Thromboprophylaxis and bleeding diathesis in minimally invasive stone surgery

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Abstract | With populations ageing and active treatment of urinary stones increasingly in demand, more patients with stones are presenting with an underlying bleeding disorder or need for regular thromboprophylaxis, by means of antiplatelet and other medication. A practical guide to thromboprophylaxis in the treatment of urinary tract lithiasis has not yet been established. Patients can be stratified according to levels of risk of arterial and venous thromboembolism, which influence the requirements for antiplatelet and anticoagulant medications, respectively. Patients should also be stratified according to their risk of bleeding. Consideration of the combined risks of bleeding and thromboembolism should determine the perioperative thromboprophylactic strategy. The choice of shockwave lithotripsy, percutaneous nephrolithotomy or ureteroscopy with laser lithotripsy for treatment of lithiasis should be determined with regard to these risks. Although ureteroscopy is the preferred method in high-risk patients, shockwave lithotripsy and percutaneous nephrolithotomy can be chosen when indicated, if appropriate guidelines are strictly followed.

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Introduction

Urinary tract lithiasis is increasing in incidence, especially in industrialized countries, probably owing to changing socioeconomic conditions in the Western world and increasing prevalence of diabetes and obesity.[1,2] Shockwave lithotripsy, flexible ureterorenoscopy and percutaneous nephrolithotomy are commonly used minimally invasive methods to treat patients with stones, either alone or in combination. With ageing populations, treatment of urinary stones in the elderly becomes a challenge, as urologists frequently encounter patients with multiple and complex comorbidities, who are on regular antiplatelet or anticoagulation medication or who have a chronic bleeding disorder. There is a delicate balance between preventing thromboembolism by maintaining thromboprophylaxis, and avoiding excessive bleeding due to surgery. The advice of internists is frequently sought regarding guidance on discontinuing and resuming treatment with aspirin, warfarin, low molecular weight heparin and various antithrombotic agents. Despite existing guidelines and recommendations for management of surgical patients who have bleeding diathesis, or are receiving antithrombotic medication, confusion is frequently encountered, and dosing and duration protocols differ between clinical practices.[3,4] Furthermore, guidelines that are mainly based on open procedures might not always apply to modern minimally invasive endourological stone management.

The management of therapeutic thromboprophylaxis in the perioperative period has not been investigated for urological surgery. In a feasibility study of general surgical patients at high risk of perioperative venous thromboembolism,[5] oral anticoagulation therapy was continued with a reduction of warfarin dose so as to achieve a preoperative international normalized ratio (INR) of 1.5–2.0, with supplemental heparin treatment to maintain these levels when required. This modified warfarin dosing had previously been shown to be safe and effective in the prevention of venous thromboembolism after hip or knee replacement. In this study,[5] 58% of surgical procedures were significantly invasive (in surgical risk category 3–5 according to the Johns Hopkins Medical Institutions Surgical Classification System). Of 100 patients, only two had major postoperative bleeding and four had minor bleeding. Although the authors acknowledged the limitations of their observational study, they concluded that this protocol might be a reasonable option in selected patients. A meta-analysis by Siegal *et al.*[6] concluded that patients with long-term vitamin K antagonist treatment who received heparin bridging seemed to have an increased risk of overall and major bleeding events in the periprocedural period, but a similar risk of thromboembolic events, compared with patients receiving no periprocedural bridging (level of evidence [LE]: 1a).

The management of thromboprophylaxis in urology in general—and stone surgery in particular—is still not conclusively decided upon. In this Review, we discuss the evidence for thromboprophylaxis and the management of anticoagulant and antiplatelet medication during stone surgery, with particular emphasis on perioperative treatment and bridging therapy.

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Key points

- Urologists frequently encounter patients with multiple and complex comorbidities who are on regular antiplatelet or anticoagulation medication or who have a chronic bleeding disorder
- Decisions regarding perioperative and postoperative thromboprophylaxis in patients undergoing urological surgery, particularly stone surgery, are frequently met with confusion
- Systematic thromboprophylaxis with low molecular weight heparin as a subcutaneous injection once daily, until complete mobilization, is recommended in high-risk patients and when lithotripsy is not day case surgery
- Patients undergoing stone surgery should be stratified into groups according to the risk of bleeding and the risk of thromboembolic events for the respective intervention (high, intermediate and low risk)
- Bridging therapy should be directed by the inherent risk of bleeding in individual patients, according to American College of Chest Physicians guidelines, as should perioperative treatment with antiplatelet agents
- A decision algorithm for each lithotripsy modality according to antithrombotic medication used should help the operating surgeon achieve the fine balance required between patient safety and treatment effectiveness

Coagulation pathways

Following injury, the process of primary haemostasis begins with vasoconstriction and the adhesion of thrombocytes (platelets) to exposed subendothelial structures (Figure 1).[7] The simultaneous release of thrombin signals irreversible platelet aggregation. This aggregation is further enhanced by the release of arachidonic acid and its conversion by cyclooxygenase enzymes into endoperoxides and thromboxanes.

