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Perioperative venous thromboembolism prophylaxis in prostate cancer surgery

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Title: Perioperative venous thromboembolism prophylaxis in prostate cancer surgery

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ABSTRACT

Purpose: To describe a patient and procedure specific approach to selecting Venous thromboembolism (VTE) prophylaxis for men who undergo radical prostatectomy.

Methods: We performed a literature search and narrative review of VTE after radical prostatectomy. We describe the current paradigm of perioperative thromboprophylaxis and underlying rationale. Relevant findings from the European Association of Urology thromboprophylaxis guidelines are interpreted and summarized.

Results: The use of extended post-operative thromboprophylaxis for patients who undergo radical prostatectomy is appropriate when the risk of symptomatic VTE outweighs the risk of major bleeding. Patient and procedure factors impact VTE risk. Patient risk can be stratified as low, moderate or high based on 4 factors; age >75, BMI>35, VTE in a first degree relative, and personal history of VTE. Procedure risk of VTE and bleeding can be stratified by modality of surgery (open, laparoscopic, robotic) and extent of pelvic lymphadenectomy. Using these factors, patients at the lowest risk for VTE will have an expected incidence of VTE of 0.4-0.8% and those at highest risk from 1.5-15.7%. Incidence of major bleeding ranges from 0.4-1.4%. These ranges emphasize the need to consider the net benefit for each specific patient. Use of mechanical prophylaxis is supported by weaker evidence but has fewer harms and is likely reasonable for most patients

Conclusion: Many patients who undergo radical prostatectomy will benefit from extended post-operative thromboprophylaxis. Risk of thrombosis is likely higher with open approach and extended lymph node dissection. The net benefit of treatment should be considered using patient- and procedure-specific criteria. When the net benefit is negligible or possibly harmful no pharmacological thromboprophylaxis should be used.

INTRODUCTION

Globally, among 185 countries, there will be an estimated 1,276,106 new incident cases (3rd highest) and 358,989 cancer-specific mortalities (8th highest) [1, 2]. Each year, more than 75,000 and 7,000 radical prostatectomies are performed in the United States and the United Kingdom [3, 4], respectively, the majority of which are now performed with robotic assistance [5]. However, despite improvements in perioperative care, surgical morbidity following oncologic operations is still commonplace, including clinical venous thromboembolism (VTE) [6-8].

VTE is associated with increased burden of care for patients and society. VTE in oncology patients is associated with a 2.2-fold increase in mortality compared to patients without VTE [9]. Prospective cohort studies report that after disease (cancer) progression, VTE is the most common cause of death among oncology patients (448 per 100,000 patients) [10]. Data from the American College of Surgeons National Surgical Quality Improvement Project (NSQIP) report a 30-day readmission rate for patients undergoing radical prostatectomy of 4.1%; the most common cause of readmission VTE (13.6% of readmissions) [11]. Furthermore, VTE is associated with significant costs for patients and the health care system. Patients with VTE have

more hospital admissions (1.07 vs 0.15), emergency room visits (0.31 vs 0.05), and greater total cost ($28,353 vs $17,712) compared to patients without VTE [12]. Therefore, there is a need to improve perioperative management and reduce the incidence of VTE.

There has been considerable evolution in the development of clinical guidelines for perioperative VTE prophylaxis. In 2012, the American College of Chest Physicians (ACCP) published a comprehensive guideline on thromboprophylaxis including guidelines for patients receiving non-orthopedic surgery[13]. The ACCP guideline used robust methodology and the GRADE approach. However, this guideline attempted to cover a very large number of surgery types using a limited number of guidance statements. To do so the authors of the ACCP guideline committed to a strategy in which the risk of thrombosis would be approximated by a catch all category of "abdominal-pelvic" surgery. This decision imposed a significant limitation on the utility of the guideline, since the estimated VTE risk for "abdominal-pelvic" surgery required an estimate of the risks across many different procedure types form a number of surgical specialties (general surgery, gynecology and urology). The actual baseline risk of any one specific surgery type may frequently not be well represented by this average. For example, the risk of VTE after open radical cystectomy is usually not the same as laparoscopic prostatectomy[14]. Therefore, the ACCP approach did not account for important surgical factors such as surgical approach (laparoscopic/robotic/open) or type of dissection (extent of pelvic lymph node dissection). Unfortunately many other available guidelines on prevention of perioperative VTE have similar limitations in the approach to determining surgical risk [15].

