Anticoagulation and Antiplatelet Therapy in Urologic Practice: ICUD and AUA Review Paper

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Introduction

A common scenario in urologic practice is that of a 55-year-old male who comes to you after his primary care physician informed him about his serially rising serum prostate specific antigen (PSA) that is now 5.8 ng/mL. He has a family history of prostate cancer in a father and brother. His comorbidities include clinically significant coronary artery disease treated with a drug-eluting stent four months ago. Medications include a statin, aspirin, and clopidogrel. He is an avid runner and is in excellent physical shape. How do you address the apparent indication for prostate biopsy in light of medications that you perceive might increase the risk of hemorrhage?

The urologist is increasingly presented with patients with multiple comorbidities that include coronary arterial disease requiring percutaneous coronary artery intervention with angioplasty (as in the case above), bare metal stents, or a drug eluting stent, cardiac dysrhythmias such as atrial fibrillation, valvular heart disease, deep venous thrombosis, and inferior vena cava filters. These comorbidities are managed with an increasing array of oral anticoagulant (AC) and oral antiplatelet (AP) drugs that require comprehensive management to mitigate the risk of complications of urologic interventions.

Given these clinical concerns and the lack of urology-specific directives, the American Urologic Association (AUA) and the International Consultation on Urological Disease (ICUD) have collaborated to create this review on Anticoagulation and Antiplatelet Therapy in Urologic Practice. An international panel was named by both organizations, which was comprised of experts that included urologists, cardiologists, hematologists, and a methodologist. Here we report consensus-based recommendations on the findings of a systematic literature review concerning the procedures performed for urology patients on anticoagulation or antiplatelet therapy. The Panel was charged with constructing a review, rather than a full clinical practice guideline. This review is a qualitative (not quantitative) but nonetheless comprehensive assessment of a topic felt to be of major importance for high quality and safe medical practice. The review's purpose is to provide direction to urologists regarding the assessment of the risk of systemic thrombotic and/or surgical hemorrhagic risk from AC/AP therapy weighed against the urgency of a urologic procedure. The urologist needs to understand the safe and effective use of oral anticoagulants (AC) and antiplatelets (AP) prophylaxis and the risks associated with their withdrawal. These risks include arterial thromboembolism, venous thromboembolism, major adverse cardiac and cerebrovascular events, and more specifically stroke, pulmonary embolus, and major cardiac adverse events which can and usually are far more life altering than hemorrhage. Overemphasis of the surgical risks of hemorrhage can reduce or minimize the medical risks of these for more severe adverse events. As urologists, an understanding of the safe and effective use of oral
AC/AP therapy is essential, but urologists are not experts in risk management of thrombosis prophylaxis. Surgeons are generally well-versed in the assessment of intraoperative risk; however, emphasis of the surgical risk related to hemorrhagic complications can reduce appreciation of the risks of more distant thrombosis. Additionally, there is significant practice variation regarding the perioperative management of AC/AP therapy in the urologic community.

There is a continually expanding body of literature on this topic, both within but primarily outside the field of urologic surgery. Furthermore, the Panel notes that this document constitutes a clinical strategy and is not intended to be interpreted rigidly. The most effective approach for a particular patient is best determined by the patient’s clinical conditions and in concert, where appropriate, with a multidisciplinary medical team. As the science relevant to AC/AP evolves and improves, the strategies presented here will require amendment to remain consistent with the highest standards of clinical care.

Section 1: Methods:

Using search terms related to anticoagulation therapy and urologic procedures, the Guidelines Medical Librarian conducted database searches of PubMed and EMBASE. Results were limited to studies of human subjects, written in English and published between January 1, 2001 and August 1, 2012. The review also included guidelines, systematic reviews from other professional medical organizations, and several key references in the fields of cardiology and hematology. In total, 2,674 non-redundant article abstracts were obtained. An abstract review was conducted to assess the possible relevance of each article to key questions outlined by the Panel.

Key Questions

1. When and in whom can AC/AP be stopped in preparation for elective, urgent, or emergent urologic surgery?
2. What procedures can be safely performed without discontinuing AC/AP?
3. What are the current periprocedural strategies that adequately balance the risk of major surgical bleeding versus the risk of major thrombotic event?

Overall, 106 articles were found to be potentially relevant and were selected for full-text review. Each article retrieved in full-text was either accepted or rejected by the methodologist based on its relation to the topic and key questions defined by the Panel, as well as the general quality of information provided. In total, 79 articles were accepted while 27 were rejected. Reasons for rejection included the following: abstract only (n=12), insufficient information or unrelated to topic (n=13), and redundancy (n=2). We
extracted important factors (e.g., study design, patient population, follow-up period, results) from all accepted articles, which serve as the basis of evidence for this report.

