise well conducted – concealed randomizations, blinding, complete follow-up. We can therefore focus on the precision of the estimates in determining inferences from the results [3].

Focusing first on the relative effects, with only 1 VTE in the heparin and 2 VTEs in the placebo group, the 95% confidence intervals ranges from relative risk reduction of 95% to a relative risk increase of over 5 (i.e. risk ratio from 0.05 to 5.51). We would therefore conclude the confidence interval is very wide, the results extremely imprecise and, despite the large sample size, uninformative.

Consider, however, the absolute estimates. The 95% confidence interval on the 0.1% risk difference of 0.1% lies between 0.0% and 0.6%. We therefore have quite precise estimates for

absolute risks – we can be sure that the reduction in VTE with prophylaxis is no more than 6 in 1,000. Considering the burden and bleeding associated with anticoagulation, we would be very comfortable recommending to our patients that they forego prophylaxis. This is because, however, of the very low risk of VTE in those not anticoagulated.

Consider now the application of these principles to the open-label randomized trial of 501 men with prostate cancer undergoing open (25%) or robotic-assisted laparoscopic (75%) radical prostatectomy reported by Patel and colleagues in this issue of *European Urology* [4]. In this study, patients in the intervention arm received prophylaxis with subcutaneous heparin (5000 units) given within 2 h prior to surgery and every 8 h after surgery until discharge from the hospital as well as intermittent pneumatic compression; control patients received intermittent pneumatic compression only. The median length of hospital stay was 1 day (no difference between arms). Patients were typically discharged on post-operative day 1 and those in the heparin arm received only a median of four doses of drug. Follow-up was at 30 days.

The trial met an early stopping point for futility based on the planned second interim analysis of 445 patients. Only 7 patients experienced VTE; the symptomatic VTE rate was 2.3% (95% CI 0.7-5.2) for routine care versus 0.9% (95% CI 0.1-3.2) for heparin. All VTE events occurred in patients undergoing pelvic lymph node dissection (80% underwent pelvic lymph node dissection). These event rates translate into a relative risk reduction of 0.40 (95% CI 0.08–2.03). This evidence tells us that the best estimate of the impact of prophylaxis is a 60% relative risk reduction, but the results are unfortunately still consistent with a decrease in relative risk of as much as 92% or a more than doubling relative risk with heparin. They thus appear uninformative. The absolute estimates are also worth noting. The point estimate of the difference is 1.4% less with prophylaxis (2.3% - 0.9%) with a 95% confidence interval between -1.3% and 4.3%.

The results of this trial are very much in line with the European Association of Urology (EAU) Guideline on Thromboprophylaxis in Urological Surgery [5], which was based on series of systematic reviews and meta-analyses estimating the baseline risks of various procedures [6]. Moderate quality evidence established that the risk of VTE in prostatectomies varied by procedure, from 0.2-0.9% in robotic prostatectomy without pelvic PLND to 3.9-15.7% in open prostatectomy with extended PLND [6].

Based on meta-analyses of data from general, urologic and gynecological surgeries, VTE prophylaxis with heparin decreases the risk of VTE by about 50% but increases the risk of bleeding by about 50% [6]. The tradeoff between prevention of thrombosis and increase in bleeding will depend on the baseline risk – that is, the incidence of both events in patients not receiving prophylaxis [5].

The authors deserve hearty congratulations for conducting this important randomized trial that provides direct evidence for effect of short-term pharmacologic prophylaxis in urologic cancer surgery. The results tell us that larger trials will be necessary to definitively establish the role of pharmacologic prophylaxis in prostatectomy.

The results of such trials, however, may be predictable. Patel's results are completely consistent with the 50% relative reduction in VTE with pharmacologic prophylaxis from the non-urologic surgery trials. One would then expect, in populations like Patel's, a reduction in VTE from approximately 2% to 1%. Would this be worth recommending prophylaxis to our patients? That is a matter of values and preferences.

The trial also supports that the procedure- and patient risk factor specific EAU Guideline remains as the best evidence summary – with a surgeon-friendly infographic [10] - for guidance of thromboprophylaxis in urologic surgery. That guideline focuses on the most important issue determining prophylaxis, suggested by the hypothetical example that opened this commentary, and by the results of the Patel trial: for any urological procedure, the prime determinant of the net benefit of prophylaxis will be the probability of bleeding and VTE in patients not receiving prophylaxis (i.e. "baseline risk"). Randomized trials remain crucial, but even more crucial is establishing patient groups with sufficiently low rates of VTE (and high rates of bleeding) that prophylaxis is undesirable, and groups with sufficient high rates of VTE (and low rates of bleeding) that prophylaxis is clearly warranted.

References

1. Violette PD, Cartwright R, Briel M, Tikkinen KA, Guyatt GH. Guidelines of guidelines: Thromboprophylaxis for urologic surgery. BJU Int 2016;118(3):351-8.

2. Violette PD, Vernooij RWM, Aoki Y, et al. An international survey on the use of thromboprophylaxis in urological surgery (ISTHMUS). Eur Urol Focus 2020 (in revision).

3. 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.

4. Patel HD, Faisal FA, Trock BJ, et al. Effect of Pharmacologic Prophylaxis on Venous Thromboembolism After Radical Prostatectomy: The PREVENTER Randomized Clinical Trial. Eur Urol 2020 (in press)

5. Tikkinen KAO, Cartwright R, Gould MK, et al. Thromboprophylaxis in urological surgery. European Association of Urology Guidelines Office 2017.

6. Tikkinen KA, Craigie S, Agarwal A, et al. Procedure-specific risks of thrombosis and bleeding in urological cancer surgery: systematic reviews and meta-analyses. Eur Urol 2018;73:242-251.

7. 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

8. Felder S, Rasmussen MS, King R, et al. Prolonged thromboprophylaxis with low molecular weight heparin for abdominal or pelvic surgery. Cochrane Database Syst Rev 2019;3:CD004318.

9. Anderson DR, Morgano GP, Bennett C, et al. American Society of Hematology 2019 guidelines for management of venous thromboembolism: prevention of venous thromboembolism in surgical hospitalized patients. Blood Adv 2019;3:3898-3944.

10. Infographic of the European Assocation of Urology (EAU) Guideline on Thromboprophylaxis in Urological Surgery. Available at http://clueworkinggroup.com/2017/12/01/thromboprophylaxis-infographic/ (accessed May 20, 2020)

Conflicts of interest: No financial conflicts of interest. Tikkinen was chair and Guyatt panel member of the European Association of Urology (EAU) *ad hoc* Guideline on Thromboprophylaxis in Urological Surgery. Tikkinen was panel member of the American Society of Hematology (ASH) Guideline Panel on Prevention of Venous Thromboembolism (VTE) in Surgical Hospitalized Patients.

Funding/Support and role of the sponsor
Kari Tikkinen is supported by the Academy of Finland (309387), Competitive Research Funding of the Helsinki and Uusimaa Hospital District (TYH2019321; TYH2020248) and Sigrid Jusélius Foundation. The sponsors had no role in the analysis and interpretation of the data or the manuscript preparation, review, or approval.