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Lesson 32 Volume 39

# Management of Antithrombotics in Urologic Surgery*

*Learning Objective:* At the conclusion of this continuing medical education activity, the participant will be able to describe evidence-based perioperative management strategies for antithrombotic therapies. The participant will also be able to state the relative safety of certain strategies for specific urologic procedures.

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## INTRODUCTION

Since the last AUA Update on antithrombotics in urologic surgery, many prospective and high quality retrospective studies have significantly contributed to the topic in both the general and urologic literature. In this Update we review the basic mechanisms of available antithrombotic medications, and highlight the most important and clinically relevant findings of those investigations.

## CLASSIFICATION OF ANTITHROMBOTIC MEDICATIONS AND THEIR MECHANISMS OF ACTION

*Antiplatelet therapy*. Circulating platelets remain in a non-adhesive state prior to activation, which is triggered by several biochemical pathways. Figure 1 summarizes the known major pathways that are pharmacologically relevant, with important aggregation inhibitors. Among those are aspirin, nonsteroidal anti-inflammatory drugs, dipyridamole (often sold as a combination drug with aspirin; trade name Aggrenox®), and thienopyridines (purinergic G protein coupled receptor inhibitors or $P2Y_{12}$ inhibitors) and their derivatives such as clopidogrel (Plavix®) and ticagrelor (Brilinta®). These medications can be classified according to their specific mechanism of action and whether the mechanism is reversible or irreversible (Appendix 1).

The average life span of circulating platelets is 8–10 days, with approximately 10%–15% being replaced daily.[1] ***Following discontinuation of irreversible platelet inhibitors (eg aspirin, clopidogrel) the number of functional circulating platelets is adequate for normal clotting within 4–5 days.[2]*** **Extensive clinical experience has shown that *nonsteroidal anti-inflammatory drugs, which are reversible platelet inhibitors, can be safely discontinued 1–2 days preoperatively*.** However, it appears platelet function following discontinuation of reversible ticagrelor has significant interpatient variability.[3] Of note, COX-2 selective inhibitors such as celecoxib (Celebrex®) have minimal effect on COX-1 and thromboxane A levels, and thus have negligible effects on platelet function.[4] Although the mechanisms of action for antiplatelet medications are the same for all patients, individual responses may vary. Thus, laboratory assessments of platelet function measuring inhibition by aspirin or clopidogrel may be of value in certain cases.

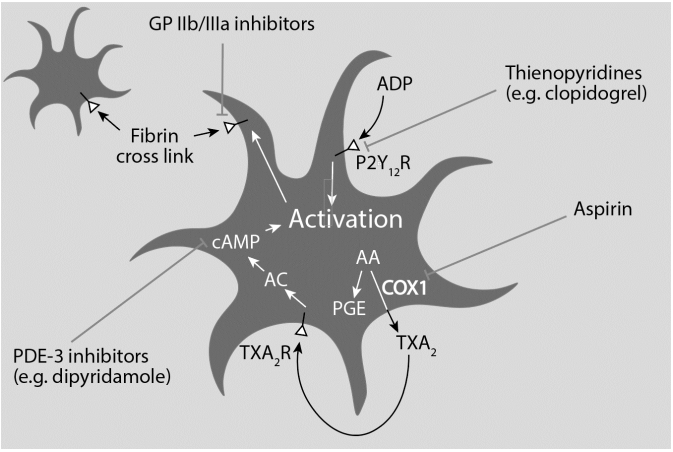


**Figure 1.** Antiplatelet therapies with mechanisms of action. *AA*, arachidonic acid. *AC*, adenylyl cyclase. *ADP*, adenosine phosphate. *cAMP*, cyclic adenosine monophosphate. *COX1*, cyclooxygenase-1. *GP*, glycoprotein. *$P2Y_{12}R$*, purinergic G protein coupled receptor for ADP. *PDE-3*, phosphodiesterase type 3. *PGE*, prostaglandins. *$TXA_2$*, thromboxane $A_2$.