Section 2: Medical Management of the patient at risk of thromboembolism

According to the United States Centers for Disease Control and Prevention, 49% of the US population has at least one risk factor for cardiovascular disease.\[1\] Similarly, as reported by the World Health Organization, cardiovascular disease causes more than half of all European deaths\[2\] making it essential for the surgeon to have familiarity with the most common medical risks that can affect the outcome of a procedure. The widespread use of oral AC/AP agents \[3\] and the advent of new therapies complicate the perioperative management of urological patients. Yet approximately 10% per year of the patients on these medications will require an invasive procedure. The periprocedural management of AC/AP should consider both the regional and systemic complications of significant bleeding against significant thromboembolic phenomenon in a multidisciplinary fashion. The risk and severity of thromboembolic complications may be markedly higher than the risk of bleeding associated with certain elective procedures. The list of patients on AC/AP for reduction of thromboembolic risks is long. It includes patients with recent thromboembolic events, such as myocardial infarction and stroke, congestive heart failure, atrial fibrillation, mechanical heart valves, deep vein thrombosis, significant vascular disease, and diseases associated with vascular disease such as diabetes. As a general rule, for an emergency procedure, the AC/AP should be resumed as soon as possible after the interventions. However, this literature review did not find guidelines as to the shortest intervals wherein significant bleeding risk is minimized.

Congestive heart failure patients, particularly with left ventricular dysfunction, and patients with a recent myocardial infarction are at higher risk of stroke and thromboembolic complications. Such patients may be on chronic AC/AP therapy to reduce those risks.

Atrial fibrillation is the most common rhythm disturbance in hospitalized patients, accounting for up to 34.5% of dysrhythmias.\[1, 3\] The rate of ischemic stroke among patients with non-rheumatic atrial fibrillation averages 5% per year, which is two to seven times the rate for people without atrial fibrillation.\[4\] The rate of stroke in patients with rheumatic heart disease and atrial fibrillation increases 17-fold when compared with age-matched controls.\[5\] The annual risk of stroke in patients with atrial fibrillation increases with age, from 1.5% in patients aged 50 to 59 years to 23.5% for those aged 80 to 89 years.\[6\] The total mortality rate is doubled in patients with atrial fibrillation compared with patients in normal sinus rhythm.\[7\] Patients with atrial fibrillation are usually stratified by their thrombosis risk using the CHADS2 score, which is calculated from the cumulative score for congestive heart failure (1 point), hypertension treated or above
140/90 (1 point), age >75 y (1 point), diabetes mellitus (1 point), previous stroke or transient ischemic attack (2 points).[8] This numerical score is directly related to the medical risk severity. However, should a patient with atrial fibrillation have no other stroke risks (CHADS2 score = 0), their stroke risk remains 1.9% (1.2-3.0) per year.

Oral anticoagulation with warfarin is highly efficacious for atrial fibrillation-associated stroke prevention, with a risk reduction of 61% (95% CI 47% to 71%) v. placebo. The target intensity of anticoagulation is usually an international normalized ratio (INR) of two to three. It is desirable to target the lowest adequate intensity of anticoagulation to minimize the risk of bleeding.[9] Recently, three new oral anticoagulant agents have been approved for the risk reduction for patients with non-valvular atrial fibrillation. These novel oral anticoagulants (NOAC) include thrombin inhibitor, dabigatran, and the factor Xa inhibitors, rivaroxaban and apixaban; however, newer agents are on the horizon (Figure 1). Each are approved for the prevention of thrombotic stroke in patients with non-valvular atrial fibrillation, none are monitored by INR as the INR will be normal for patients on NOAC. Rivaroxaban was tested against warfarin, and it was deemed to be non-inferior for the prevention of stroke or systemic embolism (HR 0.79; 95% CI, 0.66 to 0.96; P<0.001 for non-inferiority) without differences in major bleeding (HR 1.03; 95% CI, 0.96 to 1.11; P=0.44).[10] Apixaban was superior in preventing stroke or systemic embolism (HR 0.79; 95% CI, 0.66 to 0.95; P<0.001 for non-inferiority; P=0.01 for superiority), with less bleeding (HR, 0.69; 95% CI, 0.60 to 0.80; P<0.001), and resulted in lower mortality (HR, 0.89; 95% CI, 0.80 to 0.99; P=0.047).[11] Dabigatran at a dose of 150 mg showed lower rates of stroke and systemic embolism (RR 0.66; 95% CI, 0.53 to 0.82; P<0.001 for superiority) with similar rates of major hemorrhage.[12]

None of the NOAC is reversible; bleeding associated with rivaroxaban and apixaban, as both are factor Xa inhibitors, may be controlled by the administration of anti-inhibitor coagulant complex; expert consultation should be requested if the use of these intravenous concentrates is contemplated. Clotting factor administration, however, will not be helpful in the reversal of dabigatran as dabigatran causes clotting factor inhibition, not depletion. Dabigatran, however, can be partially removed by hemodialysis. Since these agents are predominantly cleared through the kidneys, they generally should be avoided in renal insufficiency (creatinine clearance less than 30 ml/min). Dose reduction is required for patients with creatinine clearance less than 60 ml/min. With renal reduction surgery, the preoperative dose of these agents may be inappropriately high.

Prosthetic valves are widely used to treat several common heart conditions. Valves can be divided into bioprosthetic valves and mechanical valves. While the bioprosthetic valves usually need less intensive anticoagulation, they are outperformed by mechanical valves, which in turn require more intensive anticoagulation and hence predispose to more bleeding.[13] The incidence of major embolism in the absence of antithrombotic therapy is 4% per 100 patient-years. With antiplatelet therapy alone, this risk is 2.2% per
100 patient-years, and with warfarin therapy it is reduced to 1% per 100 patient-years.[14] Risk is variable, dependent on the valve type and position: a prosthesis valve in the mitral position increases the embolic risk almost twice as compared with valves in the aortic position. Hence, patients with mechanical heart valves will usually receive chronic oral anticoagulation with warfarin of goals of INR 2.0-2.5 for valves in the aortic position versus INR 3.0-3.5 for valves in the mitral position.[15] Tilting disc valves and bileaflet valves decrease the incidence of major embolism when compared to older caged ball valves.