A common limitation of many guidelines on VTE prophylaxis is use of an approach that stratifies VTE risk by mixing patient and procedure factors in a single score. Several scoring systems have been developed to help stratify preoperative VTE risk in this way, including the Pannucci, Rogers, and Caprini scores [16-18]. These scoring systems have been widely used and are included in the 2012 ACCP guideline [19]. Briefly, these approaches attempt to generate a score based on procedure and patient characteristics which can be used to predict perioperative risk of thrombosis. Most data used to generate these scoring systems were not from urological surgeries and are therefore indirect. This is reflected in the types of characteristics included in scoring systems which are largely geared toward orthopedic procedures. For example the risk factors of "arthroscopic surgery, immobilizing cast, elective arthroplasty, hip, pelvis or leg fracture, acute spinal cord injury within 1 month" from the Caprini system would not typically apply to patient who undergo prostatectomy or other urological surgeries. Conversely, Caprini may over estimate VTE risk among patients undergoing radical prostatectomy resulting in the vast majority being considered high risk. This is based on the weighting of more general factors such as on age, malignancy and major surgery and the resulting risk assessment does not reflect the wide variation on VTE empirically observed in radial prostatectomy populations [14,20]. Clinical guidelines should therefor adopt a different approach to account for the impact of surgical technique as well as patient characteristics.

A growing body of evidence supports that VTE risk for patients undergoing radical prostatectomy varies by extent of lymph node dissection and surgical approach. In one study,

among 773 patients undergoing laparoscopic radical prostatectomy with 90-day follow-up, 60.8% (n=468) had a concomitant pelvic lymphadenectomy of which 1.5% of patients had a VTE, compared to no patients without pelvic lymphadenectomy experiencing a VTE [21]. In an analysis of 3,544 patients included in the multi-center LAPPRO trial, 547 patients (15.4%) had a pelvic lymphadenectomy, which was associated with an eight-fold greater risk of deep vein thrombosis (RR 7.80, 95%CI 3.51-17.32) and six-fold greater risk of pulmonary embolism (RR 6.29, 95% CI 2.11-18.73) [22]. Additionally, patients without a pelvic lymphadenectomy, who underwent an open radical prostatectomy had increased risk of VTE (RR 3.80, 95%CI 1.42-9.99) compared to those undergoing robotic radical prostatectomy. This is also supported by systematic reviews of observational data that have described a 2-4fold increase in VTE risk among patients who undergo open radical prostatectomy as compared to laparoscopic or robotic approaches [20] and an increase in VTE risk with extent of pelvic lymph node dissection. These important surgical factors have not been widely incorporated into VTE guidelines which largely depend on the aforementioned Caprini, Rogers or Panucci scoring systems to risk stratify patients [14]. This lack of face validity in prior guidelines may be one contributing factor for low adherence to VTE guidelines among urologists [23,24]. It is likely some of the observed variation in practice amongst urologist may reflect the limited availability of patient and procedure specific guidance [23,24].

FRAMEWORK FOR LITERATURE SEARCH

We performed a Medline search of the period from 1 January 2000 to 30 September 2018 to identify systematic reviews and guidelines addressing thromboprophylaxis in prostate cancer surgery. We focused on incidence and timing of VTE, and bleeding, and evidence for extended prophylaxis. The search terms used included radical prostatectomy. robotic assisted radial prostatectomy, laparoscopic radical prostatectomy, venous thromboembolism, perioperative bleeding, hemorrhage, prophylaxis, thromboprophylaxis, lymph node dissection, alone or in combination. References from review articles and guidelines were also assessed to develop a narrative review; specifically, the EAU Thromboprophylaxis guidelines and systematic review of thromboprophylaxis for urologic oncology procedures and accompanying references were extensively used to provide a narrative for thromboprophylaxis for patients undergoing radical prostatectomy. Our search also included a search of society websites for guidelines, in a manner similar to a recently published systematic review of guidelines assessing the use thromboprophylaxis for urological surgery [15].