*Anticoagulation therapy*. Outside of platelets, proteins within the serum and extravascular space generate the thrombin necessary for clot formation, and these are coagulation factors. Medications that target these factors are commonly used in patients with increased thromboembolic risk secondary to atrial fibrillation, artificial heart valves, hematological disorders causing hypercoagulable states or concomitant DVT in order to prevent cerebrovascular accident or pulmonary embolism. Frequently encountered medications in this class are warfarin, direct oral anticoagulants such as apixaban (Eliquis®), rivaroxaban (Xarelto®), dabigatran (Pradaxa®) and others, and injectable heparin (Appendix 1). Warfarin and DOACs are primarily used for chronic disease, while injectable agents are primarily administered for acute disease or while the patient is transitioning off of or onto warfarin, also known as "bridging" therapy. Figure 2 summarizes the various levels of the cascade brought about by these medications.

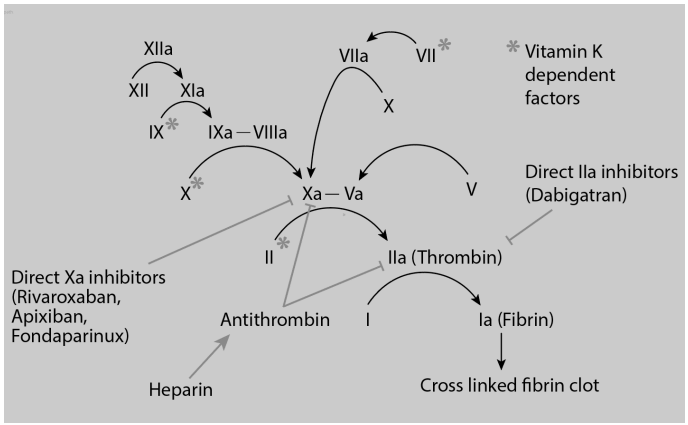


**Figure 2.** Anticoagulation therapies and their mechanisms of action; coagulation cascade.

Laboratory tests such as prothrombin time, international normalized ratio and partial thromboplastin time can be used to monitor therapeutic effects of anticoagulants. Although warfarin at many institutions is withheld 5–7 days prior to procedures, medication effects are best monitored through international normalized ratio as interpatient metabolisms can be variable. ***On average an international normalized ratio of***

**ABBREVIATIONS**: AUA (American Urological Association), DES (drug eluting stents), DOAC (direct oral anticoagulant), DVT (deep venous thrombosis), TIA (transient ischemic attack), TURBT (transurethral resection of bladder tumor), TURP (transurethral prostatectomy), VTE (venous thromboembolism)

***1.5 is reached in about 4 days after cessation of warfarin in patients with therapeutic levels at baseline.***[5] Heparins have a shorter half-life and can be monitored with partial thromboplastin time. However, it should be noted that this test can be highly variable in patients administered unfractionated heparin. For this reason among others low-molecular-weight heparin is increasingly used and in most cases is safe without monitoring, it may be monitored with anti-Xa levels if required.[6]

## PERIOPERATIVE MANAGEMENT OF ANTITHROMBOTICS IN THE GENERAL LITERATURE

Although bleeding complications are the bane of any surgeon's best efforts, perioperative thromboembolic complications all too often lead to irreversible and morbid patient outcomes. Recent advances in the literature have made an evidence-based approach to perioperative management of antithrombotics feasible and implementable for a large number of patients. **However,** ***many clinical risk factors remain excluded from contemporary trials.*** Thus, perioperative management of antithrombotic therapy should always take into consideration individual patient risk of thromboembolism against the risk of bleeding with a specific procedure. Strategies for risk stratification are available in the urologic literature.[7] ***In patients with multiple conditions or complex medical histories, ideally management involves a multidisciplinary approach including urology, anesthesiology, cardiology, hematology and/or neurology.*** **Common exclusion criteria of large trials or identified risk factors for thromboembolic and bleeding events include but are not limited to** ***patients with recent thromboembolic event, any prior stroke, any degree of renal failure, any heart valve, or uncommon bleeding or thrombophilic disorders.***

For the non-complex patients, however, non-urologic academic societies have published recent guideline updates and applicable clinical studies that are important for urologic practice. Below is a discussion of these recommendations and findings stratified by indication for antithrombotic medication.