**Deep vein thrombosis and pulmonary embolus** occur in surgical patients with risk factors including surgical position, length of procedure, time to early ambulation, but also the activation of blood coagulation, venous stasis, vascular injury,[16] and non-O blood groups.[17, 18] Studies done before the introduction of anticoagulant therapy reported a mortality rate for pulmonary embolus was ≈20% in hospitalized patients with clinically obvious venous thrombosis.[19, 20] In contrast, the short-term prognosis is good for anticoagulated patients with proximal deep vein thrombosis treated with for three months with low rates of recurrent events (5%). Inferior vena caval filters may be indicated in patients with acute deep vein thrombosis or pulmonary embolus and formal contraindications to the use of AC. A single randomized controlled trial evaluated permanent inferior vena caval filter insertion as an adjunct to AC therapy in patients with acute deep vein thrombosis who were considered to be at high risk for pulmonary embolus.[21] The findings of this study suggest that inferior vena caval filters increase the risk of recurrent deep vein thrombosis while reducing the risk of pulmonary embolus. This did not affect mortality. Retrievable filters are usually selected so that they can be removed when anticoagulants are no longer contraindicated.[22, 23] Recent guidelines on the prevention of deep vein thrombosis in non-orthopedic patients stratify prophylaxis by deep vein thrombosis risk. High-grade evidence recommends prophylaxis for high-risk patients undergoing abdominal or pelvic surgery for cancer whom not otherwise at high risk for perioperative bleeding with low molecular weight heparin for a four-week perioperative period[24]

**Percutaneous transluminal coronary angioplasty with endovascular stenting** now surpasses coronary revascularization in the treatment of coronary artery disease [25] and includes bare metal stents (e.g. plain metal alloys) and drug-eluding stents (e.g. a metal scaffold with a biocompatible polymer that delivers drugs locally). While drug eluting stents decrease the risk of restenosis to <10% [26], the drugs delay arterial healing. This phenomenon explains the prolonged need (12 months) for dual antiplatelet therapy (DAPT)[27] to reduce the risk of in-stent thrombosis. Similar considerations pertain to patients with carotid stents.
Section 3: Periprocedural AC/AP management from the general literature

Of note is that the procedural bleeding risk is increased, beyond that of AC/AP use alone, for patients with hypertension, abnormal renal or liver function, previous stroke, bleeding history or predisposition, labile INR, older age (>65 y), or drug/alcohol use.[28, 29]

The STRATEGEM trial, a 2011 RCT performed by Mantz et al., compared the cumulative rates of major thrombotic and bleeding events at 30 days post-procedure for 291 patients randomized to either aspirin 75 mg a day (n=145) or placebo (n=146). Eligible patients were receiving AP therapy (aspirin, clopidogrel, ticlopidine, or dipyridamole) for secondary prevention of coronary artery disease, stroke, transient ischemic attack or peripheral vascular ischemic disease, and undergoing elective intermediate- or high-risk elective non-cardiac surgery (i.e. surgery planned for more than two hours in duration and associated with significant volume changes). While the study was underpowered due to low recruitment, it did not identify any statistical difference between major thrombotic or bleeding events between the cohorts, including 15.5 % which were various urologic procedures. A total of 35 major adverse events occurred in 31 patients (10.7%); 18 thromboembolic events in the aspirin group and 17 in the placebo group, with nine bleeding events in the aspirin group and eight in the placebo. The consensus is that for those patients with cardiac risk factors on low-dose aspirin alone, this can be continued in perioperative period without increased risk of major bleeding.[30, 31]

Several studies discussed noncardiac surgery in patients on AP therapy after recent drug eluding stent/ coronary stent implantation.[32-36] The RECO study was a prospective observational study of 1,134 patients in 47 centers with cardiac stents undergoing noncardiac surgery. AC/AP was completely interrupted in 28.9% of patients treated with aspirin alone and in 15.7% of patients treated with DAPT. In patients treated with clopidogrel alone, 36.2% were bridged with aspirin and 34.1% interrupted all AC/AP. Their findings included perioperative major adverse cardiac and cerebrovascular events occurring in 10.9% of patients with coronary stents who underwent non-cardiac surgery or other invasive procedure, regardless of stent type. All-cause death in those with major adverse cardiac and cerebrovascular events was 14.5%. These major adverse cardiac and cerebrovascular events complications were associated with five risk factors: preoperative anemia, severe renal failure, urgent surgery, high-risk surgery, and the interruption of antiplatelet treatment for more than five days preoperatively, but not associated with the time interval from stent and surgery. Alternatively, major and minor bleeding occurred in 108 (9.5%) of the procedures, with return to the operating room in 18.5%, and a death rate of 12% who had a bleeding complication. Minor or major bleeding was associated with four preoperative risk factors: moderate renal failure, a short period between stenting and surgery (< 3 months), preoperative anemia (Hgb <10
g/dl), and high-risk surgery. As others have also concluded, operative procedures performed while treated with aspirin were not associated with major bleeding in this high risk group.

