How I Do It: Anticoagulation management for common urologic procedures

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Appropriate perioperative management of antithrombotic medications is critical; for every patient, the risk of bleeding must be balanced against individual risk of thrombosis. There has been a rapid influx of new antithrombotic therapies in the past 5 years, yet there is a lack of clear and concise guidelines on the management of anticoagulant and antiplatelet therapy during urologic surgery. Here we describe our approach to perioperative antithrombotic counseling, including the timing of stopping and restarting these medications. These practice guidelines have been developed in consultation with the Vascular Medicine service at our institution as well as after a review of current literature, and apply to common urologic procedures. Many cases are complex and require medical consultation or a multidisciplinary approach to management. We believe that by presenting our systematic method of antithrombotic management, including when to involve other discplines, we can increase knowledge and comfort amongst urologists in managing these medications in the perioperative period.

Key Words: anticoagulation, urologic surgery, guidelines

Introduction

A wide variety of disease processes and interventions require therapeutic anticoagulation or antiplatelet therapy. As survival outcomes for the population with these chronic conditions improve, there is a growing number of anticoagulated patients who will require surgical intervention. The urologist must be familiar with these agents so as to properly balance bleeding risk with the risk of thromboembolism in the perioperative period.

Historically, there were only a handful of anticoagulant and antiplatelet medications (here referred to generally as the "antithrombotic" drug class). The past several years have seen the introduction of new antithrombotic drugs to the market with novel mechanisms of action. Anticoagulant medications now include unfractionated heparin, low-molecular weight heparin, warfarin, direct thrombin inhibitors (DTIs), and the newer direct oral anticoagulants (DOACs). Common oral antiplatelet drugs include COX-1 inhibitors, $P2Y_{12}$ receptor inhibitors and GPIIb/IIIa receptor inhibitors. These drugs affect various aspects of the platelet activation, adhesion and aggregation pathway. The pharmacokinetic profile of each drug varies, and in conjunction with patient and procedure characteristics, dictates the appropriate timing for preoperative discontinuation, postoperative restart and return to therapeutic status.

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In order to increase knowledge of antithrombotics among urologists, we present here our systematic approach to their management in the perioperative period of common urological procedures.

Method and technique

These guidelines were created utilizing recent literature, the American Urological Association White Papers,[1] and in consultation with the Jefferson Acute Thrombosis Service (JATS) team at our institution. This team is unique to our hospital and manages much of the anticoagulation prescribed for the perioperative setting. In the absence of such a team, we recommend referral to Cardiology, Hematology or the managing physician that has expertise in the indication for the patient's anticoagulation. It is important to emphasize that these guidelines are a starting point for patient management and that every situation must be assessed on an individual basis. The prescribing provider's input, as well as that of experts in anticoagulation, cannot be emphasized enough.

When a patient on anticoagulation undergoes preoperative planning and evaluation in our practice, we begin by discussing the medication, indication and dosing. A review of antithrombotic medications, their pharmacokinetics and reversal agents are found in Tables 1 and 2. We also discuss with the patient who will be responsible for managing their anticoagulation during this time. We feel that it is extremely important to designate one office or person, as this eliminates confusion for providers and patients.

Next, we find it helpful to organize our thinking by answering three questions for each patient:

1. What risk factors does the patient have for thromboembolism?
2. What is the risk of bleeding given the patient's medical history and the particular procedure they are undergoing?
3. Based on these factors, should anticoagulation be stopped, for how long, and should the patient be bridged for the duration?