The coagulation cascade constitutes the secondary haemostatic mechanism, by which fibrin is produced, contributing to irreversible thrombocyte aggregation by forming bridging nets that trap platelets, therefore creating the thrombus (Figure 1).[7] Vitamin K is a cofactor required for the maturation of coagulation factors II (prothrombin), VII, IX and X. Warfarin and derivative anticoagulants block vitamin K activity by preventing its recycling, whereas heparins bind to and activate antithrombin.

Perioperative risk stratification

The management of thromboprophylactic regimens in patients undergoing stone surgery is an area of much controversy and debate, as practices vary considerably and are mostly dependent on individual departmental policies and hospital protocols. Given that the haemorrhagic risk differs with respect to each method of lithotripsy used, we argue that patients should be stratified into groups according to risk of bleeding and risk of thromboembolic events for the respective intervention. In their milestone systematic review on behalf of the American College of Chest Physicians (ACCP), Douketis *et al.*[3] describe urological surgeries that are associated with an increased bleeding risk during perioperative antithrombotic drug administration, including transurethral prostate resection, bladder resection, nephrectomy and kidney biopsy.[8–10] Data regarding periprocedural anticoagulation management of patients with urological conditions are limited and principally describe outcomes related to transurethral prostate surgery.[11] The European Association of Urology (EAU) guidelines clearly state that all lithotripsy options except ureteroscopy are contraindicated in the face of uncorrected bleeding tendencies.[12] The EAU recommend that anticoagulation therapy should be stopped before stone removal, but if treatment cessation is not possible, retrograde ureterorenoscopy with laser lithotripsy should be the treatment of choice. However, the recommendation refers only to salicylates and carries a low level of evidence (LE: 3).[12] We suggest that the need for discontinuation and bridging treatments should be individualized and balanced against the potential for intraoperative bleeding. In addition, bleeding in the postoperative period might delay resumption of necessary anticoagulation therapy, leading to an increased risk of deep vein thrombosis.[13] Thus, allocating patients into risk groups on the basis of the risk of arterial or venous thromboembolism is essential.

Arterial thromboembolism

Patients with mechanical heart-valves face an increased risk of arterial thrombosis, including ischaemic cerebrovascular events, especially when INR <2. These patients can be further classified into three risk levels according to the annual incidence of thrombotic events.[3,14] The high-risk level (>10% risk of thromboembolism per year) includes patients with mechanical heart-valves, especially mitral valves or one of the older generation aortic valves (caged-ball or tilting-disk), and also patients who have had ischaemic stroke or transient ischaemic attack within the past 6 months. The intermediate-risk level (4–10% risk per year) includes patients with a bileaflet aortic valve and one or more of the following risk factors: atrial fibrillation, history of ischaemic stroke or transient ischaemic attack, hypertension, diabetes, age ≥75 years and congestive heart failure. The low-risk level (<4% risk per year) includes patients with a bileaflet aortic valve with no additional comorbidities.

Patients with rheumatic heart-valve disease and patients on warfarin for chronic atrial fibrillation constitute a distinct, high-risk level subgroup upon discontinuation of their medication. For these patients, Gage *et al.*[15] have developed a prospectively validated risk assessment tool, $CHADS_2$, that assigns to patients an additive value according to the presence of one or more of five additional comorbidities. These comorbidities are history of congestive heart failure, previous ischaemic stroke or transient ischemic attack, hypertension, diabetes and age ≥75 years. Patients can be further stratified into high-risk, intermediate-risk or low-risk levels, based on the $CHADS_2$ scores.

