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Thromboprophylaxis in Urological and Andrological Surgery (Review article)

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Last decades urologist started to performed big amount of complicated oncological operation with substantial risk of both venous thromboembolism (VTE) and bleeding. Prophylaxis of VTE remains a vital problem, as it is potentially fatal and is associated with significant morbidity. Prophylaxis of this complication is not clearly defined and is mainly based on information from other surgical specialties (like orthopedic or general surgery). Scientific publications dedicated VTE prophylaxis in field of urology were reported only in the last decade.
Most studies showed that 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%. Main models for evaluation of different VTE risk factors were analyzed. The most important risk factors for VTE are age of 75 or more, body mass index 35 or more, prior VTE or VTE in 1st degree relative. As for urological procedure, deep venous thrombosis rates of 0.2–7.8% and pulmonary embolism of 0.2–7% have been reported.
It was shown that recommendations for VTE prophylaxis varies in different guidelines and their summary for most popular operations were described. Generally, most recommendations state that low-risk procedures need no prophylaxis or solely mechanical prophylaxis. Moderate-risk categories can either have mechanical or pharmacological prophylaxis. The high-risk category should have both mechanical and pharmacological prophylaxis, and extended prophylaxis should be considered.
Despite massive evidences about risk of VTE among different types of surgical patients, real clinical practice doesn't show the strict adherence to VTE prophylaxis recommendations.
Keywords: *venous thromboembolism, bleeding, prophylaxis.*

Тромбопрофілактика в урологічній та андрологічній хірургії (Огляд літератури)

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Останнім часом спостерігається збільшення кількості складних онкологічних операцій, що виконуються урологами, з істотним ризиком виникнення як венозної тромбоемболії (ВТЕ), так і кровотечі. Профілактика ВТЕ залишається життєво важливою проблемою, оскільки вона потенційно смертельна і пов'язана зі значною захворюваністю. Профілактика цього ускладнення чітко не визначена і здебільшого базується на інформації з інших хірургічних спеціальностей (таких, як ортопедична або загальна хірургія). Наукові публікації, присвячені профілактики ВТЕ в галузі урології, були зареєстровані тільки в останнє десятиліття.
Результати більшості досліджень продемонстрували, що фармакологічна профілактика знижує відносний ризик ВТЕ у хірургічних пацієнтів приблизно на 50%, але зі збільшенням відносного ризику післяопераційної великої кровотечі на 50%. У статті проаналізовано основні моделі оцінки різних факторів ризику ВТЕ. Найбільш важливими факторами ризику ВТЕ є вік 75 років і більше, індекс маси тіла 35 або більше, ВТЕ в анамнезі або ВТЕ у родичів першого ступеня. Що стосується урологічних процедур, то частота розвитку глибокого венозного тромбозу становить 0,2–7,8%, легеневої емболії – 0,2–7%.
Зазвичай, більшість рекомендацій стверджують, що процедури з низьким ризиком не потребують профілактики або вимагають виключно механічної профілактики. При операціях з категорії помірного ризику повинна використовуватись фармакологічна профілактика, часто в комбінації з механічною. Категорія високого ризику повинна мати як механічну, так і фармакологічну профілактику, слід також враховувати розширену профілактику. Відомості щодо профілактики ВТЕ відрізняються в різних рекомендаціях та були описані для більшості найбільш частих урологічних операцій.
Незважаючи на масові докази ризику ВТЕ серед різних типів хірургічних пацієнтів, реальна клінічна практика не вимагає суворого дотримання рекомендацій щодо профілактики ВТЕ.
Ключові слова: *венозна тромбоемболія, кровотеча, профілактика.*

The intensive use of thromboprophylaxis in millions of COVID-19 patients stimulates an interest in the perioperative prescription of antiplatelet agents in urological patients. Most of urological associations have hitherto published guidelines on thromboprophylaxis in urological surgery.