TABLE 1. **Characteristics of common anticoagulant medications**

Medications	**Warfarin**	**Heparin**	**Rivaroxaban**	**Apixaban**
Half-life	40 hours	30-90 minutes	5-9 hours	8-15 hours
Renal dosing	No adjustment necessary	No adjustment necessary	Lower dosing if CrCl ≤ 50 mL/min	Lower dosing if serum Cr ≥ 1.5 mg/dl or if pt is 80 y or older
Reversal agents	Vitamin K, fresh frozen plasma, 4-factor PCC	Protamine sulfate	Andexanet alpha, 3-factor PCC	Andexanet alpha, P 3-factor CC
Ideal preoperative stop time	5-7 days (if INR therapeutic range: 5 days; if supratherapeutic: 7 days)	4-5 hours	1-3 days[a]	1-3 days[a]
Medications	**Argatroban**	**Enoxaparin**	**Dabigatran**	**Fondaparinux**
Half-life	40-50 minutes	3-5 hours	14-17 hours	17-21 hours
Renal dosing	No adjustment necessary	Lower dosing if CrCl ≤ 30 mL/min	Lower dosing if CrCl ≤ 30 mL/min	Lower dosing if CrCl ≤ 50 mL/min
Reversal agents	No known reversal	Protamine sulfate	Idarucizuma[b]	No known reversal
Ideal preoperative stop time	1-2 hours	1 day	2-3 days[b]	2-4 days

PCC = prothrombin complex concentrate; INR = international normalized ratio
[a]based on CrCl: CrCl < 15 = 3 days, CrCl 15-30 = 2 days, CrCl > 30 = 1 day
[b]based on CrCl: CrCl < 15 = 4 days, CrCl 15-29 = 3 days, CrCl 29-59 = 2 days, CrCl > 60 = 1 day

TABLE 2. **Characteristics of common antiplatelet medications**

Medications	Aspirin 81 mg	Aspirin 325 mg	Clopidogrel	Prasugrel	Ticagrelor
Half-Life (platelet effect ~7-10 days)	2-4 hours	2-4 hours	6 hours	7 hours	7-9 hours
Renal dosing	Not recommended for CrCl < 10 mL/min	Not recommended for CrCl < 10 mL/min	No adjustment necessary	No adjustment necessary	No adjustment necessary
Reversal agents	Platelet transfusion, DDAVP (Desmopressin)[a]				
Ideal preoperative stop time	Secondary prevention of ASD[b]; Continue if low bleeding risk	Secondary prevention of ASD; 7 days	3 days	5 days	3-5 days
	Occlusion prevention of stent/CABG: Continue medication or stop 7 days prior (if outside of post-stent/ CABG window)	Occlusion prevention of stent/CABG: Continue medication or stop 7 days prior (if outside of post-stent/ CABG window)			
Ideal postoperative start time	After surgery	After surgery	Within 1 day	1-3 days	1-3 days

[a]limited evidence exists to support the overall mortality benefit of administering these agents for reversal of bleeding events.
ASD = atherosclerotic disease; CABG = coronary artery bypass graft

Question 1: What risk factors does the patient have for thromboembolism?

When considering anticoagulation therapy, it is important to remember that these drugs are prescribed for two primary reasons: 1) A patient has formed a clot and is likely to form another (or to prevent worsening of the clot while the body breaks it down), or 2) An underlying disease process increases a patient's risk of clot formation. Factors that increase the risk of thromboembolism include, but are not limited to, a recent VTE,[2] active cancer,[3] a prosthetic mitral valve,[4] atrial fibrillation (with a CHA_2DS_2-VASc score ≥ 2)[5] and recent placement of drug-eluting coronary artery stents.[6] The risk factors can be stratified into "low" and "high" risk, as some conditions convey a more significant risk of thromboembolism, Table 3. Surgical intervention itself is a risk factor for thromboembolism - tissue damage, inflammation, fluid shifts and hemodynamic changes contribute to a situation conducive to clot formation[6].

Importantly, patients with more than two unprovoked VTEs (irrespective of cause) have proven that they are likely to form clots in future. These patients are often managed with chronic anticoagulation and this should be considered a "high risk" condition when deciding preoperative anticoagulation management.