*Mechanical heart valves*. Perioperative thromboembolic risk for patients with mechanical heart valves is on the order of 1%.[8] The most recent American College of Chest Physicians guidelines recommend risk stratification of patients on vitamin K antagonists, consisting of bridging in high risk, no bridging in low risk and consideration of bridging in moderate risk.[9] ***High risk is defined as having any prosthetic mitral valve, recent stroke or transient ischemic attack, any aortic caged ball or tilting disk.*** Moderate risk is defined as having a bileaflet aortic valve and 1 other risk factor, a number of which are listed in the guidelines.

*Recent cardiac stents*. The RECO study remains the most robust prospective multicenter investigation of patients with cardiac stents discontinuing antiplatelet therapy.[10] Approximately 10% of the patients >3 months after stenting underwent urologic surgery, and thus the results are highly relevant to our patients. ***Of the 1134 patients who underwent surgery following cardiac stent placement 10.9% had cardiovascular events, mostly myocardial infarctions, of whom 14.5% expired.*** Five risk factors were elucidated, which included preoperative hemoglobin <10 gm/dl, creatinine clearance <30 ml per minute, emergent or high risk surgery and complete discontinuation of dual antiplatelet therapy for more than 5 days preoperatively. Bleeding complications were seen in 9.5% of patients, of whom 12% expired. Four risk factors for bleeding were found, which consisted of preoperative hemoglobin <10 gm/dl, creatinine clearance between 30 and 60 ml per minute, <3 months since stent placement and high risk surgery. All intraperitoneal surgeries were considered high risk.

The 2016 American Heart Association updated recommendations have changed the optimal duration of dual antiplatelet therapy after drug eluting stent and subsequent recommendations regarding perioperative management (previously 12 months after DES).[11] These recommendation changes come in the wake of multiple randomized controlled trials that included newer generation DES. **In short,** ***elective surgery less than 3 months after placement of DES is not recommended and can be considered 3 to 6 months after placement of DES with discontinuation of dual antiplatelet therapy if the delayed surgical risk is greater than the risk of cardiac ischemia.*** Optimally elective surgery should be delayed until 6 months after placement of DES. For bare metal stents recommendations are to delay non-urgent non-cardiac surgery for at least 1 month after bare metal stent placement. If dual antiplatelet therapy must be discontinued, then the guidelines recommend discontinuing $P2Y_{12}$ inhibitor therapy while continuing aspirin.

*Atrial fibrillation*. **Results of the randomized BRIDGE trial were reported in 2015, which showed** ***a no-bridge protocol was non-inferior to bridging in a large cohort of 1884 patients with atrial fibrillation.***[12] The overall thromboembolic and major bleeding rates were 0.3% and 1.3%, respectively, in the no-bridge protocol vs 0.4% and 3.2% in the bridging protocol (p=0.01 for non-inferiority of thromboembolic events; p=0.005 for superiority of no-bridge for bleeding). A large proportion of patients underwent urologic procedures, ie 5.6% underwent minor and 25.1% underwent major procedures that included prostatectomy and TURBT. This provides level 1 evidence that most patients with atrial fibrillation do not require bridging, keeping in mind the inclusion and exclusion criteria from this trial. Baseline demographics for study participants included $CHADS_2$ score (congestive heart failure, hypertension, age >75 years, diabetes and prior stroke/TIA), ie the stroke risk classification schema for patients with atrial fibrillation. Notably the average $CHADS_2$ score was 2.3, and only 2% of patients had a $CHADS_2$ score of 5 or 6. ***Major exclusion criteria were history of stroke or recent TIA, poor creatinine clearance and thrombocytopenia.*** Thus, bridging may still be appropriate in select high risk patients.

Another large prospective clinical trial for patients with atrial fibrillation, ***the PAUSE trial, investigated a simple periprocedural management strategy of DOACs that showed overall low thromboembolic events (<1%) and major bleeding rates (<2%) at 30 days.***[13] ***DOACs were discontinued 1 day before low bleeding risk procedures and 2 days before high bleeding risk procedures, and restarted 1 day after low risk procedures and 2–3 days after high risk procedures.*** This included 278 urologic procedures (9.2% overall), where "bladder resections," prostatectomies and nephrectomies were listed as high bleeding risk procedures, and no urologic procedures were named under low bleeding risk procedures. A total of 3007 patients on apixaban, dabigatran and rivaroxaban were studied. ***Patients with cognitive impairment or low creatinine clearance were excluded.*** Patients with prior stroke were not excluded and made up 7.9% of the cohort.

