

EAU GUIDELINES ON THROMBOPROPHYLAXIS IN UROLOGICAL SURGERY

K.A.O. Tikkinen (Chair), R. Cartwright, M.K. Gould, R. Naspro, G. Novara, P.M. Sandset, P.D. Violette, G.H. Guyatt

Introduction

Utilising recent studies and newly summarised evidence, the EAU Guidelines on Thromboprophylaxis provide practical evidence-based guidance regarding post-surgery thromboprophylaxis and peri-operative management of antithrombotic agents in urology.

The Thromboprophylaxis Panel used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach for assessment of quality of evidence and grading of recommendations. GRADE offers four levels of evidence quality, reflecting the degree of certainty or confidence in the evidence: high, moderate, low, and very low. The strength of a recommendation reflects the extent to which we can be confident that desirable effects of an intervention outweigh undesirable effects. GRADE classifies recommendations as strong or weak.

Thromboprophylaxis post-surgery

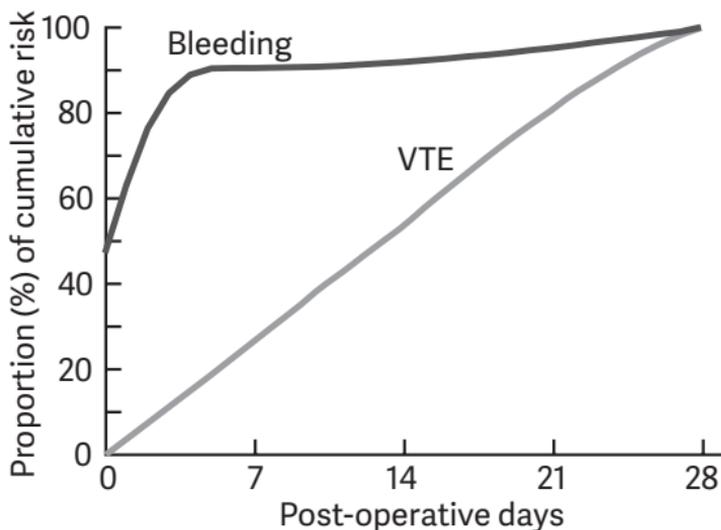
This guideline provides procedure and patient risk-specific guidance weighing the benefit of reduced venous thromboembolism (VTE) against the harm of increased bleeding. The Panel provides recommendations for numerous urologic procedures, with variation across patient risk strata (Table 1). When creating recommendations, the Panel

first calculated the net benefit (absolute reduction in VTE risk – absolute increase in bleeding risk) and then considered quality of evidence for both pharmacological and mechanical prophylaxis (Figure 1).

Table 1: Venous thromboembolism (VTE) according to patient risk factors

	Risk factors
Low risk	No risk factors
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).
High risk	Prior VTE Patients with any combination of two or more risk factors

Figure 1: Proportion of cumulative risk (%) of venous thromboembolism (VTE) and major bleeding by week since surgery during the first four post-operative weeks



	Proportion of 28-day cumulative bleeding risk
Operation day	47.4%
Post-operative day 1	63.3%
Post-operative day 2	76.6%
Post-operative day 3	84.9%
Post-operative day 4	89.2%
Post-operative day 28	100.0%

The bleeding pattern depicted applies to most bleeds for most surgeries. However, some urological surgeries, such as transurethral resection of the prostate (TURP), are associated with later bleeding. This is typically minor and occurs around ten days post-surgery.

General statements for all procedure-specific recommendations

The following apply to all recommendations for pharmacological prophylaxis:

- All recommendations are based on a starting time of the morning after surgery.
- The optimal duration of pharmacological prophylaxis for all recommendations is approximately four weeks post-surgery.
- There are number of acceptable alternatives for pharmacologic prophylaxis (Table 2).
- All recommendations for mechanical prophylaxis are until ambulation.

Table 2: Alternative regimens for pharmacological prophylaxis

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.

Recommendations for prophylaxis in specific procedures according to patient risk

Ambulatory day surgery

R1. In all patients undergoing minor ambulatory day surgery (for example, circumcision, hydrocelectomy and vasectomy), the Panel recommends against use of pharmacological prophylaxis (**strong, moderate-quality evidence**), and against use of mechanical prophylaxis (**strong, moderate-quality evidence**).

Open radical cystectomy

R2. In all patients undergoing open radical cystectomy, the Panel recommends use of pharmacological prophylaxis (**strong, moderate or high-quality evidence depending on risk stratum**), and suggests use of mechanical prophylaxis (**weak, low-quality evidence**).