DEVELOPMENT OF GUIDELINES

The EAU guidelines for VTE prophylaxis use a different approach to VTE risk stratification which we feel is more applicable for patients undergoing urologic procedures [25]. With respect to radical prostatectomy, these guidelines provide very detailed, evidence-based recommendations, which are stratified by patient risk factors, and procedure risk factors including surgical approach (open, laparoscopic or robotic) and extent of pelvic lymph node

dissection. In order to provide guidance at this level of detail a different methodological approach was used, which built on previous work by the ACCP [13,19].

This new approach centered on generating absolute estimates of baseline risks of VTE and bleeding for patients undergoing each urological procedure. In other words, the approach is patient and procedure specific. Estimates of baseline risk were generated by systematic review for each outcome of each specific surgery type (i.e. open, laparoscopic or robotic radical prostatectomy) and are based on direct evidence from real world data. This represents a kind of "natural history" of the incidence of VTE and bleeding for each procedure with no intervention to reduce risk. Knowledge of baseline risk provides urologists with a starting point to judge situations in which giving thromboprophylaxis may provide a net benefit. For instance, for a surgery with high baseline risk of VTE and low baseline risk of bleeding, there would be net benefit to giving pharmacological thromboprophylaxis. Conversely, there may be net harm in giving pharmacological prophylaxis when a surgery has low baseline risk of VTE and high baseline risk of bleeding.

In general, the tradeoff between VTE and bleeding may also be influenced by patient level risk. One important caveat to risk stratification in this framework is that one cannot use risk strata that combine patient and procedure risks, since the procedure level risks are already accounted for by the baseline risk for each procedure. For example, a radical prostatectomy will always be a pelvic surgery, the patient will always have malignancy, and a number of other procedure characteristics will always be present that could impact VTE and bleeding risk (duration, positioning, etc…). For instance, a risk stratification approach that includes the predominant patient-level characteristics has been developed and is shown in Table 1. These four characteristics were identified by systematic review as the predominant patient-level predictors of VTE and the independent relative impact of each factor was estimated [20, 26]. This simple approach allows a clinician to judge how the most common patient-level risk factors impact the tradeoff of VTE and bleeding when deciding on use of prophylaxis. For example, if a patient has a personal history of VTE, this will increase their baseline VTE risk 4-fold [26]. Consequently, this may change the net benefit for use of prophylaxis for a given procedure specific baseline risk. Therefore, very specific patient and procedure-level guidance can be provided with this approach.

To calculate a precise net benefit one must also know the relative effect of the intervention used on critical outcomes of symptomatic VTE and major bleeding. The EAU guideline relied on an updated systematic review and meta-analysis of efficacy of heparins initially generated by the ACCP. This updated meta-analysis demonstrated that giving post-operative pharmacological thromboprophylaxis will decrease the risk of symptomatic VTE by 50% and increase the risk of major bleeding by 50% [13, 20]. When we apply this relative effect of pharmacological prophylaxis to estimates of baseline risk which are stratified by key patient factors a net benefit can be calculated for very specific clinical scenarios.

With regard to radical prostatectomy, data indicate that VTE and bleeding risk vary by surgical approach and extent of pelvic lymph node dissection. Therefore, the baseline risks of

each procedure type (open, laparoscopic, robotic) are calculated separately and pelvic lymph node dissection was estimated as an additional procedure-level risk modifier. Specifically, limited/standard pelvic lymphadenectomy doubles the risk of VTE and extended pelvic lymph node dissection increases the risk 4-fold compared to no lymph node dissection [21, 27-29]. Conversely, limited/standard pelvic lymph node dissection increases bleeding risk by 1.5-fold whereas extended pelvic lymphadenectomy increases the risk of bleeding by a factor of 2 compared to no pelvic lymphadenectomy [20]. In this way each specific patient undergoing a radical prostatectomy can be given tailored advice on the risk and benefits of thromboprophylaxis (Table 2).