With the increased amount and diversity of operations performed for urological diseases the amount and diversity of their complications consequently increased. Moreover, in the last decades urologists started performing complicated oncological operations with substantial risk of both venous thromboembolism (VTE) and bleeding – both potentially lethal. VTE includes deep vein thrombosis and pulmonary embolism and represents a serious and sometimes fatal complication of surgery [1]. The lack of appropriate urological studies additionally contributed to the problem of thromboprophylaxis. Prophylaxis of this complication is not clearly defined and is mainly based on informa-

tion from other surgical specialties (like orthopedic or general surgery). Scientific publications dedicated VTE prophylaxis in field of urology were reported only in the last decade. Decisions regarding pharmacologic thromboprophylaxis in urologic surgery involve a trade-off between decreased risk of (VTE) and increased risk of bleeding. Currently, there exists substantial practice variation in the use of thromboprophylaxis in urology, both within and between countries. This variation is unsurprising given often conflicting recommendations from national and international guidelines [2].

The aim of our paper was to review the existing proposals of thromboprophylaxis for practical usage in most typical urological operations. Therefore, we analyzed the recent guidelines and publications on thromboprophylaxis in urological surgery.

Most studies showed that 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% [3]. The right balance between VTE prophylaxis and bleeding complications is the main challenge for any recommendation.

VTE is the presence of deep venous thrombosis (DVT) or pulmonary embolism (PE). They can either be symptomatic or diagnosed on a screening ultrasound but sometimes found only on autopsy. Although most of the DVT are subclinical, they can develop into post-thrombotic syndrome and can lead to chronic edema, pigmentation and ulceration. The majority of symptomatic DVT originate in calf veins, and might extend to the proximal leg. If untreated, proximal VTE can develop PE in up to 50% of cases [1, 4]. DVT is a major preventable cause of mortality and morbidity worldwide. DVT and PE account for 60,000 to 100,000 deaths annually in the United States [5].

PE is preceded by a symptomatic DVT in just one-quarter of cases. After a PE, 2–4% of patients will develop chronic pulmonary hypertension. Between 17% and 25% of PEs are fatal and PE remains the most common form of preventable hospital mortality [4].

Other early complications include phlegmasia cerulea dolens and venous gangrene. Late complications include post-phlebitic syndrome, chronic venous insufficiency and chronic thromboembolic pulmonary hypertension.

High-quality evidence suggests that, of the cumulative risk during the first four weeks post-surgery, approximately 50% of major bleeds occur between surgery and the next morning and approximately 90% during the first four post-surgical days. In contrast, the risk of VTE is almost constant during these first four post-surgical weeks [2].

The principles of DVT formation were studied for decades and we now understand the main mechanisms and processes involved in that pathological condition. Generally, the balance of procoagulant and anticoagulant factors in the blood that prevents thrombus formation could be shifted according to the triad of Virchow. The formation of DVT occurs when at least one or more factors of the triad of Virchow is present.

Triad of Virchow

1. Venous stasis (for example, immobility and congestive heart failure.
2. Endothelial injury (for example, surgery and trauma).
3. Hypercoagulability (for example, cancer, thrombophilia, severe inflammation).

Venous stasis is the most important factor but the presence of endothelial injury and/or hypercoagulability further increases the risk of DVT. Compared to patients in the community, hospitalized patients are at risk of venous stasis which combined with other factors increases the risk of DVT [5].

Risk factors for DVT

The very first step to decide on the necessity of thromboprophylaxis is understanding of risk factors (RF) for thrombosis. Not all patients and all operations need thromboprophylaxis. There are different interpretations and evaluations of thrombosis RF. The most important perioperative RF are displayed in table 1.

Several algorithms have been proposed to assess the risk of developing thrombosis based on the analysis of the patient's risk factors. For example, Caprini model assigns a score from more than 35 known RF. Each RF is scored between 1 and 5 based on its attributable risk toward VTE. The higher the score, the higher the risk of VTE. However, some of the RF have now been disproven, and the model itself is too complicated for everyday use in clinical practice [7]. The score has been validated within the urological literature; although there are inconsistencies with its correlation to VTE risk in certain urological surgeries [8].