Robotic radical cystectomy

R3. In all patients undergoing robotic radical cystectomy, the Panel suggests use of pharmacological prophylaxis (**weak, low-quality evidence**), and suggests use of mechanical prophylaxis (**weak, low-quality evidence**).

Laparoscopic radical prostatectomy

R4. For patients undergoing laparoscopic radical prostatectomy without pelvic lymph node dissection (PLND), for those at low risk of VTE, the Panel recommends against use of pharmacological prophylaxis (**strong, moderate-quality evidence**) and suggests against use of mechanical prophylaxis (**weak, low-quality evidence**); for those at moderate and high risk, the Panel suggests against use of pharmacological prophylaxis (**weak, moderate- or high-quality evidence**) and suggests use of mechanical prophylaxis (**weak, low-quality evidence**).

R5. For patients undergoing laparoscopic radical prostatectomy with standard PLND, for those at low risk of VTE, the Panel recommends against use of pharmacological prophylaxis (**strong, moderate-quality evidence**); for those at medium risk, the Panel suggests against use of pharmacological prophylaxis (**weak, moderate-quality evidence**); for those at high risk, the Panel recommends use of pharmacological prophylaxis (**strong, high-quality evidence**); and for all patients, the Panel suggests use of mechanical prophylaxis (**weak, low-quality evidence**).

R6. For patients undergoing laparoscopic radical prostatectomy with extended PLND, for those at low risk of VTE, the Panel suggests against use of pharmacological prophylaxis (**weak, moderate-quality evidence**); for those at medium risk, the Panel suggests use of pharmacological prophylaxis (**weak, high-quality evidence**); for those at high risk, the Panel recommends use of pharmacological prophylaxis (**strong, high-quality evidence**); and for all patients, the Panel suggests use of mechanical prophylaxis (**weak, low-quality evidence**).

Open radical prostatectomy

R7. For patients undergoing open radical prostatectomy without PLND or with standard PLND, for those at low risk of VTE, the use of pharmacological prophylaxis is suggested (**weak, moderate-quality evidence**); for those at medium and high risk, use of pharmacological prophylaxis is recommended (**strong, moderate- or high-quality evidence**); and for all patients, the Panel suggests use of mechanical prophylaxis (**weak, low-quality evidence**).

R8. For all patients undergoing open radical prostatectomy with extended PLND, the Panel recommends use of pharmacological prophylaxis (**strong, moderate or high-quality evidence**), and suggests use of mechanical prophylaxis (**weak, low-quality evidence**).

Robotic radical prostatectomy

R9. For patients undergoing robotic radical prostatectomy without PLND, for those at low risk of VTE, the Panel recommends against use of pharmacological prophylaxis (**strong, moderate-quality evidence**) and suggests against use of mechanical prophylaxis (**weak, low-quality evidence**); for those at medium and high risk, the Panel suggests against use of pharmacological prophylaxis (**weak, moderate-quality evidence**) and suggests use of mechanical prophylaxis (**weak, low-quality evidence**).

R10. For patients undergoing robotic radical prostatectomy with standard PLND, for those at low risk of VTE, the Panel recommends against use of pharmacologic prophylaxis (**strong, moderate-quality evidence**); for those at medium risk, the Panel suggests against use of pharmacologic prophylaxis (**weak, moderate-quality evidence**); for those at high risk, the Panel suggests use of pharmacologic prophylaxis (**weak, moderate-quality evidence**); and for all patients, the Panel suggests use of mechanical prophylaxis (**weak, low-quality evidence**).

R11. For patients undergoing robotic radical prostatectomy with extended PLND, for those at low risk of VTE, the Panel suggests against use of pharmacologic prophylaxis (**weak, moderate-quality evidence**); for those at medium risk, the Panel suggests use of pharmacologic prophylaxis (**weak, moderate-quality evidence**); for those at high risk, the Panel recommends use of pharmacologic prophylaxis (**strong, moderate-quality evidence**); and for all patients, the Panel suggests use of mechanical prophylaxis (**weak, low-quality evidence**).

Nephrectomy

R12. For patients undergoing laparoscopic partial nephrectomy, for those at low and medium risk of VTE, the Panel suggests against use of pharmacologic prophylaxis (**weak, low-quality evidence**); for those at high risk, the Panel recommends use of pharmacologic prophylaxis (**strong, moderate-quality evidence**); and for all patients, the Panel suggests use of mechanical prophylaxis (**weak, low-quality evidence**).

R13. For all patients undergoing open partial nephrectomy, the Panel suggests use of pharmacologic prophylaxis (**weak, very low quality evidence**), and suggests use of mechanical prophylaxis (**weak, very low quality evidence**).