The results of the BRIDGE and PAUSE trials will undoubtedly be incorporated into the next American College of Chest Physicians guidelines. However, as it stands, the 2012 guidelines recommend bridging in high risk patients with atrial fibrillation.[9] High risk includes $CHADS_2$ score of 5 or 6, recent stroke/TIA within 3 months and having concurrent rheumatic valvular disease. A recent large retrospective study using the Danish National Patient Register (481,183 patients) showed risk of 30-day thromboembolism decreased with time since ischemic stroke, with history of atrial fibrillation having less of an effect than not having atrial fibrillation (OR 2.18 with atrial fibrillation vs 4.74 without).[14]

*Venous thromboembolism*. VTE is the most common cause of 30-day mortality in abdominal and pelvic cancer surgeries.[15] Two recent meta-analyses investigated VTE risk in cancer and non-cancer urologic procedures specifically.[16, 17] ***The highest VTE rates were seen in both open and robotic cystectomies (2.6%–11.6%), as well as open prostatectomies with extended lymph node dissections (3.9%–15.7%).***[15] Lymph node dissection alone is associated with an eightfold increase in DVT risk.[18] Renal cancer surgeries were variable dependent on specific risk factors such as prior VTE, body mass index and age, and varied from 0.7%–11.6%. The majority of non-cancer surgeries had low VTE risk. However, the quality of evidence was determined to be low or very low by the authors.

Overall guidelines are highly diverse in recommendations regarding prophylaxis.[19] The AUA determined in 2009 that there was insufficient evidence available to perform a meta-analysis and provide subsequent evidence-based guidelines. Instead, a Best Practices Statement was released recommending stratification of individual patients into 4 different risk categories (low, moderate, high and very high risk) based on age and other risk factors (Appendix 2).[20] These were adopted from existing American College of Chest Physicians guidelines.[19] The number of risk factors was not explicitly defined.

Low risk patients require no prophylaxis, moderate and high risk patients require either intermittent pneumatic compression or pharmacoprophylaxis, and very high risk patients require both. Extended prophylaxis was briefly discussed and recommended in select very high risk patients.[20]

**However, there is moderate grade evidence to show *extended thromboprophylaxis reduces both symptomatic and asymptomatic DVTs without an increase in major bleeding events in major abdominal and pelvic surgery.***[21] Many of the randomized clinical trial data come from the general surgery literature, specifically colorectal surgery. The effect was seen for both open and laparoscopic surgery. Four weeks appears to be superior to short courses.[22] American College of Chest Physicians guidelines for perioperative anticoagulation management recommend in patients already on anticoagulation for VTE bridging for high risk cases (VTE in last 3 months or severe thrombophilia), no bridging in low risk cases and consideration of bridging for intermediate risk cases (VTE in last 3–12 months, recent cancer or non-severe thrombophilia).

*Secondary prevention for coronary artery disease and stroke*. Lifelong aspirin therapy is often indicated for patients with prior stroke or myocardial infarction. **A recent meta-analysis confirmed *the discontinuation of aspirin therapy in this context is associated with a measurable increased risk of recurrent thromboembolic events.***[23] Thus, more than ever, perioperative management of aspirin therapy is a crucial skill for any practicing urologist.

**In the general literature *the STRATEGEM study* was a randomized trial to investigate the bleeding risks of continued aspirin vs placebo.[24] A total of 291 patients on antiplatelet therapy received either *substitution with 75 mg aspirin or placebo* during the perioperative period.** Of the procedures 15.5% were urologic. The trial ended early and was underpowered. However, no difference was seen between the 2 groups in terms of thromboembolic or major bleeding events.

Of course, urologic procedures may be at exceptionally high risk for bleeding, notably prostatic surgery.[25] Thus, for that reason among others urology specific data are needed to identify bleeding risks for specific procedures and strategies.