GRADE APPROACH to GUIDELINES

Different organizations use a variety of systems to evaluate evidence and make recommendations. Increasingly, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach is becoming the standard and has been widely adopted by organizations such as EAU, Cochrane collaboration, World health Organization (WHO), Uptodate and over 100 organizations internationally [30]. This approach systematically assesses the evidence accounting for (i) risk of bias, (ii) inconsistency, (iii) indirectness, (iv) imprecision, (v) publication bias(vi) effect size, (vii) dose response, and (viii) confounding [30, 31], which allows guideline panelists to describe the quality of evidence that support each recommendation. A detailed description is outside the scope of this manuscript, but the goal is to produce transparent evidence-based guidelines in a systematic way.

It is important to understand the meaning of strong and weak recommendations within the GRADE approach in order to correctly interpret guideline statements provided. Within GRADE, strong or weak recommendations are made either for or against a course of action. From a patient perspective, strong recommendations usually imply that the vast majority of patients in this situation would want to proceed with the recommendation, typically over 90%. For the clinician, this is a situation of informed consent in which the patient may decline the recommended course but there should be a clear reason for doing so. Conversely, weak recommendations imply that the majority of patient would still want to proceed with the recommended course, but a significant proportion may not. For the clinician this is an opportunity for shared decision making, since the “best course” is less clear and therefore the decision is more sensitive to patient values and preferences.

Guideline recommendations may be weak when evidence is strong but the tradeoff is close. Alternatively, benefits or harms may appear large but evidence is weak and therefore less certain. The EAU guideline on thromboprophylaxis made strong recommendations if the net benefit was greater than 10 per 1000 and quality was high or moderate. Weak recommendations were made if benefit was 5-10 per 1000 with strong or moderate evidence, or >10 per 1000 but with weak or very weak quality evidence.

WHO BENEFITS FROM EXTENDED VTE PROPHYLAXIS AFTER RADICAL PROSTATECTOMY?

The landscape of radical prostatectomy has evolved over the past several decades from a primarily open procedure with longer lengths of stay to one that is primarily robotic with relatively short lengths of stay. This has likely changed the relative tradeoffs for VTE and bleeding among this patient population. The 9th edition of the ACCP guidelines recommend that most patients who undergo prostatectomy have high VTE risk and would benefit from 4 weeks of pharmacological prophylaxis in addition to perioperative compression stocking (sections 3.6.5 and 3.6.6 of ACCP guideline) [13]. However, this may not adequately reflect the reality of contemporary prostate cancer surgery and may result in overtreatment [17, 18]. A new approach has been put forward by the EAU which more selectively identified patients who may benefit from prophylaxis [25]. A summary of these recommendations are provided in Table 3.

The question remains: which patients will benefit from extended (4 weeks) VTE prophylaxis after radical prostatectomy? To address this Tikkinen et al., conducted simple modelling studies that describe the timing of symptomatic VTE and bleeding requiring reoperation (Figure 1). Figure 1 describes the incidence of symptomatic VTE as a linear function over the first month. This means that the risk of developing a symptomatic VTE is the same on any one day post-operatively [25, 26]. This is consistent with the observation from NSQIP data which demonstrated that among 16,848 patients undergoing radical prostatectomy, 82.6% of VTEs occurred after hospital discharge [32, 33]. Conversely, major bleeding usually occurs soon after surgery with nearly 50% of bleeding events on the day of surgery itself [25, 26]. Therefore, among patients for whom it is worth giving pharmacological prophylaxis the benefit of the intervention occurs after the period of highest bleeding risk, essentially on post-operative day 1and continues for 28 days. Consequently, for a given patient who is recommended to have thromboprophylaxis, evidence suggests they should receive this starting on post-operative day 1 and should continue for 28 days.

For patients who undergo radical prostatectomy, net benefit is more favorable among higher risk patients, with open surgical approach and increasing pelvic lymph node dissection. It is recommended to look up specific recommendations for any one patient pre-operatively at the time of discussion with that patient. In general, patients at any VTE risk strata, who undergo open radical prostatectomy regardless of extent of lymph node dissection will benefit from extended thromboprophylaxis. It must be cautioned that the net benefit for use of pharmacological prophylaxis with open radical prostatectomy ranges from a borderline value of 4.5/1000 to a relatively high value of 77/1000 [20]. As such, patient values and preferences may vary for some clinical situations and should be addressed when deciding whether to use extended prophylaxis.