Venous thromboembolism

Patients at risk of venous thromboembolism can be similarly classified into three risk levels according to the annual incidence of thrombotic events.[3] Patients with recent (within 3 months) episodes of deep vein thrombosis or pulmonary embolism, hereditary thrombophilia (Protein S or C deficiency, antithrombin deficiency, homozygosity for Factor V Leiden and G20210A prothrombin gene mutations), antiphospholipid syndrome or active cancer belong in the high-risk level (>10% of

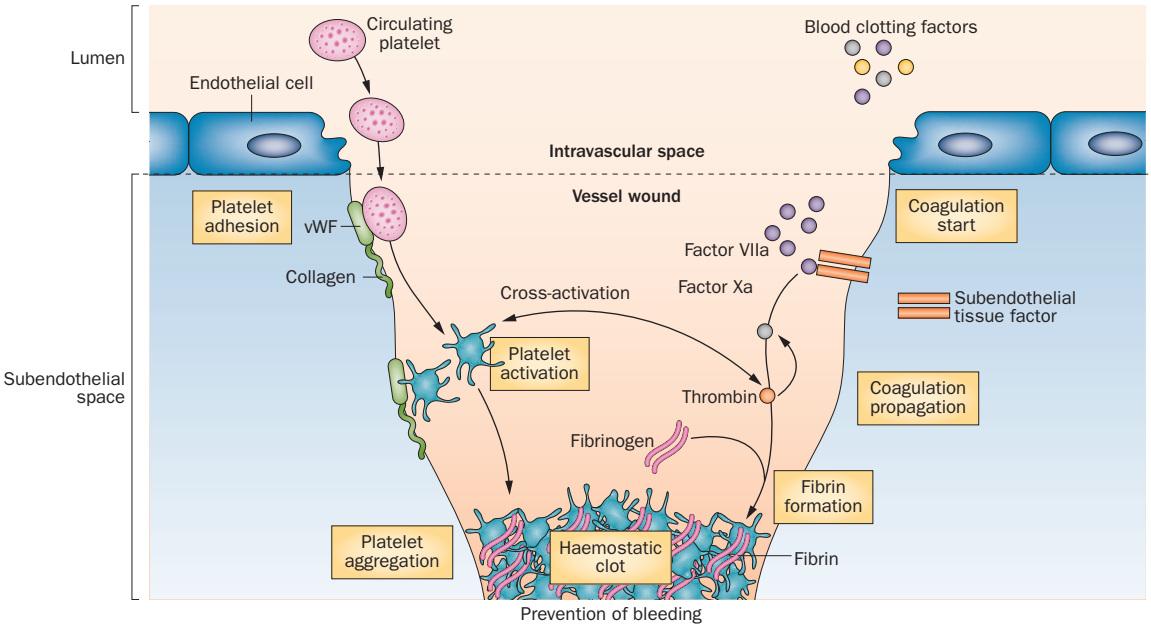

Figure 1 | Haemostasis involves two principle components, platelets and fibrin, acting in concert to generate a wound-sealing clot. Recruitment of platelets involves specific surface receptors, such as the platelet glycoprotein Ib complex (not shown), which recognize subendothelial ligands, including von Willebrand factor (vWF), that are normally concealed by the endothelial barrier, becoming exposed only after vessel damage. Coagulation requires sequential activation of blood-based serine proteases and their cofactors. The process is initiated by a subendothelial tissue factor, which is exposed on vessel injury, enabling interaction with factor VIIa to trigger the coagulation cascade, which culminates in the formation of fibrin. Permission obtained from Nature Publishing Group © Engelmann, B. & Massberg, S. *Nat. Rev. Immunol.* **13**, 34–45 (2013).

thromboembolism per year). Patients with history of deep vein thrombosis or pulmonary embolism 3–12 months prior to operation, heterozygosity for Factor V Leiden or prothrombin gene mutation, and patients with previous malignancy are considered to be in the intermediate-risk level (5–10% per year). All other patients are considered in the low-risk level (<5% per year).