## PERIOPERATIVE MANAGEMENT OF ANTITHROMBOTICS IN UROLOGIC LITERATURE

As previously emphasized, periprocedural management of antithrombotic therapy should focus on individual patient risk stratification for thromboembolic events vs major bleeding events. Multiple observational studies exist in the urology literature that focus on the perioperative bleeding risk in patients on chronic antiplatelet or anticoagulation therapy, and some have even generated bleeding risk stratification systems for various procedures.[26] However, more data are needed regarding specifically the thromboembolic event rate for urologic procedures, which we know also varies between different surgeries. Since the last AUA Update, many studies have been published regarding the safety of perioperative continuation of low dose aspirin as well as updates on ureteroscopy and partial nephrectomy.

*Prostate biopsy*. ***Multiple studies have shown transrectal prostate biopsy is safe to perform on low dose aspirin without increase of major bleeding events.***[27] There are some survey data for transrectal biopsy showing no increase in bleeding complications for patients on anticoagulation including warfarin when compared to men who are not on chronic anticoagulation.[28] Another small study compared the outcomes of patients on warfarin who were bridged to others who were not bridged; however, the sample size was small with high selection bias.[29] More research is needed in this area. One study has investigated antithrombotics in 598 patients receiving transperineal biopsies and found that although clot retention was more frequent in patients taking at least 1 antiplatelet or anticoagulant medication compared to controls not on medication (2% vs 0.2%, $p < 0.05$), other complications between the 2 groups were similar.[30]

*Sacral neuromodulator placement*. Neurological damage secondary to epidural hematoma has been reported in around 0.03%–0.12% of patients.[31] However, no literature investigating anticoagulation management for sacral neuromodulator placement exists. Thus, more research is needed in this area.

*Bladder outlet procedures*. Transurethral prostatectomy has long been thought to be unsafe to perform in patients on continued antiplatelet or anticoagulation due to high transfusion rates even without antithrombotic medication. ***Multiple studies, including a small randomized trial of 53 patients, have shown that continued use of low dose aspirin does not increase bleeding complications in TURP.***[32, 33] Early reinitiation of aspirin within 24 hours of continuous bladder irrigation

discontinuation did not increase the need to restart continuous bladder irrigation, rehospitalization or time to catheter removal in a randomized trial of 120 patients undergoing TURP, open prostatectomy or TURBT.[34]

Few studies have directly reported bleeding related complications for patients on continued anticoagulation. In a study of 57 patients on continued oral anticoagulation during TURP only slightly increased continuous bladder irrigation, catheter and hospitalization times were seen, although patients were threefold more likely to have postoperative urinary retention (18% vs 6%, p=0.06).[33] Bridging does appear to increase the number of bleeding complications overall, although available studies were not powered to further categorize the types of complications.[35, 36]

The data are mixed as to whether or not bleeding complications are increased for patients on anticoagulation or antiplatelet therapy undergoing holmium laser enucleation of the prostate compared to controls not on therapy.[37–40] However, reports of increased complications show only modest elevation over controls. A recent study of 2178 patients showed ceased anticoagulation use increased bleeding complications compared to controls not on anticoagulation.[39] Of patients on DOACs 7.4% experienced clot retention and 1.3% required a blood transfusion, with similar rates for patients on vitamin K antagonists, vs 2.2% and 0.2% in the control group. Outcomes are similar for thulium vapoenucleation of the prostate on anticoagulation. One study compared bridging to continued anticoagulant/antiplatelet use in 103 patients, and the hemoglobin drop was significantly higher in the bridging group.[41] ***In contrast to TURP and laser enucleation procedures, photoselective (potassium-titanyl-phosphate laser) vaporization of the prostate has produced a mounting body of research showing it is safe on both continued anticoagulation and continued antiplatelet therapy, with most series reporting no immediate significant bleeding complications***.[42,43] Delayed significant bleeding risks, however, have been reported, up to 4% in one series.[42]

*Transurethral resection of bladder tumor*. Overall, significant bleeding complications from TURBT are variably reported in the literature. In many recent reviews the rate may be as low as 1%–3%,[44] while unplanned readmissions due to hematuria and clot retention have been reported as high as 7.6%.[45] Not many studies are available in the literature investigating antithrombotic management specifically. In 1 small, single institution study (174 patients) there appears to be a higher rate of clot retention with continued antithrombotic therapy but not of transfusions or larger hemoglobin drop.[46] There was a non-significant higher rate of clot retention in the continued antithrombotic group for tumors >1 cm. However, type of antithrombotic therapy appeared to have no effect. In a study of monopolar TURBT (213 patients) continuous perioperative use of aspirin did not increase risk of transfusion, reintervention or hospitalization.[47]