Antiplatelet therapy is prescribed for primary and secondary prevention of atherosclerotic disease, as well as the prevention of stent thrombosis after percutaneous coronary intervention (PCI) or graft occlusion after coronary artery bypass graft (CABG).[6,7] Patients with these conditions possess a different risk of thrombosis that must be considered during preoperative planning. The risk of thrombosis resulting in occlusion of a stent or graft appears to be highest in the first month after intervention.[8] Current guidelines recommend at least 6 months of dual antiplatelet therapy (DAPT) for stents placed for stable ischemic disease and at least 12 months for stents and CABGs performed secondary to acute coronary syndrome.[7] For patients undergoing urologic procedures, it is necessary to consider whether the surgery is urgent or time-sensitive (e.g. a cystectomy for muscle invasive bladder cancer) or elective and not time-

TABLE 3. **Conditions conveying increased thromboembolic risk, stratified by level of risk**

Thromboembolic risk	Example causes
Low	Aortic valve prosthesis with no additional risk factors, Atrial fibrillation with CHA_2DS_2-VASc < 2, VTE over 12 months ago, Caprini VTE score < 5
High	Recent (< 6 months) stroke or TIA, recent (< 3 months) VTE, severe thrombophilia[a], active malignancy, prosthetic mitral valve, Atrial fibrillation with CHA_2DS_2-VASc ≥ 2, Recent (< 6 months[b]) coronary stent placement (drug-eluting), Caprini VTE score ≥ 5

[a]antiphospholipid antibodies, protein S and C deficiencies, lupus anticoagulant antithrombin III deficiency, and compound deficiencies.
[b]studies have shown that if necessary, DAPT can safely be stopped between 3-6 months for surgical interventions; if considering this for earlier than 3 months, we recommend a multi-disciplinary approach with cardiology.
CHA_2DS_2-VASc = commonly utilized method to predict thromboembolic risk in atrial fibrillation; stands for (Congestive heart failure, Hypertension, Age (> 65 = 1 point, > 75 = 2 points), Diabetes, previous Stroke/transient ischemic attack (2 points); VTE = venous thrombo-embolism; TIA = transient ischemic attack; DAPT = dual antiplatelet therapy

sensitive (e.g. a radical prostatectomy for localized prostate cancer). DAPT should be continued for as long as possible without interruption, with the minimum duration before time-sensitive surgeries typically being 6 months (1 month for a bare metal stent).[7] Should a patient require interruption prior to completing the minimum duration of antiplatelet therapy, we recommend a conversation between Urology, Cardiology and the patient to determine the risks and benefits of surgery and the most appropriate course of action. Table 2 demonstrates the optimal starting and stopping time for antiplatelet therapy based on indication. Interruptions of anti-platelet therapy for primary and secondary prevention of atherosclerosis is less stringent as the risk of thrombosis is considered lower and less dangerous.

Question 2: What is the risk of bleeding given the patient's medical history and the particular procedure they are undergoing?

Patient factors (medical history)

Patient comorbidities impart specific, additive risks of bleeding. These comorbidities can include renal and hepatic functional derangements, a prior stroke, history of bleeding, hypertension or alcohol or drug use. These parameters are addressed in the validated HAS-BLED score, with a score greater than 3 indicating an increased risk of bleeding.[9] Additional parameters that must be considered in periprocedural management include a prior bleeding event in the past 3 months, a qualitative or quantitative platelet abnormality, supratherapeutic INR at the time of procedure and

TABLE 4. **Bleeding risk of common procedures**

Risk of bleeding by procedure	Example procedures
Low	Ureteroscopy, laser lithotripsy, urethrotomy, minimally invasive prostate procedures, cystoscopy, bladder biopsy, Botox injections, Coaptite injection
Intermediate	TURP, TURBT, TRUS and biopsy, sling, colporrhaphy, Interstim, robotic pyeloplasty, robotic ureteral reimplantation
High	Partial nephrectomy, cystectomy, radical prostatectomy, PCNL, AUS, IPP placement, urethroplasty, robotic sacrocolpopexy, nephroureterectomy, lymph node dissection(s)