Thromboprophylaxis in stone surgery

In general, surgical patients can be considered at low, intermediate or high risk of experiencing thromboembolic events.[3] Although it is minimally invasive, lithotripsy—whether extracorporeal (by shockwave lithotripsy) or intracorporeal (by ureterorenoscopy and percutaneous nephrolithotomy)—is a surgical procedure that can have complications and postoperative effects on the physiology of the individual. In the absence of protracted immobilization, shockwave lithotripsy and ureteroscopy performed as day cases seem to have very low risk of thromboembolism, whereas percutaneous nephrolithotomy and complicated ureteroscopy (prolonged operating time, impacted stone or large stone burden) carry an intermediate risk of thromboembolic events, with incidences of deep vein thrombosis (in 2–8% of patients), pulmonary embolism (1–4% of patients) and fatal pulmonary embolism (<1%).[16–18] This intermediate-risk level might be upstaged to a high-risk level, depending on individual patient factors and characteristics, such as high BMI, pre-existing systemic disease, family history and age. Current international guidelines on postoperative thromboprophylaxis recommend systemic anticoagulation therapy with low molecular weight heparin as a subcutaneous injection once daily in high risk patients during the whole period of hospitalization or until complete mobilization of the patient is achieved.[3,16] Procedures that can be performed as day cases, such as ureteroscopy and shockwave lithotripsy, do not usually require pharmacological thromboprophylaxis. Additional measures have to be taken into consideration for patients who have undergone bariatric surgery or who have chronic renal failure, in whom low molecular weight heparin use has to be adjusted, and mechanical thromboprophylaxis such as use of graded compression elastic stockings and calf muscle pumps might also be required.[3,16] The placement of a temporary inferior vena cava filter is advisable when low molecular weight heparin is contraindicated in obese patients with previous positive history for deep vein thrombosis.[3,16] For patients with inherent or acquired risk factors (such as thrombophilia or malignancy, respectively), further anticoagulation treatment for 10 days following discharge is recommended.[3,16]

Perioperative thromboprophylaxis

Perioperative anticoagulant therapy

The choice and dose of the anticoagulant is one of the most troublesome and confusing decisions faced by the clinician in contemporary practice. Vitamin K antagonists, such as warfarin, are the most commonly used oral anticoagulants. Oral heparin formulations have also been developed. Dabigatran and rivaroxaban are next-generation anticoagulants that are as effective as warfarin

Table 1 | Oral anticoagulants[19]

Mode of action	Non-proprietary name	Proprietary name	Indications
Vitamin K antagonism	Warfarin sodium	Marevan® (Mercury Pharma, UK)	Prevention of systematic embolization in AF or after insertion of metallic heart-valve
	Acenocoumarol	Sinthrome® (Novartis, Switzerland)	Treatment of DVT and PE
	Phenidione	NA	
Direct thrombin inhibition	Dabigatran etexilate	Pradaxa® (Boehringer Ingelheim, Germany)	DVT prophylaxis post THR or TKR Prevention of stroke and systemic embolization in AF
Direct inhibition of activated factor X (factor Xa)	Apixaban	Eliquis® (Bristol-Myers Squibb, USA)	Option for DVT prophylaxis post THR or TKR
	Rivaroxaban	Xarelto® (Bayer, Germany)	Option for the prevention of stroke and systemic embolization in AF

Abbreviations: AF, atrial fibrillation; DVT, deep vein thrombosis; NA, not applicable; PE, pulmonary embolism; THR, total hip replacement; TKR, total knee replacement

Box 1 | Parenteral anticoagulants

Heparin and heparinoids
Heparin (unfractionated)
Danaparoid sodium (heparinoid)

Low molecular weight heparins
Dalteparin sodium (Fragmin®, Pfizer, Sweden)
Enoxaparin sodium (Clexane®, Aventis, France)
Tinzaparin sodium (Innohep®, LEO, Denmark)

in anticoagulation and have a better safety profile with regards to bleeding complications.[19] According to the National Institute for Health and Care Excellence guidelines (UK), both are options for venous thromboembolism prophylaxis in adults having elective total hip replacement surgery or elective total knee replacement surgery, as well as for prevention of stroke and systemic embolism in patients with atrial fibrillation.[19] A number of parenteral and oral anticoagulant preparations are commonly used (Table 1 and Box 1), and low molecular weight heparin treatment encompasses both prophylactic and therapeutic dose regimens (Table 2).[4]

Bridging therapy

Bridging therapy is defined as the administration of a short-acting anticoagulant, consisting of subcutaneous low molecular weight heparin or intravenous unfractionated heparin for a 10–12 day period during interruption of vitamin K antagonist therapy when the INR is not within a therapeutic range.[3] In patients with a mechanical heart-valve, atrial fibrillation or at high risk of thromboembolism, bridging anticoagulation is recommended (LE: 2c).[3] In patients at low risk of thromboembolism, bridging of anticoagulation is no longer recommended during interruption of warfarin (LE: 2c). In patients at moderate risk, the decision is based on an assessment of individual factors related to the patient and the surgery (LE: 2c).[3]

It is recommended that warfarin administration should be stopped at least 5 days prior to any surgical intervention, so as to achieve INR <1.5 (LE: 1b).[3] Vitamin K is administered to those patients who maintain an INR >1.5 for more than 2 days despite discontinuation of warfarin. The recommended dose is 1–2.5 mg single dose (LE: 2c).[3] The same dose is also recommended for rapid reversal of INR in cases of urgent surgery.