Table 1

Risk factors for VTE [4]

Preoperative	History of VTE
	Thrombophilia
	Obesity (BMI >30)
	Pregnancy
	Trauma
	Age >60 years
	Estrogen therapy
	Comorbidities: acute medical illness, congestive cardiac or respiratory failure, nephrotic syndrome, inflammatory bowel disease
	Malignancy (advanced/ metastatic > localized)
	Trauma
	Immobility
	Smoking
	Chemotherapy
	Ethnicity: Black > Caucasian > Hispanic > Asian/ Pacific Islanders
Intraoperative	Length of surgery >2 h
	Volume of blood loss
	Lack of mechanical thromboprophylaxis
	Type of anesthesia - epidural and spinal anesthesia are associated with a reduction of DVT and PE by 55%.
Postoperative	Immobilization >4 days
	Prolonged hospital stay
	Lack of thromboprophylaxis
	Recovery: sepsis, reoperation, nutrition
	Lymphocoeles

Table 2

Venous thromboembolism (VTE) according to patient risk factors

	Risk	Likelihood of VTE
Low risk	No risk factors	1x
Medium risk	Any one of the following: age 75 years or more; Body mass index 35 or more; VTE in 1st degree relative (parent, full sibling, or child).	2x
High risk	Prior VTE Patients with any combination of two or more risk factors	4x

The Rogers model is another risk-scoring system that includes variant risk factors and is less comprehensive. It was originally designed for vascular and general surgery patients and has not been modified or validated for the urological population [7].

European Association of Urology recommends another, more simple and practical classification of DVT RF [2].

This classification is widely used for urological research in real practice [2].

Timing of thromboprophylaxis

Another discussion point is the timing of thromboprophylaxis. There are no studies with direct comparison of effectivity and side effects of thromboprophylaxis before and after surgery. Some nonurological studies have, however, suggested that prophylaxis can begin 24 hours after surgery without an increase in VTE but with a decrease in bleeding complications [9, 10]. Therefore, most authors recommend beginning of thromboprophylaxis the day after surgery.

As for duration of pharmacological thromboprophylaxis, the majority of guidelines suggest prolonged thromboprophylaxis for high-risk abdominal or pelvic surgery for up to 4 weeks post-discharge. Existing guidance may result in the under-treatment of procedures with low risk of bleeding and the over-treatment of oncological procedures with low risk of VTE [11, 12].

Types of thromboprophylaxis

There are several options of thromboprophylaxis which are typically combined.

- Intermittent pneumatic compressions (IPC)
- Graduated compression stockings (GCS)
- Venous foot pump

The more traditional mechanical thromboprophylaxis has almost no side effects. First of all, it should be kept in mind that early mobilization is an essential part of any thromboprophylaxis regime. Mechanical prophylaxis devices are used to reduce venous stasis and release of anti-thrombotic factors from leg muscles. They have been shown to decrease DVT rates but do not decrease the risk of PE- or VTE-related deaths [13].

Intermittent pneumatic compressions. Calf compressors reduce the risk of DVT by 60% and proximal DVT by 50% but do not decrease the rates of PE. A combination of calf compressors and stockings are more efficacious as they work by different mechanisms – stockings prevent distention and calf compressors empty veins. In Cochrane analysis, calf compressors and anticoagulation were found to be equally effective in reducing DVT [14, 15].

Evidence from clinical trials has shown that although the rate of distal thrombi is reduced significantly, that of proximal thrombi is not. This finding may lead to a false sense of security because, while the total number of deep venous thrombi may be similar to the numbers observed with pharmacologic prophylaxis, the proportion of the relatively more dangerous proximal clots is increased (Table 3) [18].

Table 3

Frequency of Thrombi at Different Sites With Intermittent Pneumatic Compression vs Warfarin

Thrombi	Warfarin, n=72	IPC, n=67
Iliac and femoral	5	14
Calf, popliteal, plantar	10	2
Total	15	16

Graduated compression stockings

These generate pressure at the ankle, and gradually decrease the pressure moving up the leg. These should be fitted to every patient and worn continuously until a return to full mobilization. They reduce the risk of DVT by 31–65% with Number Needed To Treat of 28 to prevent one DVT. No consistent difference has been noted in efficacy between calf-length and thigh-length stockings. Contraindications include peripheral arterial disease, severe peripheral edema, leg cellulitis, diabetic neuropathy, skin graft and severe lower limb deformity [1, 16, 17].