*Ureteroscopy*. The bleeding risk of performing ureteroscopy with holmium:YAG lithotripsy in patients on antiplatelet or anticoagulation in a large meta-analysis was 5 times that of controls, although the absolute risk was low in both groups (2.5% vs 0.42%).[48] A large, single center, retrospective study (314 patients) that specifically examined the effect of antiplatelet therapy indicated that there was no significant bleeding between study and control groups.[49] Current AUA Guidelines recommend with grade C evidence that ureteroscopy is the preferred procedure for stone treatment in patients who require continuous antiplatelet/anticoagulant use.

However, anticoagulation in ureteroscopy is not without risk. **A sister study of the above continued antiplatelet cohort analyzed the effect of anticoagulation (272 patients) and showed that *the significant bleeding rate in ureteroscopy may be as high as 15% in those on continued anticoagulation, compared to 9% in those who were bridged and 3% in those who withheld anticoagulation without bridging*.[50]** The authors of this study had a broad definition of significant bleeding including 1) procedure termination explicitly due to bleeding and difficult visualization resulting in a second operative intervention, 2) unplanned, immediate postoperative admission for bleeding, 3) emergency room visit for hematuria, 4) subsequent hospital admission for hematuria management (after dismissal home following the procedure) and (5) unplanned return to the operating room for evaluation of ongoing bleeding. The majority of these events were made up of patients who required a second non-urgent operation to complete their definitive stone treatment. Notably 75% of cases (3 of 4) requiring a return to the operating room involved a DOAC as opposed to warfarin. Thus, although ureteroscopy may be the safest option for patients on anticoagulation, patients should be appropriately counseled on their increased risk and providers should subsequently choose a perioperative plan for medication management.

*Percutaneous nephrolithotomy*. In the largest multicenter global registry of percutaneous nephrolithotomy cases (the CROES study) bleeding was the second most common complication after fever, at an overall rate of 7.8%.[51] Externally validated clinical scoring systems have been shown to predict estimated blood loss.[52] A recent retrospective review (274 patients) indicated that patients who continued low dose aspirin throughout the perioperative setting did not have a higher overall complication rate, bleeding complication rate or transfusion rate compared to patients who were not on aspirin.[53] In contrast, chronic anticoagulation use in this setting is associated with increased Clavien-Dindo grade complications even with a discontinuation plan.[54] In a small study of 26 patients on antiplatelet or anticoagulation medication a careful perioperative management strategy was investigated with acceptably low bleeding complication rates.[55]

*Extracorporeal shock wave lithotripsy.* Historically continued antithrombotic therapy around the time of ESWL® has been contraindicated due to fear of the increased risk of perinephric hematoma. Indeed, patients with clotting disorders treated with ESWL have been reported to have a 20 to 40-fold increase in their risk of hematoma.[56] One retrospective review of 6172 patients undergoing ESWL reported a hazard ratio of 4.2 (p=0.036) for patients on an antiplatelet at the time of preoperative evaluation, although the perioperative management strategy was not explicitly described.[57] A small series of 14 patients on chronic anticoagulation requiring a heparin bridge did not have any bleeding complications.[58]

*Laparoscopic prostatectomy*. **A recently published large meta-analysis showed that *continued perioperative use of low dose aspirin in robot-assisted laparoscopic prostatectomy is not associated with increased complication rates, blood loss or length of stay, and although there was a higher transfusion rate, absolute rates in both groups were low, at 2.6% and 1.6% for continued aspirin and no aspirin, respectively*.[59]** This is reflected in multiple retrospective studies, many of which did

not see a difference in transfusion rates,[60–63] and is consistent with the general surgery literature, which has also indicated the safety of continued single antiplatelet use in laparoscopic surgery.[64] In a case-control study of patients on chronic anticoagulation undergoing robot-assisted laparoscopic prostatectomy low-molecular-weight heparin bridging was associated with a higher transfusion rate (23% vs 2%, p=0.042) compared to no bridging but not more complications or re-hospitalizations.[65]

*Laparoscopic cystectomy*. Robot-assisted laparoscopic radical cystectomy is likely associated with fewer transfusions compared to open surgery.[66] However, no studies to our knowledge have investigated the effect of antithrombotics on laparoscopic cystectomy outcomes. Notably the rate of both preoperative and postoperative thromboembolic events with radical cystectomy is high, at 16% during preoperative chemotherapy and 6.2% within 90 days of surgery.[67] Thus, many patients will either be on anticoagulation at the time of surgery (assuming they are still surgical candidates) or, regardless, have a very high perioperative risk of thromboembolism. More research is needed in this area.