Patients who receive bridging anticoagulation with a therapeutic dose of parenteral unfractionated heparin should stop this heparin treatment 4–6 h before surgery (LE: 2c).[3] Bridging therapy with low molecular weight heparin in a therapeutic dose should stop 24 h before surgery (LE: 2c).[3] Suggested low molecular weight heparin formulations include: enoxaparin, 1 mg/kg body weight twice daily by subcutaneous injection or dalteparin, 100 anti-Xa international units/kg twice daily by subcutaneous injection (LE: 2c).[3]

For patients at low risk of bleeding, warfarin can be resumed 24 h after the surgical procedure. In all other patients, warfarin is best withheld for 48–72 h postoperatively (Table 3). Prophylactic low molecular weight heparin can be administered during that period (LE: 2c).[7] Special consideration has to be provided for patients with renal impairment. For prophylactic doses, no adjustment is required for those with mild or moderate renal insufficiency (eGFR >30 ml/min/1.73m^2). For those with severe impairment, enoxaparin should be decreased to 30 mg daily.[3]

Perioperative management of antiplatelet drugs

Antiplatelet drugs that irreversibly inhibit platelet aggregation and function include acetylsalicylic acid (aspirin), clopidogrel, ticlopidine and prasugrel. Dipyridamole, cilostazol and NSAIDs represent reversible inhibitors of platelet aggregation. The latest review by Douketis *et al.*[3] contains the recommendation for patients who require noncardiac surgery that aspirin can be continued up to the time of surgery instead of stopping 7–10 days beforehand (LE: 2c). For patients with a coronary stent who require surgery, treatment should be deferred to ≥6 weeks after bare-metal stent placement and ≥6 months after drug-eluting stent placement (LE: 1c); for patients requiring surgery within these time limits, continuing antiplatelet therapy perioperatively is recommended instead of stopping therapy 7–10 days before surgery (LE: 2c).[3] In a 2013 review of new antiplatelet agents, it was recommended that for intermediate-bleeding-risk procedures, at least one antiplatelet agent (usually aspirin) should be continued, clopidogrel or ticagrelor should be discontinued 5 days before, and prasugrel should be discontinued 7 days before surgery.[20] Gupta *et al.*[21] have indicated that management of patients with coronary stents undergoing urological surgery should be multidisciplinary. The authors recommended that the postoperative risk of active bleeding should be considered in the decision for continuation of antiplatelet agents. They concluded that expert assistance, usually from a cardiology specialist, is required in such cases, especially for high-risk procedures. Such assistance could be of particular value when planning a technically challenging percutaneous nephrolithotomy, although no consideration was given, in this particular article, to complex stone surgery.

Table 2 | Dosing regimens for low molecular weight heparins[47]

Non-proprietary name	Proprietary name	DVT prophylaxis dose	DVT/PE treatment dose*
Dalteparin sodium	Fragmin®	5,000 IU 12 h before surgery, 5,000 IU daily thereafter	BW <46 kg: 7,500 IU daily BW 46–56 kg: 10,000 IU daily BW 57–68 kg: 12,500 IU daily BW 69–82 kg: 15,000 IU daily BW >82 kg: 18,000 IU daily
Enoxaparin sodium	Clexane®	40 mg 12 h before surgery, 40 mg daily thereafter	1.5 mg/kg BW daily
Tinzaparin sodium	Innohep®	3,500 IU 2 h before surgery, 3,500 IU daily thereafter	175 IU/kg BW daily

*For DVT/PE treatment, dosing continues alongside concurrent oral anticoagulation until adequate anticoagulation is established. Abbreviations: BW, bodyweight; DVT, deep vein thrombosis; IU, international units; PE, pulmonary embolism.

Perioperative management of bleeding diathesis

The term bleeding diathesis includes all diseases that influence the coagulation cascade directly or indirectly, namely chronic hepatic failure, haemophilia A (factor IX) and B (factor VIII), von Willebrand disease, various functional platelet disorders and thrombocytopenias. Current recommendations suggest that precise diagnosis and targeted therapy governed by expert haematologists should precede any surgical intervention in such patients, as they are considered at high risk of bleeding complications and, therefore, in danger of uncontrollable, profuse bleeding and haemodynamic instability leading to mortality.[3]