The authors of the RECO study further discuss that the interruption of aspirin perioperatively in this cohort of high-risk patients may be associated with an increase in cardiac complications due to platelet rebound coupled with a hypercoagulable state occurring with extensive surgery. While there is an established association between the discontinuation of clopidogrel and an increase in platelet reactivity, there is little data on the risk of bleeding or thrombosis for clopidogrel-treated patients during noncardiac surgery. Contrariwise, perioperative bleeding is associated with a higher risk of thrombosis causing a ST segment elevation myocardial infarction or non-ST segment elevation myocardial infarction.[35]

Hammerstingl and colleagues[37] performed a similar study of various major and minor surgeries for 116 mechanical heart valve recipients to determine the safety and feasibility of a standardized low molecular weight heparin bridging regimen in patients at inherent high thromboembolic risk. The bridging protocol included discontinuation of phenprocoumon for four to six days before the procedure, followed by subcutaneous enoxaparin (1 mg/kg) two times daily once the patient’s INR fell below 2.0. Enoxaparin therapy was withheld on the evening before the procedure and restarted at 12 to 48 hours postoperatively. Phenprocoumon was then restarted post-procedurally with concomitant low molecular weight heparin bridging therapy until an effective INR was achieved. There were no thromboembolic complications; contrariwise, there was one major bleed and 10 (8.6%) minor bleeds. The total low molecular weight heparin treatment time in patients with bleeding complications was not significantly different to that for patients without bleeds; the authors concluded that this protocol was safe and effective for this high-risk patient population.

Three studies [38-40] investigated perioperative bridging programs for patients undergoing various major and minor surgeries for whom interruption of chronic warfarin therapy was required. Two of these studies discontinued warfarin five days preoperatively, while another discontinued warfarin three to four days prior to surgery. Low molecular weight heparin (nadroparin, enoxaparin, or dalteparin) was used in two studies and unfractionate heparin in one. All studies found their protocols to be effective in their anticoagulated cohorts with no evidence of thrombotic complications, and only minor occasional bleeding events.

Dual Antiplatelet Therapy (DAPT) should be continued for at least 30 days after a bare metal stent, and for at least 12 months after a drug-eluting stent according to the American College of Cardiology/American Heart Association/Society for Cardiovascular Angiography and Interventions 2011 percutaneous coronary intervention Guidelines[41] and American College Of Chest Physicians 2012 Guidelines[42], DAPT with aspirin and
clopidogrel, prasugrel, or ticagrelor should be continued for two weeks after simple angioplasty, six weeks after bare metal stent placement and at least 12 months after insertion of drug-eluting stent.[43, 44] In patients who require emergency surgery within six weeks of placement of a bare metal stent or within twelve months of placement of a drug-eluting stent, the recommendation is to continue DAPT perioperatively.[43] Stopping one or both of the antiplatelet agents before the recommended time can result in major adverse cardiac and cerebrovascular events and death,[42, 45, 46] as the morbidity and mortality of stent thrombosis are very high; 64% rate of myocardial infarction and mortality rates of from 10% to 46% .[47] Indeed, if a patient cannot be compliant with this regime, the recommendation is that percutaneous coronary intervention with coronary stenting not be performed.[41] No elective surgery should be performed, as DAPT should not be tapered nor stopped. Hence, only lifesaving procedures should be performed for the patients in the critical time period after stent deployment and continuing both aspirin and clopidogrel perioperatively.

It is only if there is a high risk of morbidity from bleeding associated with emergency high-risk surgery, that the use of only aspirin alone, with the discontinuation of clopidogrel, prasugrel, or ticagrelor may be considered reasonable.[41] However, the American College of Cardiology /American Heart Association/ Society for Cardiovascular Angiography and Interventions 2011 Percutaneous Coronary Intervention Guidelines categorizes that level of evidence as "C" or the lowest level of evidence, coming from limited populations and/or based on consensus.[41] Bridging patients that require emergency surgery with any other anticoagulants or intravenous antiplatelet medications has been poorly studied, and is discouraged.

For patients who elect procedures beyond the high risk period of thrombosis of a coronary stent, the AP agents can be discontinued 7-10 days before the procedure. AP agents irreversibly inhibit platelet function; as a result, the recovery time for platelet function depends only on turnaround of platelet generation. For each day the therapy is interrupted, about 14% of normal platelet function is restored, taking up to 10 days to replenish an entire population of platelets. Once the surgery is completed, oral AP medications can be restarted within a few hours if the bleeding risk is acceptable. With normal dosing of clopidogrel, prasugrel, or ticagrelor, it may take up to 10 days to achieve an acceptable platelet inhibition. If earlier platelet inhibition is needed, oral loading doses (e.g., 300-600 mg of clopidogrel, 60 mg of prasugrel, or 150 mg of ticagrelor) should be considered.