All types of mechanical compression reduce the incidence of DVT compared to no prophylaxis is administered. However, these modalities are generally less effective than pharmacologic methods. No mechanical prophylaxis method has been shown to reduce the risk of PE or death. The use of IPC devices is therefore recommended primarily as an adjunct to anticoagulant-based prophylaxis or in patients who are at high risk of bleeding [18].

Pharmacologic prophylaxis

Many pharmacologic agents are currently available to prevent thrombosis. Agents that delay or inhibit the process belong under the general heading of anticoagulants.

Table 4

Alternative regimens for pharmacological prophylaxis. All recommendations are based on a starting time of the morning after surgery

Pharmacological agent	Dosage*
Low molecular weight heparins:	
Dalteparin	5,000 IU injection once a day
Enoxaparin	40 mg injection once a day
Tinzaparin	3,500/4,500 IU injection once a day
Unfractionated heparin	5,000 IU injection two or three times a day
Fondaparinux†	2.5 mg injection once a day
Direct acting oral anticoagulants†:	
Dabigatran	220 mg tablet once a day
Apixaban	2.5 mg tablet once a day
Edoxaban	30 mg tablet once a day
Rivaroxaban	10 mg tablet once a day

** Dosages may not apply in renal impairment.*

† Fondaparinux and direct acting oral anticoagulants have not been sufficiently studied in urology to warrant on-label use for post-surgery thromboprophylaxis.

Agents that prevent the growth or formation of thrombi are properly termed antithrombotics and include anticoagulants and antiplatelet drugs [18].

EAU recommendations for pharmacologic prophylaxis agents displayed in table 4 [2].

As for urological procedure, DVT rates of 0.2–7.8% and PE of 0.2–7% have been reported (Table 5) [1]. Generally, most recommendations state that low-risk procedures need no prophylaxis or solely mechanical prophylaxis. Moderate-risk categories can either have mechanical or pharmacological prophylaxis. The high-risk category should have both mechanical and pharmacological prophylaxis, and extended prophylaxis should be considered [2, 4, 5, 18, 19, 20].

VTE prophylaxis recommendations for urological operations

Recommendations for DVT prophylaxis varies in different guidelines and their summary for most popular operations are listed below [2, 6, 7, 20, 21, 22].

Ambulatory day surgery – no prophylaxis necessary.

Transurethral resection of the prostate or equivalent procedures – no use of pharmacologic or mechanical prophylaxis; for those at high risk – use of mechanical prophylaxis until ambulation.

Open or robotic radical cystectomy – use pharmacological prophylaxis and suggests use of mechanical prophylaxis until ambulation.

Laparoscopic radical prostatectomy without pelvic lymph node dissection (PLND), for those at low risk of VTE – no use of pharmacologic or mechanical prophylaxis; for those at moderate and high risk – no use of pharmacologic prophylaxis and use of mechanical prophylaxis until ambulation.

Laparoscopic radical prostatectomy with standard PLND, for those at low or medium risk of VTE – no use of pharmacologic prophylaxis; for those at high risk – use of pharmacologic prophylaxis; and for all patients – use of mechanical prophylaxis until ambulation.

Open radical prostatectomy without PLND or with standard PLND any risk – use of pharmacologic prophylaxis is suggested plus use of mechanical prophylaxis until ambulation.

Laparoscopic partial nephrectomy for those at low or medium risk of VTE – no use of pharmacologic prophylaxis; for those at high risk – use of pharmacologic prophylaxis and for all patients use of mechanical prophylaxis until ambulation.

Open partial nephrectomy use pharmacological prophylaxis and suggests use of mechanical prophylaxis until ambulation.