R14. For patients undergoing robotic partial nephrectomy, for those at low risk of VTE, the Panel suggests against use of pharmacologic prophylaxis (**weak, moderate-quality evidence**); for those at medium risk, the Panel suggests use of pharmacologic prophylaxis (**weak, moderate-quality evidence**); for those at high risk, the Panel recommends use of pharmacologic prophylaxis (**strong, high-quality evidence**); and for all patients, the Panel suggests use of mechanical prophylaxis (**weak, low-quality evidence**).

R15. For patients undergoing laparoscopic radical nephrectomy, for those at low or medium risk of VTE, the Panel suggests against use of pharmacologic prophylaxis (**weak, very low quality evidence**); for those at high risk, the Panel suggests use of pharmacologic prophylaxis (**weak, very low quality evidence**); and for all patients, the Panel suggests use of mechanical prophylaxis (**weak, very low quality evidence**).

R16. For patients undergoing open radical nephrectomy, the Panel suggests use of pharmacologic prophylaxis (**weak, very low quality evidence**), and suggests use of mechanical prophylaxis (**weak, low-quality evidence**).

R17. For all patients undergoing radical nephrectomy with thrombectomy, the Panel suggests use of pharmacologic prophylaxis (**weak, very low quality evidence**), and suggests use of mechanical prophylaxis (**weak, very low quality evidence**).

R18. For all patients undergoing open nephroureterectomy, the Panel suggests use of pharmacologic prophylaxis (**weak, very low quality evidence**), and suggests use of mechanical prophylaxis (**weak, very low quality evidence**).

R19. For all patients undergoing primary nerve sparing retroperitoneal lymph node dissection, the Panel suggests use of pharmacologic prophylaxis (**weak, very low quality evidence**), and suggests use of mechanical prophylaxis (**weak, very low quality evidence**).

Non-cancer urological procedures

R20. For all patients undergoing transurethral resection of the prostate (TURP) or equivalent procedures, the Panel suggests against use of pharmacologic prophylaxis (**weak, very low quality evidence**); for those at low or medium risk of VTE, the Panel suggests against use of mechanical prophylaxis (**weak, low-quality evidence**); and for those at high risk, the Panel suggests use of mechanical prophylaxis (**weak, low-quality evidence**).

R21. For patients undergoing laparoscopic donor nephrectomy or open donor nephrectomy, for those at low risk of VTE, the Panel suggests against use of pharmacologic prophylaxis (**weak, very low or low-quality evidence**), and suggests against use of mechanical prophylaxis (**weak, very low or low-quality evidence**); for medium-risk patients, the Panel suggests against use of pharmacologic prophylaxis (**weak, very low or low-quality evidence**), and suggests use of mechanical prophylaxis (**weak, very low or low-quality evidence**); and for high-risk patients, the Panel suggests use of pharmacologic prophylaxis (**weak, very low or low-quality evidence**), and suggests use of mechanical prophylaxis (**weak, very low or low-quality evidence**).

R22. For all patients undergoing open prolapse surgery or reconstructive pelvic surgery, the Panel suggests against the use of pharmacologic prophylaxis (**weak, very low quality evidence**); for those at low or medium risk of VTE, the Panel suggests against use of mechanical prophylaxis (**weak, very low or low-quality evidence**); while for those at high risk, the Panel suggests use of mechanical prophylaxis (**weak, very low or low-quality evidence**).

R23. For all patients undergoing percutaneous nephrolithotomy, the Panel suggests against use of pharmacologic prophylaxis (**weak, very low quality evidence**); for those at low or medium risk of VTE, the Panel suggests against use of mechanical prophylaxis (**weak, very low quality evidence**); while for those at high risk, the Panel suggests use of mechanical prophylaxis (**weak, very low quality evidence**).

Peri-operative management of antithrombotic agents in urology

In principle, there are four options to manage use of antithrombotic agents (Figure 2) during the peri-operative period:

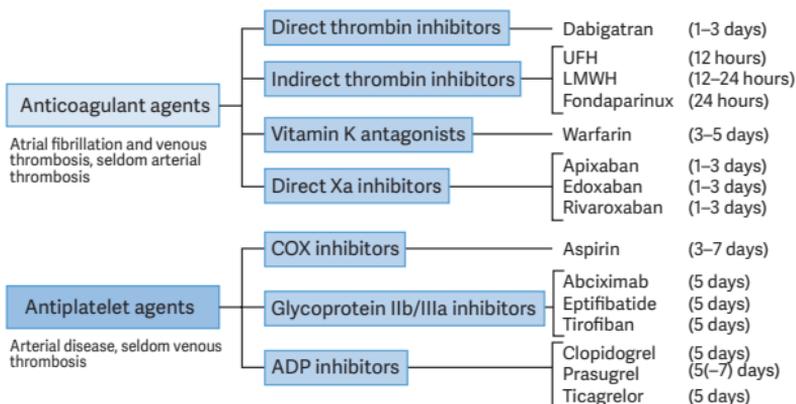
- 1) to defer surgery until antithrombotic agents are not needed;
- 2) stop antithrombotic agents prior to surgery and restart sometime after surgery;
- 3) continue through the surgical procedure;
- 4) administer alternative antithrombotic agents that may still reduce the risk of thrombosis but with less risk of bleeding than agents patients are currently using (“bridging”).

Recent evidence has demonstrated that bridging increases bleeding without preventing thrombosis. The Panel therefore makes one of two recommendations for patients receiving antithrombotic agents regularly and contemplating surgery:

- 1) discontinue antithrombotic therapy for the period around surgery;
- 2) in those with a temporary very high risk of thrombosis, delay surgery until that risk decreases. If it is not possible to delay, continuing antithrombotic therapy or bridging through surgery may be advisable.

Figure 2: The most widely used antithrombotic agents in patients undergoing urologic surgery

Required period of stopping drug before surgery (if desired) provided in parentheses.



Recommendations for peri-operative management

Five days is an appropriate time to stop antiplatelet agents before surgery, while the optimal time to stop varies across anticoagulants (for details, see Figure 2).

R24. In all patients receiving antiplatelet agents (aspirin, clopidogrel, prasugrel, ticagrelor), except those with very high risk of thrombosis (see recommendations 26 and 27), the Panel recommends stopping antiplatelet agents before surgery and not initiating any alternative antithrombotic therapy (**strong, high-quality evidence**).

R25. In patients in whom antiplatelet agents have been stopped before surgery, the Panel recommends restarting when bleeding is no longer a serious risk - typically four days post-surgery - rather than withholding for longer periods (**strong, moderate-quality evidence**).

R26. In patients with very high risk of thrombosis receiving antiplatelet agents (those with drug-eluting stent placement within six months, those with bare metal stent placement within six weeks, those with transient ischemic attack (TIA) or stroke within 30 days) in whom surgery can be delayed, the Panel recommends delaying surgery (**strong, high-quality evidence**).

R27. In patients with very high risk of thrombosis receiving antiplatelet agents (those with drug-eluting stent placement within six months, those with bare metal stent placement within six weeks, those with TIA or stroke within 30 days) in whom surgery cannot be delayed, the Panel suggests continuing the drugs through surgery (**weak, low-quality evidence**).

R28. In all patients receiving anticoagulant agents (unfractionated heparin, low molecular weight heparin [LMWH], warfarin, fondaparinux, dabigatran, apixaban, rivaroxaban, edoxaban), except those with very high risk of thrombosis (see recommendation 26), the Panel recommends stopping drugs before surgery (see Figure 2) and not initiating any alternative antithrombotic therapy (**strong, high-quality evidence**).

Note: Patients with creatinine clearance <30 ml/min should not receive dabigatran, apixaban, rivaroxaban or edoxaban.

R29. In patients in whom anticoagulants have been stopped before surgery, the Panel recommends restarting when bleeding is no longer a serious risk - typically four days post-surgery - rather than withholding for longer periods (**strong, moderate-quality evidence**).

R30. In patients with a new VTE, it is recommended that surgery is delayed for at least one month, and if possible three months, to permit discontinuation of anticoagulation pre-operatively, rather than operating within one month of thrombosis (**strong, high-quality evidence**).

R31. In patients receiving any anticoagulant with a severe thrombophilia, such as antithrombin deficiency and antiphospholipid antibody syndrome, the Panel suggests anticoagulation with either heparin or LMWH through surgery, rather than stopping anticoagulation before and after surgery (**weak, low-quality evidence**).

R32. In patients with high-risk mechanical prosthetic heart valves, such as cage-ball valves, receiving warfarin, the Panel recommends bridging with LMWH prior and subsequent to surgery, rather than discontinuing anticoagulation peri-operatively (**strong, high-quality evidence**). Anticoagulation in these patients involves stopping the warfarin five days prior, commencing LMWH four days prior, omitting LMWH on the day of surgery, and recommencing LMWH and warfarin after surgery.

This short booklet text is based on the more comprehensive EAU Guidelines (ISBN: 978-90-79754-91-5), available to all members of the European Association of Urology at their website: <http://www.uroweb.org/guidelines/>.