For the perioperative management of patients with deep vein thrombosis, the risk of bleeding during a surgical procedure performed in a patient receiving antithrombotic therapy has to be weighed against the increased risk of a thromboembolism caused by stopping the therapy. The CHADS2 score has not been validated in the perioperative setting, however; it can stratify the patients into high, moderate, or low risk for thromboembolic events. If the patient has a low CHADS2 score, it is possible that
bridging with low molecular weight heparin or unfractionated heparin is unnecessary. For patients with high CHADS2 score, mechanical valves, prior thromboembolism during interruption of warfarin, recurrent venous thromboembolism, thrombophilia, or active cancer bridging is recommended.[43]

Most patients in the acute phase of deep vein thrombosis will receive intravenous unfractionated heparin, subcutaneous low molecular weight heparin, fondaparinux, or oral rivaroxaban. With the exception of rivaroxaban, oral anticoagulation with vitamin K antagonists, such as warfarin, is commonly started at diagnosis and is continued for chronic treatment. Warfarin has a half-life elimination of 36 to 42 hours. Assuming that every half-life elapsed corresponds to a 50% reduction in anticoagulant effect it would take about five days to reverse the anticoagulation effect of warfarin.[43]

Recently rivaroxaban was tested against warfarin in an open label, randomized non-inferiority study that showed similar efficacy (36 events [2.1%], v. 51 events with enoxaparin-vitamin K antagonist [3.0%]; hazard ratio [HR], 0.68; 95% confidence interval [CI], 0.44 to 1.04; P<0.001)).[48] Dabigatran was tested in a similar fashion and was deemed to be non-inferior to warfarin for patients with venous thromboembolism who had completed at least three initial months of therapy (recurrent thromboembolism in the dabigatran group was 1.8% v. 1.3% in the warfarin group (HR, with dabigatran, 1.44; 95% CI, 0.78 to 2.64; P=0.01 for non-inferiority). Major or clinically relevant bleeding was less frequent with dabigatran (hazard ratio, 0.54; 95% CI, 0.41 to 0.71). However, acute coronary syndromes occurred in 13 patients in the dabigatran group (0.9%) and only in three patients in the warfarin group (0.2%) (P=0.02).[49] Both rivaroxaban and dabigatran are used for chronic oral treatment for deep vein thrombosis.

The thromboembolic risks of aspirin cessation for high-risk patients often outweigh the minor bleeding risks for the vast majority of operative procedures.[50-52] As only a small subset of invasive surgical procedures confers the higher risks for a complicating hemorrhage, these authors reiterated the importance of multidisciplinary stratification of risks of bleeding versus thrombotic events. Aspirin is important in ischemic protection and presents little risk to major bleeding, except for transurethral resection of the prostate and intracranial procedures, according to this group of authors. They also emphasize that the ischemic risk is greatest during the early postoperative days when oral absorption of clopidogrel may not be adequate. They do not recommend an alternative parenteral antithrombotic therapy in the setting of clopidogrel discontinuation; as again, there is no evidence of efficacy. Unfractionated heparin or low molecular weight heparin were felt not to be recommended due to an increase in bleeding yet uncomplicated by antiplatelet protection.

A 2012 review by Wysokinski and McBane[53] discusses the low (1%) risk of periprocedural thromboembolic complications with deep vein thrombosis, but recommends that bridging, nonetheless, be employed if the clinical presentation of the
deep vein thrombosis was less than three months prior and in the setting of malignancy. The NOAC require timely discontinuation as their half-lives are long, but due to the rapid onset of action, however, full-anticoagulation with NOAC will result within hours of adequate oral absorption.

The review of Armstrong et al.[54] focused on perioperative cerebrovascular events that occur with cessation of AP/AC given for secondary stroke prevention compared to the known low risk of perioperative hemorrhage. They make a case that the continuation of aspirin therapy carries less risk for invasive procedures than cessation. Douketis et al.[55] published a set of recommendations on usage of low molecular weight heparin as bridging therapy in 650 consecutive patients undergoing various invasive procedures with temporary interruption of warfarin and bridging with low molecular weight heparin. In the 108 patients undergoing high-risk bleeding procedures, inclusive of cardiac, neurosurgical, vascular procedures, and 10 transurethral resection of the prostate, there were two sudden cardiac deaths (1.8%) possibly due to thromboembolism and two nonfatal but clinically obvious major hemorrhagic events (either not at the surgical site or a drop of Hgb greater than 20g/L over 24 hours.) Notably, none of the patients undergoing transurethral resection of the prostate had an adverse clinical outcome from bleed or thromboembolism.

**Section 4: Risk Assessment of AC/AP for Urologic Procedures**

Daniels [56] emphasized the risk-benefit ratio for urology patients taking long-term warfarin. A low risk of thrombosis with a high risk of perioperative bleeding would favor discontinuing warfarin without bridging therapy, whereas high risk of thrombosis with a low risk of bleeding suggest that the procedure, if necessary, be bridged. Likewise, for major post-procedural bleeding, administration of vitamin K or fresh frozen plasma will rapidly reverse the effect of warfarin. The effects of unfractionated heparin abate within about four hours after stopping a continuous infusion, and when necessary can be reversed more quickly with administration of protamine. The AC effects of low molecular weight heparin may be incompletely reversed with protamine.

Meyer et al.[57] emphasized the timing-related risks of hemorrhage for patients on warfarin who are scheduled for urologic surgery. The time to reduce risk by withdrawing the medication or plan contingencies is reduced by the emergency of the procedure. Elective cases present the possibility of risk reduction through perioperative management of AC/AP. Alternatively, if risk of hemorrhagic complications is significant, an elective case can be deferred.