TURP = transurethral resection of the prostate; TURBT = transurethral resection of bladder tumor; TRUS = transrectal ultrasound; PCNL = percutaneous nephrolithotomy; AUS = artificial urinary sphincter; IPP = intracorporeal penile prosthesis

a history of bleeding with prior bridging or with a similar procedure.[10] The presence of each of these characteristics increases the risk of bleeding inherent to the type of procedure the patient is undergoing, and may affect whether a procedure is considered to have a "low" or "high" risk of bleeding. We calculate a HAS-BLED score for every patient and consider the additional bleeding risks characterized above.

Procedural bleeding risk factors

In addition to patient factors, the risk of bleeding of the specific procedure must be considered. For the purposes of this discussion, we stratified the risk of urological procedure into three categories - low, intermediate and high.

Low bleeding risk procedures

Cystoscopic and ureteroscopic procedures are classified as "low risk" based on their minimally invasive nature and shorter operative time. In our opinion, the risk of perioperative bleeding is low. The decision to continue antithrombotic therapy should thus be based on a patient's risk of thrombosis; a patient at low risk of thromboembolic events, Table 4, and high risk of bleeding may not need to continue therapy, and can safely hold these drugs (the preoperative stop time is medication-dependent and can be found in Tables 1 and 2 and restarted between 5-7 days postoperatively. Patients at high risk of thrombosis may need to continue antithrombotic medications through the procedure, and we recommend consultation with the managing physician to determine the appropriate course or if bridging therapy is necessary (see discussion of bridging therapy under "Issues of special importance"). If anticoagulation is held in high thrombotic risk patients, it may be restarted within 24-48 hours after surgery.

TABLE 5. **Recommendations for anticoagulation management based on bleeding and thromboembolic risk**

Procedure bleeding risk	**Thromboembolic risk**	**Recommendation for anticoagulation management**	
		Preoperative	**Postoperative**
Low	Low	Hold AC and follow recommendations based on medication half-life	Wait 5-7 days before resuming AC
	High	Hold AC preoperatively if able to, may also consider the procedure on AC or bridging therapy if unable to stop per managing doctor	Resume AC within 2-4 days if held
Intermediate	Low	Follow recommendations based on medication half-life with additional input from the managing doctor	Wait 5-7 days before resuming AC
	High	Hold preoperatively if possible according to half-life, may require bridging before the procedure per discussion with the managing doctor	Wait at least 2-3 days before resuming
High	Low	Follow recommendations based on medication half-life with input from the managing doctor	Wait 7 days to resume
	High	Hold AC preoperatively if possible according to half-life; likely to require bridging before the procedure per discussion with the managing doctor	Wait at least 3 days before resuming

AC = anticoagulation

Intermediate bleeding risk procedures

We classify procedures like transurethral resection of the prostate as having intermediate risk of bleeding, Table 4; these procedures are minimally invasive, but manipulate highly vascular areas. In these patients, the management of antithrombotics is not definitive, and the balance of individualized bleeding and thromboembolism risks is most critical in planning. In certain cases, it may be beneficial to consult the institution's team that routinely manages anticoagulation for their recommendations.

As a rule of thumb, patients undergoing procedures in this category should ideally stop therapy prior to the procedure. However, depending on a patient's risk of bleeding, patients may resume anticoagulation therapy after 2-3 days for high thromboembolic risk, or 5-7 days for low thromboembolic risk. Regardless of the physician's decision for management, we strongly advocate for involving and counseling patients on their relative risk of thromboembolism and bleeding, including a conversation about the need for blood products should complications arise.