Thromboprophylaxis in urinary lithiasis

Treating stones in patients receiving antithrombotic therapy or with bleeding diathesis is challenging. A survey published in 2011 showed wide variations in perioperative management practices for patients receiving chronic anticoagulation therapy undergoing urological procedures.[22] A fine balance has to be achieved between patient safety and treatment effectiveness. To reach that goal, two questions need to be answered. First, which lithotripsy modality is the most appropriate, and second, how will the choice of treatment affect the final outcome in view of an increased chance of bleeding? The answer to the first question might be that the choice for the individual patient is determined by a combination of the respective guidelines for active stone removal and antithrombotic management. The answer to the second question might be more elaborate, as it seems to largely depend on technical considerations of each of the modalities in the context of thromboprophylaxis and bleeding diathesis. We compiled data relating to perioperative anticoagulation with warfarin (Table 3) and antiplatelet medication (Table 4), based on a review of studies relating to each treatment option (Table 5).

Shockwave lithotripsy

Shockwave lithotripsy has been reported to be safe and efficient in cases of corrected anticoagulation and stable or corrected haemorrhagic diathesis (namely haemophilia and von Willebrand disease, supplemented with von Willebrand factor).[23–26] In such patients, the incidence of asymptomatic retroperitoneal haematoma is reported to be ~4%, and that of symptomatic perirenal haematoma is 0.7%.[27] It is important to note, however, that ureterorenoscopy is the method of choice in these patients.[12,18,28] Factors that have been associated with perirenal haematoma following shockwave lithotripsy are age, uncontrolled hypertension, type of lithotripter (electrohydraulic, electromagnetic or piezoelectric) and high-frequency treatment rate.[29–32]

No clear guideline exists for patients requiring antiplatelet agents and shockwave lithotripsy. The evidence relating to such treatment derives largely from retrospective studies and case reports. Klingler *et al.*[33] reported the results of 35 patients on such medication or with controlled bleeding disorders who underwent stone treatment during a 6-year period. In 18 patients treated with shockwave lithotripsy, the effectiveness was lower than expected. The complication rate was also high in this group (33.3%), and the overall poor performance was attributed to prolonged time to complete stone clearance. Another retrospective study suggested that a coagulopathy screen for known blood factor deficiencies is warranted prior to shockwave lithotripsy, to enable instigation of appropriate treatment if necessary.[25] In a

Table 3 | Risk-stratified anticoagulation protocols for patients on warfarin undergoing stone surgery[3]

Procedure	Risk of bleeding	Risk of thrombosis*		
		Low	Intermediate	High
fURS	Low	Stop warfarin 5 days preoperatively; no bridging therapy; can resume warfarin 24 h postoperatively	Stop warfarin 5 days preoperatively; bridging therapy recommended; can resume warfarin 24 h postoperatively	Stop warfarin 5 days preoperatively; bridging therapy recommended; resume warfarin 24 h postoperatively
SWL	Intermediate	Stop warfarin 5 days preoperatively; no bridging therapy; can resume warfarin 48–72 h postoperatively	Stop warfarin 5 days preoperatively; bridging therapy recommended; resume warfarin 48–72 h postoperatively	Stop warfarin 5 days preoperatively; bridging therapy recommended; resume warfarin 48–72 h postoperatively
PCNL	High	Stop warfarin 5 days preoperatively; no bridging therapy; can resume warfarin 48–72 h postoperatively	Stop warfarin 5 days preoperatively; bridging therapy recommended; resume warfarin 48–72 h postoperatively	Stop warfarin 5 days preoperatively; bridging therapy recommended; resume warfarin 48–72 h postoperatively

*Resume oral anticoagulation therapy when there is no longer a concern for active bleeding. Abbreviations: fURS, flexible ureterorenoscopy; PCNL, percutaneous nephrolithotomy; SWL, shockwave lithotripsy.

Table 4 | Risk-stratified surgery and antiplatelet protocols for stone surgery methodologies[3,20]

Procedure	Risk of bleeding	Risk of thrombosis		
		Low	Intermediate	High*
fURS	Low	Withhold aspirin and clopidogrel (maximum 7 days)	Continue aspirin perioperatively and stop clopidogrel (maximum 7 days)	Continue aspirin perioperatively
SWL	Intermediate	Withhold aspirin and clopidogrel (maximum 7 days)	Expert opinion required (cardiology); defer treatment or consider other treatment option if absolutely necessary	Defer treatment or consider other treatment option if absolutely necessary
PCNL	High	Withhold aspirin and clopidogrel (maximum 7 days)	Expert opinion required (cardiology); defer treatment or consider other treatment option if absolutely necessary	Defer treatment or consider other treatment option if absolutely necessary

*High risk of thrombosis includes patients with recent insertion of coronary stents (<6 weeks for placement of bare metal stent and <6 months for placement of drug-eluting stent). Abbreviations: fURS, flexible ureterorenoscopy; PCNL, percutaneous nephrolithotomy; SWL, shockwave lithotripsy.

series of 23 patients, Zanetti *et al.*[34] found that suspending antiplatelet agents for 8 days while offering a bridging therapy with unfractionated heparin before shockwave lithotripsy resulted in no haemorrhagic or thromboembolic complications. It must be stressed, however, that heparin does not have antiplatelet properties.