Shock wave lithotripsy complications rates were assessed in two small studies. A categorization of 23 patients by low or high thromboembolic risk determined
how anticoagulation would be managed. In the low-risk group, therapy was simply discontinued eight days prior to shock wave lithotripsy; in the higher risk group, AC/AP was discontinued eight days prior to shock wave lithotripsy, and subcutaneous unfractionated heparin 5,000 IU three times a day was administered until the evening before treatment and then restarted the evening after the procedure. Patients requiring multiple shock wave lithotripsy sessions remained on subcutaneous unfractionated heparin until stone treatment was completed. No postoperative hematuria beyond two days occurred in any patient. There were no thromboemboli, significant reduction in hemoglobin or hemorrhagic complications in any patient.[58]

In the management of cohort of 140 elderly (average age 75.1 years) shock wave lithotripsy patients, AP agents were withdrawn 7 to 10 days before treatment, and patients on warfarin therapy (n=14) were converted to low molecular weight heparin. There were no extracorporeal shock wave lithotripsy-related urologic or thrombotic complications in the series.[59]

While the American College Of Cardiology/American Heart Association guidelines for patients on single AP therapy after cardiac stenting recommend that AP therapy be stopped at least five days before and resumed at least 24 hours after the risk of bleeding had safely diminished, a recent review proposes caution for the shock wave lithotripsy population in the resumption of post-procedural AC because of case reports of massive hemorrhage occurring five days after the procedure. They conclude that alternative modalities of shock wave lithotripsy should be considered for patients on chronic AC.[60]

Ureteroscopy with holmium:YAG laser lithotripsy was evaluated in three retrospective reviews in patients on AC/AP agents that were not modified nor interrupted. A series of 25 patients with uncorrected bleeding diathesis reported a significant bleeding complication occurred in 1 of 30 accessed ureters (3%); this patient was concurrently treated with electrohydraulic lithotripsy, and required transfusion for a retroperitoneal bleed.[61] A matched control study [42] compared complications of holmium:YAG laser lithotripsy in 37 patients on full anticoagulation with 37 matched controls. The hemorrhagic/thromboembolic adverse events were comparable between the two groups. No patient required a blood transfusion in either group. The AC group did have a significantly larger postoperative drop in hemoglobin: median postoperative hemoglobin decrease was 0.7, 0.65, 0.3, 0.6 and 0.2 gm/dL in patients on aspirin, warfarin, clopidogrel, and overall AC, and in controls, respectively (AC v. control, p < 0.0001).

A study of 44 patients undergoing ureteroscopy included 12 patients with coagulopathies treated with no interruption of antithrombotic medication, and 32 control subjects with normal bleeding profiles. In the patients with coagulopathies, one-quarter of these patients underwent ureteroscopy for biopsy of ureteral lesions, the majority underwent holmium: YAG laser lithotripsy; while all controls underwent holmium: YAG laser lithotripsy. Postoperatively, two patients with coagulopathy (16.7%) were readmitted due
to gross hematuria but no controls experienced complications. No patients required blood transfusion.[44]

One study commented that while many of these ureteroscopic studies were of modest quality (retrospective, no randomization, no blinding), there was a low risk of bias concerning the potential risks of the procedure, and that ureteroscopy with holmium:YAG laser lithotripsy appears safe and efficient for treating the anticoagulated patient with minimal early postoperative complications.[62]

Percutaneous nephrolithotomy complications of patients on AC/AP therapy were reported in a large-scale prospective study by Labate et al.[63] that characterized the risk factors for complications using consecutive patients entered worldwide for cases occurring over one year into the Clinical Research Office of the Endourological Society (CROES) Percutaneous Nephrolithotomy Global Study database. From 5,724 analyzed patients, researchers found that anticoagulant medication use (n=310) was associated with a slight increase in mean modified Clavien-Dindo complication grade of 0.29[64]. While the majority of complications (n=634, 54.0%) were classified as Clavien grade I, on multivariate regression analysis it was the operative time and the American Society of Anesthesiologists physical status classification of III or IV that were predictors of an increase in Clavien scores, not the use of anticoagulant medications. They concluded from this, the largest clinical experience reported, that with the planned discontinuation of AC medications 10 days preoperatively and resumed 5 days post-operatively is safe and effective, and that the majority of complications in percutaneous nephrolithotomy treated patients on AC/AP are minor. The paper does not report specifically on thromboembolic complications. A 2012 review[60] comments that there are no studies which have evaluated low dose aspirin and percutaneous nephrolithotomy.

There is a relatively large body of evidence regarding prostatic outlet procedures and the management of AC/AP therapy, including holmium laser enucleation, other laser prostatectomies, photoselective vaporization of the prostate, and transurethral resection of the prostate.

One retrospective case-control study [65] found that holmium laser enucleation patients who continued their aspirin (n=25) or warfarin (n=13) medications had no significant differences in bleeding complication rates from controls not on AC/AP medication. Additionally, there were no differences between the groups in standard postoperative outcomes and no blood transfusions were needed. A second retrospective analysis[66] assessed 81 holmium laser enucleation patients on AC with differing perioperative management. In the most comprehensive protocol, AC was stopped five days before surgery, and subcutaneous low molecular weight heparin was administered 24 hours after discontinuation of AC, stopped 12 hours before surgery and restarted 12 hours after surgery. Low molecular weight heparin was discontinued upon the INR reaching >2. Thirty-four subjects underwent surgery with this specific bridging protocol with no
major intraoperative or postoperative complications or thromboembolic events. However, seven of 34 (23%) patients required an early postoperative blood transfusion coinciding with the recommencement of AC.