Similarly there are no studies on perioperative antithrombotic management around the time of simple cystectomy. However, it has been shown that the overall thromboembolic risk, specifically DVT risk, is much lower than with radical cystectomy (2.1%).[68]

*Laparoscopic partial and radical nephrectomy*. There have been many recent publications on the safety of perioperative antithrombotic therapy for renal surgery. ***Most studies have shown that continued low dose aspirin is not associated with higher bleeding complications in robotic partial nephrectomies.***[69, 70] Of note, there was a trend toward increased urgent selective embolization in patients with continued aspirin use vs patients who withheld aspirin. However, this did not reach statistical significance (3% vs 6%, p=0.07).[70] Perioperative DVT prophylaxis has also been shown to be safe in robotic partial nephrectomy.[71] Continued clopidogrel use, however, appears to be associated with significant bleeding risk in partial nephrectomy. In a small retrospective review 5 of 8 patients on continued clopidogrel experienced a major bleeding complication, whereas patients with continued aspirin use did not experience a higher bleeding rate compared to controls.[69]

In a large single institution retrospective study of patients undergoing nephrectomy on chronic anticoagulation who required bridging there was a higher overall complication rate, transfusion rate and length of stay than would be expected.[72] Both robotic and open procedures were studied, and of note, the minimally invasive approach did not appear to decrease complication rate or need for additional transfusions. However, there was a non-significant observation of less blood loss and lower number of transfusions required.

*Open surgery*. To our knowledge, there are no studies on the effect of chronic antithrombotic therapy or perioperative management in patients undergoing orchiectomy, urethral slings, hydrocele or varicocele surgery. There are some data about the increased bleeding complication risks for patients undergoing pelvic reconstruction.[73] However, specific management strategies are not discussed.

Compared to minimally invasive approaches, open urologic cancer surgeries likely have more blood loss and bleeding complications.[74] However, both open cystectomies and prostatectomies are likely safe on continued aspirin therapy. ***A large 2-center study of open cystectomy on continued aspirin therapy indicated no difference in blood loss, transfusion rates or complications compared to controls who withheld aspirin or patients not on aspirin*** **(461 patients, 50 on continued aspirin).**[75] Open prostatectomy may also be safe on aspirin. In a study of 2461 patients, of whom 137 had continued aspirin therapy, transfusion rates were higher during open prostatectomy on aspirin compared to no aspirin (21% vs 8%).[62] However, the effect of aspirin was not present after propensity score matching. The authors conclude this may be due to a higher transfusion threshold in cardiac patients.

## CONCLUSION

Many strides have been made in recent years in our understanding of perioperative antithrombotic management. In large part randomized clinical trials have clarified which groups of patients on anticoagulation do not require perioperative bridging and standardized protocols for discontinuing therapy in high bleeding risk surgery. Additionally low dose aspirin appears to be very safe to operate on for the vast majority of procedures. Future trials will clarify the role of high dose aspirin so a definitive perioperative strategy can be identified. Other antiplatelet medications appear to carry higher perioperative bleeding risks when continued. However, many can be safely supplanted with low dose aspirin around the time of surgery.

### DID YOU KNOW?

- Patients with complex perioperative bleeding and/or thromboembolic risk factors should be co-managed with an interdisciplinary team involving urology, cardiology, neurology, anesthesiology or other specialists.
- Elective urologic procedures should be delayed at least 6 months after placement of drug eluting stents.
- Most patients with atrial fibrillation on chronic anticoagulation do not require perioperative bridging in the absence of specific risk factors such as prior stroke.
- There is evidence to support the safety of performing the vast majority of urologic procedures on continued low dose aspirin.
- Extended thromboprophylaxis should be considered in abdominal cancer operations.