In contrast, patients who undergo laparoscopic or robotic prostatectomy the determination of net benefit is more sensitive to patient specific risk and extent of lymph node dissection. In this case the majority of patients who undergo laparoscopic or robotic prostatectomy without lymph node dissection will not have net benefit from pharmacological

prophylaxis. Only patients with high VTE risk (Table 1) who undergo radical prostatectomy with standard lymph node dissection will have net benefit from pharmacological prophylaxis. Patients with moderate or high risk of VTE, who have laparoscopic or robotic prostatectomy with extended lymph node dissection, will also benefit from pharmacological prophylaxis.

The use of mechanical thromboprophylaxis has a different magnitude of effect on the chief tradeoff of VTE and bleeding. Since bleeding is not thought to be substantially increased with this intervention in principle there may be net benefit with lower efficacy at reducing VTE. However, it is important to note that studies of mechanical prophylaxis are uniformly low quality and therefore estimates of effect are highly uncertain and benefit may be negligible [20, 34]. The EAU guideline recommends for the use of mechanical thromboprophylaxis for the majority of patients who undergo radical prostatectomy, which is consistent with previous guidelines including the 9th edition of the ACCP. However, this is based on a threshold of net benefit of >2.5/1000, which is arguably low from the point of view of some stakeholders. Potentially this can be clarified further with higher quality studies of mechanical thromboprophylaxis.

There are some limitations to the approach to choosing VTE prophylaxis described. Although the approach to patient level risk stratification is pragmatic, there may be additional patient-level factors which have not been accounted for. As additional independent patient level factors are identified through systematic review, future iteration of this risk stratification approach may be modified accordingly. Likewise this risk stratification approach has yet to validated prospectively. Future research should aim to validate and refine patient level risk stratification. Likewise, as procedures and perioperative care continues to evolve this may impact incidence of adverse events. Therefore estimates of baseline risk should be revised and updated over time to reflect contemporary practice. Additionally, future directions of research include evaluation of novel agents such as direct oral anticoagulants (DOAC) for post-operative prophylaxis and agents such as tranexamic acid to reduce harms of major bleeding after radical prostatectomy.

CONCLUSION

Previous approaches to risk stratification of patients who undergo radical prostatectomy did not account for important patient and procedure specific characteristics. Radical prostatectomy can be performed by open approach, laparoscopically or robotically with varying extent of pelvic lymph node dissection, and these are different surgeries with different risks of VTE and bleeding. A better approach to providing specific advice for our patients evaluates the tradeoff between VTE and bleeding for the specific surgery the patient will have. When the net benefit is in favor of thromboprophylaxis then it should be initiated on post-op day 1 and continued for 28 days. When the tradeoff is close or evidence is weak there is less certainty about the best course of action. In these situations, it is important to engage our patient in shared decision making so that therapies received correspond to patient values and preferences.

Author Contributions

Z Klaassen: project development, literature search, manuscript writing/editing
CJD Wallis: literature search, manuscript writing/editing
LT Lavallée: manuscript writing/editing
PD Violette: project development, manuscript writing/editing, supervision

Conflict of Interest

Drs. Klassen,Wallis and Lavallee, declare no conflict of interest. Dr Lavallee has accepted honoraria from Sanofi, Ferring and Abbvie and has an unrestricted research grant from Sanofi. Dr Violette has accepted honoraria in 2016 from Sanofi, Janssen, and Astellas, but no longer accepts honoraria from industry.