A prospective study [67] in 30 laser prostatectomy patients continuing warfarin derivatives or platelet aggregation inhibitors showed slight but significant decreases in hemoglobin but similar levels of intraoperative and postoperative complications relative to a group of 45 controls. No blood transfusions were necessary in either cohort.

Thirteen articles [68-80] examined complications and outcomes associated with photoselective vaporization of the prostate for treatment of benign prostatic obstruction. Seven photoselective vaporization of the prostate studies examined outcomes for patients continuing AC/AP agents during the perioperative period. Patient cohort sizes ranged from 18 to 500 patients. None required intraoperative blood transfusions, implying that continuation of warfarin is safe during photoselective vaporization of the prostate for the patient with high risk for thrombosis. The authors of all 13 studies concurred that photoselective vaporization of the prostate is safe and effective for patients who continue oral AC/AP therapy, with two studies who qualified this conclusion due to the short follow-up period.

Two reviews on the topic of laser prostatectomy,[81, 82] for the anticoagulated patient population concluded that (i) laser prostatectomy appears to be safer than transurethral resection of the prostate in patients on AC, (ii) performing laser prostatectomy in patients who continue AC/AP medications during the perioperative period. Patient cohort sizes varied considerably across these studies, preventing a rigorous comparison. While these authors acknowledged that patients undergoing transurethral resection of the prostate who are on long-term AC/AP, with or without bridging, have a higher risk of bleeding complications upon resuming AC/AP, stratifying the thromboembolic risk for outlet procedures, as presented in the 2012 American College Of Chest Physicians guidelines, is recommended .[43]

Complications for patients undergoing transrectal ultrasound guided biopsy of the prostate while continuing aspirin or low-dose aspirin were studied [83-87] in prospective controlled trials. In a study of 200 men, 36 of whom were continued on low-dose aspirin during a prostate biopsy, there was no statistically significant difference in hematuria or other bleeding after biopsy between those on and not on low-dose aspirin, concluding that low-dose aspirin does not need to be discontinued before sextant
prostate biopsy. A meta-analysis including each of the prior four studies adding a fifth cohort from their own institution, thereby totaling 3,218 subjects across all five studies. The degree of hematuria was described as severe in only four patients. Analyzing the reported complication rates, this meta-analysis found that minor hematuria was statistically more frequent (P = 0.001) among patients taking aspirin than in the control group (OR 1.36, 95% CI [1.13-1.64]), suggesting an increased risk of minor bleeding of approximately 36%. However, the occurrence of rectal bleeding and hematospermia was not statistically different between patients taking aspirin and controls. A large prospective study of 1,000 transrectal ultrasound guided biopsy of the prostate patients, 49 of whom received warfarin, 220 received aspirin continuing AC/AP therapies through the periprocedural period and 731 did not take any AC/AP drugs. Among the warfarin group, 18 patients (36.7%) had hematuria compared with 440 patients (60.2%) in the control group (p=0.001). Hematospermia was reported by four of 49 patients (8.2%) in the warfarin group and 153 of 731 patients (21%) in the control group (p=0.03). There was no significant difference in rates of postoperative rectal bleeding between the warfarin and control groups. Each of these authors concluded that uninterrupted use of aspirin does not increase the risk of overall bleeding, or moderate/severe hematuria after transrectal ultrasound guided biopsy of the prostate, and thus halting aspirin before such biopsies is unnecessary.

For the low-risk patient, there is strong evidence that AC/AP can be safely discontinued without an increased risk of bleeding complications. A study of 336 patients [89] discontinued AC/AP in 108 low-risk patients five days prior to biopsy, while 228 served as controls. Over a four-week follow-up period, 6.5% (22/336) of all patients had more than two weeks gross hematuria, eight of whom had taken aspirin/thrombolytics. However, there was no statistically significant association between hematuria and aspirin/thrombolytic drug use (p = 0.170). A retrospective study of 1,875 transrectal ultrasound guided biopsy of the prostate patients, with a small proportion taking AP/AC agents (173 on aspirin and 7 on warfarin) [90] also found no significant association between AP/AC usage and incidence of complications after transrectal ultrasound guided biopsy of the prostate.

One review article [91] suggests that for transrectal ultrasound guided biopsy of the prostate for the high-risk individual that it may be preferable to biopsy patients with an INR in the therapeutic range of 2 to 3 without halting warfarin therapy, thus reducing risk of thrombosis. This is consistent with a study of 183 patients [92], 88 of whom were continued on monotherapy or dual therapy (with aspirin, warfarin, clopidogrel or low molecular weight heparin), with 95 controls not on anticoagulation. Complications were compiled for one week postoperatively. The overall incidence of hematuria was 40/88 patients (46%) in the AC/AP group compared with 60/95 controls (63%) (p=0.018). Again, the incidence of hematospermia and rectal bleeding was comparable in the two groups.
Radical prostatectomy and the use of AC/AP has been studied in small case series[93-101] including one study that found administration of aspirin to patients prior to surgery did not result in increased intraoperative complications.[98] Another study[100] determined that in radical prostatectomy patients, those receiving bridging with ≥80 mg enoxaparin (n=51) were 4.1-fold more likely to require a blood transfusion relative to controls that received a lower prophylactic dose of 40 mg enoxaparin (n= 1327, p = 0.02). Similarly, patients receiving ≥80 mg were 3.2-fold more likely to have a drainage duration of ≥4 days from a routinely placed drain if lymphadenectomy was performed than in patients receiving prophylactic low molecular weight heparin (p = 0.03). There was no increased risk of lymphocele formation; unfortunately, the authors do not comment on the rate of thromboembolic complications in these cohorts.