**Appendix 1.** Antithrombotic medication classes by mechanism of action

| | Mechanism of Action | Examples |
|---|---|---|
| Antiplatelet medications | Irreversible non-selective COX inhibitors | aspirin |
| | Reversible non-selective COX inhibitors | ibuprofen (Advil®, Motrin®), naproxen (Aleve®) |
| | Irreversible thienopyridines ($P2Y_{12}R$ inhibitors) | clopidogrel (Plavix®) |
| | Reversible thienopyridines ($P2Y_{12}R$ inhibitors) | ticagrelor (Brilinta®) |
| | Glycoprotein IIb/IIIa inhibitors | abciximab, eptifibatide |
| | Phosphodiesterase-3 inhibitors | dipyridamole (with aspirin=Aggrenox®) |
| Anticoagulant medications | Vitamin K antagonists | warfarin (Coumadin®) |
| | Direct IIa inhibitors | dabigatran (Pradaxa®) |
| | Direct Xa inhibitors | rivaroxaban (Xarelto®), apixaban (Eliquis®), fondaparinux (Arixtra®) |
| | Antithrombin activators | heparin, low-molecular-weight heparin (Lovenox®) |

**Appendix 2.** American College of Chest Physicians VTE risk factors[19]

| |
|---|
| Acute medical illness |
| Cancer |
| Cancer therapy |
| Central venous catheterization |
| Erythropoiesis-stimulating agents |
| Estrogen containing contraception or hormone replacement |
| Immobility, lower extremity paresis |
| Increasing age |
| Inflammatory bowel disease |
| Myeloproliferative disorders |
| Nephrotic syndrome |
| Obesity |
| Paroxysmal nocturnal hemoglobinuria |
| Pregnancy or postpartum |
| Previous thromboembolism |
| Selective estrogen receptor modulator therapy |
| Surgery |
| Thrombophilia |
| Trauma |
| Venous compression |

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# Study Questions Volume 39 Lesson 32

1. A 64-year-old man with a short bulbar urethral stricture has elected to undergo urethroplasty. He had 2 drug eluting stents placed 4 months ago and is currently taking both aspirin and clopidogrel. It is recommended that this patient
   a. continue both clopidogrel and aspirin perioperatively given his high thrombotic risk
   b. hold his clopidogrel for 10 days before surgery but continue aspirin
   c. hold both clopidogrel and aspirin
   d. delay surgery for 2 additional months

2. A 72-year-old woman with a history of atrial fibrillation on warfarin therapy, recent TIA and stress urinary incontinence has elected to undergo a sling procedure. The optimal perioperative management of this patient's anticoagulation is
   a. discussion by an interdisciplinary team
   b. hold warfarin preoperatively without bridging
   c. hold warfarin preoperatively with bridging
   d. continue warfarin perioperatively

3. A 69-year-old man with a history of stroke is on clopidogrel. He has an elevated prostate specific antigen and is scheduled to undergo transrectal prostate biopsy. The optimal periprocedural management of this patient's antiplatelet therapy is
   a. discussion by an interdisciplinary team
   b. hold clopidogrel preprocedurally
   c. substitute clopidogrel for aspirin preprocedurally
   d. continue clopidogrel periprocedurally

4. An 80-year-old woman with a history of multiple strokes, atrial fibrillation on apixaban and a 1 cm ureteropelvic junction calculus is in the office to discuss definitive stone treatment options. Ureteroscopy is recommended. Following interdisciplinary discussion of management of her anticoagulation a decision is made to continue her apixaban perioperatively. The most common bleeding complication in this situation is
   a. blood transfusion
   b. clot retention
   c. early termination due to poor visualization, requiring a second procedure
   d. pseudoaneurysm

5. A 75-year-old man with benign prostatic hyperplasia is on maximal medical therapy. He has a 50 gm prostate and acute urinary retention and is considering a surgical intervention. He has a prosthetic mitral valve and is on anticoagulation. His cardiologist has told him it is too high a risk to discontinue his anticoagulation. The bladder outlet procedure associated with the lowest bleeding risk on continued anticoagulation is
   a. TURP
   b. holmium laser enucleation of the prostate
   c. thulium laser ablation of the prostate
   d. photoselective vaporization of the prostate

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