Table 5

Risk of VTE in common urological procedures

Urological procedure	Risk of VTE, %
Transurethral/ureterorenoscopic	0–0.4
Nephrectomy (radical/partial)	0.2–2.9
High-risk disease (vascular invasion etc.)	2.6–22.6
Radical prostatectomy	0.2–0.9
Extended lymph node dissection	3.9–15.7
Radical cystectomy	6–24.4
RPLND	0–1

Laparoscopic radical nephrectomy – no use of pharmacologic prophylaxis; for those at high risk – use of pharmacologic prophylaxis and for all patients use of mechanical prophylaxis until ambulation.

Open radical nephrectomy – use of pharmacologic prophylaxis is suggested plus use of mechanical prophylaxis until ambulation.

Radical cystectomy performed by open or robotic approach – use pharmacological prophylaxis plus use of mechanical prophylaxis until ambulation.

Thromboprophylaxis in urological procedures in real practice

Despite the massive evidence of VTE risk among different types of surgical patients, real clinical practice does not show the same adherence to VTE prophylaxis recommendations. For example, adherence to mechanical prophylaxis ranges from 53.5% to 75% in a meta-analysis, however, the compliance with pharmacological prophylaxis even in high-risk patients is relatively poor [23, 24].

An extensive study which included 12,887,080 medical discharges in a large number of hospitals across the U.S. showed that the thromboprophylaxis rate was low, despite the presence of guidelines recommending thromboprophylaxis in this patient population. Additionally, only a slight increase was observed during the 4-year study period from 26% in 2001 to 33% in 2004 [25]. The rates of thromboprophylaxis varied among the five disease groups with cancer patients having the lowest (18–25%). Rates of thromboprophylaxis slightly improved in patients classified to the other groups, namely severe lung disease (24–32%), ischemic stroke (27–32%), and heart failure (29–38%). The evaluations of clinical outcomes indicated that the patients receiving thromboprophylaxis had significantly lower risk-adjusted mortality rates than those who did not receive thromboprophylaxis ($p < 0.001$).

Superior compliance results were shown in a French study [26]. This analysis included 2380 patients admitted to hospital for abdominal (47.8%), urological (41%), or gynaecological (11.2%) cancer surgery. Perioperative antithrombotic prophylaxis, consisting mainly of low-molecular-weight heparin, was given to 99.5% of patients. Thromboprophylaxis was continued in 91.7% of patients at hospital discharge while 57.4% received a 4-6 week prophylaxis. This management strategy was associated with an overall venous thromboembolic event rate of 1.9% while 34.7% of events occurred after discharge.

There are some urological studies about the usage of VTE prophylaxis recommendations. In an international study of 1051 urologists contacted, 570 (54%) participated in the survey [27]. Japanese urologists were less likely to prescribe pharmacological prophylaxis than Canadian or Finnish urologists ($p < 0.001$ for all procedures). Finnish urologists were most likely to prescribe extended prophylaxis versus Canadian and Japanese urologists (Open radical cystectomy 98%, 84%, and 26%; Open radical prostatectomy 25%, 8%, and 3%; robotic radical prostatectomy 11%, 9%, and 0%; and radical nephrectomy 43%, 7%, and 1%, respectively; $p < 0.001$ for each procedure). Less variation was found regarding the prescription of mechanical prophylaxis, which was the most commonly used until ambulation or discharge.

Contraindications for DVT Prophylaxis

For some surgical patients DVT Prophylaxis cannot be prescribed mainly due to increased risk of bleeding [5].

Contraindications for Pharmacological DVT Prophylaxis:

- Active bleeding or recent bleeding or high risk for bleeding (active PUD)
- Patients with coagulopathy (INR greater than 1.5)

A planned surgical procedure in the next 6 to 12 hours

- Thrombocytopenia (Less than 50,000, sometimes less than 100,000)
- Bleeding disorders

Contraindications for Mechanical Prophylaxis:

- Limb ischemia due to peripheral vascular disease
- Skin breakdown.

So in the era of big and complicated urological operations venous thromboembolism remains serious and sometimes fatal complication. Decisions regarding pharmacologic thromboprophylaxis in urologic surgery is a ballance between decreased risk of venous thromboembolism and increased risk of bleeding.

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