Currently, shockwave lithotripsy is contraindicated in pregnancy and in patients with uncontrolled bleeding disorders.[12] Severe and life-threatening complications have been reported in patients taking clopidogrel and undergoing shockwave lithotripsy.[35,36] Appropriate bridging therapy should be provided for patients on warfarin, whereas it is wise to involve associated specialties in reaching a decision for patients on antiplatelet agents (Table 4). Deferring treatment or opting for expectant management or ureteroscopy is advised for high risk patients. A study assessing the relative risk of bleeding from shockwave lithotripsy in patients assigned to the same risk level for thromboembolic events would provide useful information for planning treatment and the potential requirement for further intervention.

Percutaneous nephrolithotomy

Percutaneous nephrolithotomy is the preferred approach for large volume renal stone disease, partial or complete staghorn calculi and in selected cases of abnormal anatomy, such as horseshoe kidney and ectopia.[17] Intraoperative and postoperative bleeding are the most frequent and troublesome complications of percutaneous intrarenal surgery.[37] Currently, it is recommended that anticoagulants should be discontinued before percutaneous nephrolithotomy.[12,38] Two retrospective studies and one review have directly addressed the issue of percutaneous lithotripsy in the setting of anticoagulation. Kefer *et al.*[39] presented a retrospective analysis of 27 patients who underwent percutaneous nephrolithotomy following reversal of warfarin anticoagulation (to normalize INR) and bridging therapy (LE: 2c). Two patients had significant bleeding and one had a thromboembolic complication; these complications were all successfully managed conservatively. The reported stone-free rate was 93%. Nerli *et al.*[40] reviewed data from 36 patients who had similar stone-free results, but higher bleeding rates. In the review by Gross and Bach,[41] the use of risk stratification for thromboembolism was emphasized, with reference to an early classification system proposed by Van Cangh,[42] which also divides patients into high-risk, intermediate-risk and low-risk groups according to underlying comorbidity. Percutaneous nephrolithotomy is a unique surgical approach that does not routinely involve haemostasis, except in the control of bleeding as a complication. Thus, interdisciplinary consultation is advised for patients receiving anticoagulation therapy who are planning to undergo the procedure. For those with recent insertion of cardiovascular stents, the procedure is best deferred (Table 4).

Flexible ureterorenoscopy

Flexible ureterorenoscopy with laser lithotripsy is considered to be the preferred method of stone surgery in patients receiving anticoagulation therapy or with bleeding tendency.[12,18,43] This preference has been further supported by a systematic review presenting evidence for the safety and effectiveness of this technique in these patients (LE: 2a).[18] A deterrent factor for most urologists is bleeding in the microenvironment of the ureter during ureteroscopy, which could result in premature termination of the procedure. For this reason, it is common practice to interrupt antiplatelet and anticoagulant treatment before the procedure; however, this interruption might not always be necessary. Kuo *et al.*[44] successfully treated eight patients with stone disease ureteroscopically with the holmium laser without discontinuing anticoagulation, with no reported bleeding complications. Watterson *et al.*[45] presented results for 25 patients with known, uncorrected bleeding diathesis of various aetiologies who underwent ureteroscopic laser lithotripsy without major bleeding complications. Turna *et al.*[46] retrospectively reviewed ureterorenoscopy records to identify 37 patients in whom antithrombotic therapy was not discontinued before surgery, and compared them with a similar cohort who were not receiving antithrombotics. The median postoperative haemoglobin decrease was greater in the antithrombotic group than in the control group. The stone-free rate, intraoperative and postoperative complications and haemorrhagic or thromboembolic adverse events were comparable between the two groups. Of interest, no procedure had to be terminated in the antithrombotic group due to poor visibility from bleeding. Ureteroscopy is safe and efficient in such patients and can be conducted even without discontinuing treatment.