Research involving human participants ethical approval

As this is a review article no ethical approval was required

Informed Consent

As this is a review article no informed consent was required

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Table 1: Model for risk of venous thromboembolism according to patient risk factors (Adapted with permission [23])

	Risk	
Low Risk	No risk factors	1x
Medium Risk	Any one of the following: • Age ≥ 75 years • Body mass index ≥35 kg/m^2 • VTE in first-degree relative (parent, full sibling, child)	2x
High Risk	• Prior VTE • Patients with any combination of ≥2 risk factors indicated under Medium risk category	4x

Table 2: The 4-week postoperative risk of symptomatic nonfatal venous thromboembolism and bleeding requiring reoperation after radical prostatectomy (Adapted with permission [23])

	Venous thromboembolism		Bleeding requiring reoperation	
Radical Prostatectomy Procedure	**Estimate of event by patient risk strata (%)**	**Certainty in Estimate**	**Estimate of event (%)**	**Certainty of estimate**
Laparoscopic without PLND	Low risk: 0.4 Medium risk: 0.8 High risk: 1.5	Moderate	0.7	Moderate
Laparoscopic with standard PLND	Low risk: 0.8 Medium risk: 1.5 High risk: 3.0	Moderate	1.0	Moderate
Laparoscopic with extended PLND	Low risk: 1.5 Medium risk: 3.0 High risk: 6.0	Moderate	1.4	Moderate
Open without PLND	Low risk: 1.0 Medium risk: 2.0 High risk: 3.9	Moderate	0.1	Moderate
Open with standard PLND	Low risk: 2.0 Medium risk: 3.9 High risk: 7.9	Moderate	0.2	Moderate
Open with extended PLND	Low risk: 3.9 Medium risk: 7.9 High risk: 15.7	Moderate	0.2	Moderate
Robotic without PLND	Low risk: 0.2 Medium risk: 0.5 High risk: 0.9	Moderate	0.4	Moderate
Robotic with standard PLND	Low risk: 0.5 Medium risk: 0.9 High risk: 1.9	Moderate	0.6	Moderate
Robotic with extended PLND	Low risk: 0.9 Medium risk: 1.9 High risk: 3.7	Moderate	0.8	Moderate

PLND – pelvic lymphadenectomy

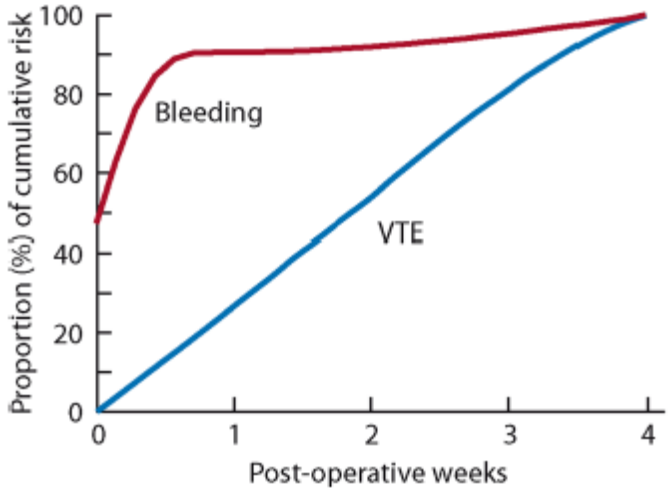
Table 3 Abbreviated summary of EAU recommendations for post-operative VTE prophylaxis

Surgery	**Pharmacological Prophylaxis**		**Mechanical Prophylaxis**
	Risk Stata	Strength and Recommendation	Strength and Recommendation
Open prostatectomy (no PLND)	Low Moderate or High	Weak for Strong for	Weak for Weak for
Open Prostatectomy (standard PLND)	Low Moderate or High	Weak for Strong for	Weak for Weak for
Open prostatectomy (extended PLND)	All	Strong for	Weak for
Robotic or laparoscopic prostatectomy (no PLND)	Low Moderate or high	Strong against Weak against	Weak against Weak for
Robotic or laparoscopic prostatectomy (standard PLND)	Low Moderate High	Strong against Weak against Weak for*	Weak for Weak for Weak for
Robotic or laparoscopic prostatectomy (extended PLND)	Low Moderate High	Weak against Weak for Strong for	Weak for Weak for Weak for

Abbreviations: PNLD, pelvic Lymph node dissection

*Laparoscopic prostatectomy with PLND showed net benefit of 10 per 1000 but was included with robotic prostatectomy to simplify presentation of this table.

Figure 1 Cumulative incidence of symptomatic VTE and major bleeding in the first 4 weeks post-operatively



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