High bleeding risk procedures

Procedures with high risk of bleeding include major surgeries such as nephrectomy, cystectomy and prostatectomy. These patients should generally hold antithrombotic medications prior to surgery, as the risk and complications of bleeding outweigh the benefits of anticoagulation therapy. We strongly recommend that experts in anticoagulation management are consulted to ensure that appropriate recommendations are made, and that specialist care is available should complications arise. Our standard practice is to place a consult to the vascular medicine team at our institution at the time of the preoperative planning visit, requesting their recommendations for stopping and restarting the medication. After a multidisciplinary discussion with the managing providers, anticoagulation is usually held for 3 days after the procedure for patients at high risk of developing thromboembolic events or 7 days in patients with low risk.

Question 3: Based on these factors, should anticoagulation be stopped, for how long, and should the patient be bridged for the duration?

Considerations of the drug pharmacokinetics, Tables 1 and 2, a patient's risks of thromboembolic events, Table 3, and the procedure bleeding risk, Table 4, have been synthesized for convenience into Table 5, our general management of antithrombotic drugs for urologic procedures. Figure 1 summarizes a cogent, step-wise process to assist in evaluating the risks and benefits of antithrombotic continuation. We must reiterate that these guidelines are not rigid. Physicians should utilize an individualized, patient-based approach when considering a change to a medication regimen.

Issues of special importance

Anticoagulation bridging: "Bridging" refers to the practice of administering a short-acting anticoagulant in the perioperative period rather than completely continuing or stopping their regular anticoagulation regimen. One often used bridging agent is low molecular weight heparin (LMWH), which has a short half-life of 3-5 hours. Recommendations are based on the Bridge trial;[12] identification of patients who should be bridged again comes down to an analysis of the risks for thromboembolism and bleeding. We consider those at moderate or high risk for bleeding, Table 4, and classified as "high risk" for thromboembolism, Table 3, for bridging therapy, and work with anticoagulation experts at our institution to create an appropriate bridging plan for the patient. We strongly recommend that this group of patients is managed by a multidisciplinary team to optimize expert care of anticoagulation.

Neuraxial anesthesia: While most urologic procedures currently utilize general anesthesia with endotracheal intubation or laryngeal mask airways, neuraxial anasthesia is intermittently used. Anesthesia guidelines for anticoagulation management in neuraxial anesthesia require longer periods of time off anticoagulation prior to surgery, to reduce the risk of spinal hematoma.[13] If you plan to operate using neuraxial anesthesiology, we recommend discussing with anesthesiologists at your institution their preferences for perioperative anticoagulation timing; doing this early in the preoperative process prevents delays in surgery due to inappropriate anticoagulation levels for spinal anesthesia.

Extended duration postprocedural anticoagulation: There is an increased risk of venous thromboembolism following oncologic urology procedures such as radical cystectomy, and multiple studies have found the majority of VTE events occur after discharge.[14,15] The European Association of Urology recommends extended duration (4 weeks) of VTE prophylaxis with low-molecular weight heparin in patients undergoing oncologic surgery who are at high risk of thrombosis and otherwise have low risk of bleeding complications (e.g. those undergoing open and robotic radical cystectomy, and certain nephrectomy and prostatectomy procedures).[16]