Table 5 | Studies on the treatment of patients with stones receiving antithrombotic agents

Study	*n*	Lithotripsy	Bleeding diathesis	Mean stone size (mm)	Stone-free rate (%)	Complications (%)
Zanetti *et al.* (2001)[34]	23	SWL	Aspirin, ticlopidine, dipyridamole	NA	61	No bleeding reported
Klingler *et al.* (2003)[33]	18	SWL	Warfarin, thrombocytopenia, liver cirrhosis	Renal: 9.7 Ureteric: 7.0	88.9	33.3 (bleeding, MI)
Ruiz Marcellán *et al.* (1992)[25]	17	SWL	Thrombocytopenia, platelet defects	NA	NA	No bleeding reported
Kefer *et al.* (2009)[39]	27	PCNL	Warfarin, clopidogrel, cilostazol	NA	93	11.1 (bleeding, DVT)
Nerli *et al.* (2012)[40]	36	PCNL	Warfarin, clopidogrel, aspirin	6.4	75	41.6 (postoperative bleeding)
Kuo *et al.* (1998)[44]	8	fURS	Warfarin, thrombocytopenia, vWD	NA	75	25 (epistaxis, urinary retention)
Watterson *et al.* (2002)[45]	25	fURS	Warfarin, thrombocytopenia, vWD, liver cirrhosis	11.9	96	8 (renal colic, AF)
Turna *et al.* (2008)[46]	37	fURS	Warfarin, clopidogrel, aspirin	13.2	81.1	10.8 (haematuria, UTI)

Abbreviations: AF, atrial fibrillation; DVT, deep vein thrombosis; fURS, flexible uereterorenoscopy; MI, myocardial infarction; *n*, number of patients; NA, not available; PCNL, percutaneous nephrolithotomy; SWL, shockwave lithotripsy; vWD, von Willebrand disease.

Conclusions

Stone surgery has enough particularities to be considered as a separate category among urological interventions. The regulation of antithrombotic treatment and the relative risk of thromboembolic events ultimately rest with the operating surgeon under the auspices of the anaesthesiologist and with expert opinion from cardiology and haematology specialists when required. Ureteroscopy is favoured in patients receiving antithrombotic therapy, always with respect to stone size and location. Shockwave lithotripsy is a special form of stone treatment, which requires strict adherence to bridging protocols and assessment of patient risk factors in most cases. The same applies for percutaneous nephrolitholapaxy, although further studies are warranted to establish the safety and cost-effectiveness of this procedure, especially in comparison to ureteroscopy. Patients with cardiovascular stents constitute a unique risk group and specialist input should always be sought regarding their treatment. A working panel of the EAU is currently conducting a systematic literature research and meta-analysis in order to compose the first complete guideline addressing thromboprophylaxis and anticoagulation for urological surgery as a whole, including stone surgery in particular.

Review criteria

We searched for original articles focusing on randomized studies, original articles, review articles and case reports in PubMed, MEDLINE and Embase published between April 1969 and March 2013. The search terms we used were “stone surgery”, “lithotripsy”, “antiplatelet treatment”, “anticoagulation treatment”, “perioperative thromboprophylaxis”, “perioperative bridging therapy” and “coagulopathy”. All papers identified were full-text papers. We also searched the reference lists of identified articles for further papers. A total of 46 articles, published between April 1988 and March 2013, were selected, according to the highest level of relevance and evidence.

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16. Nicolaides, A. N. *et al.* Prevention and treatment of venous thromboembolism. International consensus statement (guidelines according to scientific evidence). *Int. Angiol.* **25**, 101–161 (2006).
17. Srisubat, A., Potisat, S., Lojanapiwat, B., Setthawong, V. & Laopaiboon, M. Extracorporeal shock wave lithotripsy (ESWL) versus percutaneous nephrolithotomy (PCNL) or retrograde intrarenal surgery (RIRS) for kidney stones. *Cochrane Database of Systematic Reviews*, Issue 4. Art. No.: CD007044. http://dx.doi.org/10.1002/14651858.CD007044.pub2.

18. Aboumarzouk, O. M., Somani, B. K. & Monga, M. Flexible ureteroscopy and holmium:YAG laser lithotripsy for stone disease in patients with bleeding diathesis: a systematic review of the literature. *Int. Braz. J. Urol.* **38**, 298–305 (2012).
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Author contributions

A. Bourdoumis, T. Stasinou and S. Kachrilas researched the data for the article. A. Bourdoumis and T. Stasinou provided a substantial contribution to discussions of the content. A. Bourdoumis wrote the article. A. Bourdoumis, S. Kachrilas, A. G. Papatsoris, N. Buchholz and J. Masood contributed to review and/or editing of the manuscript before submission.