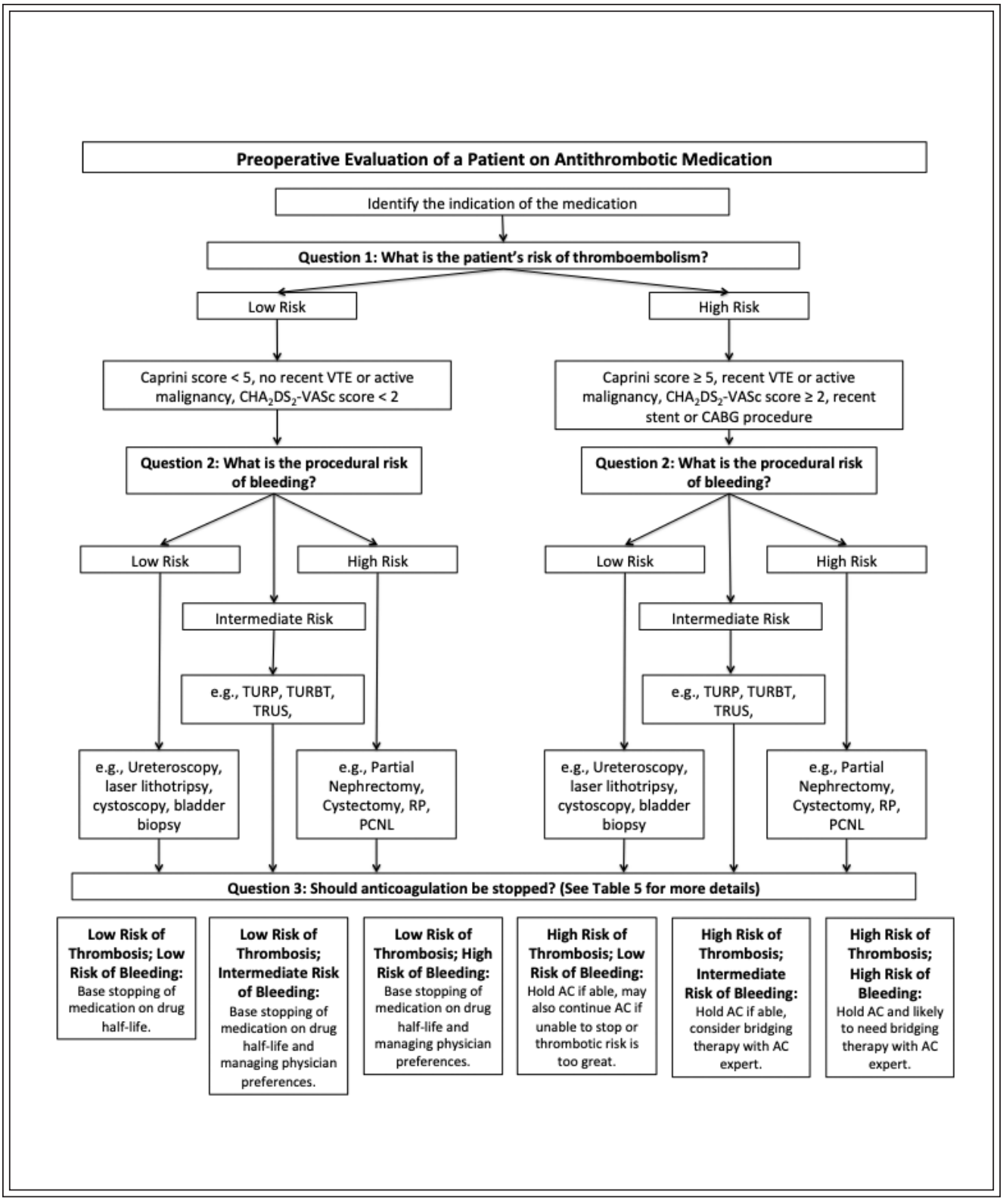

Figure 1. Flowchart of the Decision Making Process for Stopping Anticoagulation. The process of deciding to stop anticoagulation should be performed in a stepwise manner that takes into account the patient's risk of thromboembolism, their risk of bleeding based on medical history and the risk of bleeding of the procedure.

Discussion and conclusions

As the number of patients on anticoagulation grow, urologists will increasingly encounter these medications in the periprocedural period. Here we present our methodology, structuring our decision-making process around three issues: the patient's risk of thrombosis, the patient and procedure's risk of bleeding, and the subsequent implications this has for an individual's antithrombotic management. This primer is intended to prepare urologic surgeons with a logical, step-wise approach to current antithrombotic management, so that they may work as part of a multidisciplinary team where concerns for bleeding are weighed against the risk of thromboembolism. While initiation and management of these medications largely falls under the purview of other specialties, urologists are the experts on intra and postoperative bleeding complications and must embrace their responsibility for guiding these specialties. □

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