Two retrospective studies addressed the management of AC/AP therapy associated with surgical renal procedures. One case-control study[102] of 94 patients undergoing partial nephrectomy, in which 47 patients discontinued AC/AP therapy prior to surgery with or without bridging based on thromboembolic risk, were matched with 47 controls. Interestingly, controls had significantly higher intraoperative blood loss (300cc vs 200cc, p < 0.05) and a greater postoperative decrease in hemoglobin (p < 0.001). Transfusion rates were similar in the two groups however (each 15%). During the 30-day follow-up period, five patients on AC had thrombotic events postoperatively, compared to zero in the control group showing no statistical significance underscoring the inherent risks despite meticulous perioperative management.

The risk of complications in renal biopsy patients continuing the use of AP agents[103] from an analyzed population (N=1,120) from two centers consisted of 135 patients on AP agents (aspirin, dipyridamole, or clopidogrel). In one center, all AP agents and non-steroidal anti-inflammatory drugs were discontinued five days before elective biopsy, and in the other they were continued. Among the 135 elective renal biopsy patients on AP agents, in comparing the 75 patients who continued to take their medication (68 aspirin, 7 clopidogrel) to the 60 patients who discontinued their prescribed AP agent, there was no difference in the rate of major bleeding complications (1/75 v. 0/60). However, a minor bleeding complication (defined as ≤1.0 g/dL reduction in hemoglobin after the biopsy without the need for transfusion or intervention) was significantly higher in the group that continued AP medications (31.0 versus 11.7%; P =0.008).

Section 5: Surveys of Urologist Management Practices

Four survey-based articles aimed to quantify the perioperative AC/AP management trends of urologists. All four articles concluded that wide variation exists in urologists’ protocols for managing patients on AC/AP agents.
Several articles focused on the urologic periprocedural management of aspirin. Survey responses from 297 UK-based urologists concerning transrectal ultrasound guided biopsy of the prostate found that only 44% of urology departments have protocols in place relating to aspirin use prior to this procedure.[104] Of the responding urologists, 65% did not routinely stop aspirin before transrectal ultrasound guided biopsy of the prostate. Of those who did halt regular aspirin prior to transrectal ultrasound guided biopsy of the prostate, 52% stopped one week before, 41% two weeks before, and 6% greater than three weeks before. A third of the urologists felt that aspirin increases periprocedural bleeding complications, whereas 59% stated that the cerebrovascular risks of stopping aspirin outweigh the benefit of stopping aspirin for bleeding concerns. [105] In a similar study emphasizing aspirin usage during transurethral resection of the prostate, UK-based survey of urologists, and found from 287 responses that only 62% of practitioners ask patients to stop aspirin prior to transurethral resection of the prostate – on average 9.8 days prior to surgery (median: 10 days; range: 2 to 30 days). Aspirin was recommenced on average 8.8 days (median: 7 days; range: 1 to 42 days) after surgery. In respondents that request cessation of aspirin, 40% responded that they would cancel a transurethral resection of the prostate procedure if aspirin use had been inadvertently continued. [105]

Warfarin management practices were surveyed among the Ireland-based urology community demonstrating wide ranges in the reinstitution of warfarin post procedure; procedure complexity significantly affected the length of time to warfarin recommencement with respondents restarting warfarin on average 2.41 ± 2.31 days (range 1 to14 days) after minor procedures, 3.07 ± 3.52 days (range 1 to 28 days) after endoscopic procedures and 4.38 ± 3.53 days (range 1 to14 days) after major procedures (p < 0.0001). [106]

A 2009 survey of clopidogrel management found that the majority of 297 responding urologists stop clopidogrel prior to transrectal ultrasound guided biopsy of the prostate (90.6%), shock wave lithotripsy (81.8%), transurethral resection procedures (96.6%) and major urological surgery (97.1%), and slightly less so for cystoscopy and biopsy (70.1%) [107]. The majority of respondents stated they would halt clopidogrel sometime between 5 and 14 days before surgery, with the most frequent reported interval being 10 days followed by 7 days. A small set of respondents would stop the clopidogrel less than 3 days or greater than 14 days prior to the procedure. A significant number (ranging from 16.3 to 32.5% of respondents) were unsure or did not have a fixed protocol regarding discontinuation of clopidogrel. The highest respondent variation was in the management of clopidogrel prior to shock wave lithotripsy. After stopping clopidogrel, 139 (46.9%) would routinely prescribe bridging therapy, 129 (43.3%) would not, and 29 (9.8%) base their decision on the indication for clopidogrel. [107] Patients placed on clopidogrel are placed on AP due to risk of coronary artery disease, cerebrovascular disease and deep vein thrombosis; these disease entities are not within
the expertise of the practicing urologist. As such, multidisciplinary consultation is recommended for safe management in this setting.

Section 6: Limitations of the Review

Several limitations to this systematic review are apparent. The evidence summary is primarily qualitative. There is insufficient information to investigate study quality, document effect sizes or assess confounding variables. High level evidence strength does not exist for many of the urologic procedures. Many studies reporting on periprocedural complications for patients on AC/AP therapy had insufficient sample sizes to stratify the subjects by particular AC/AP agent, or by cardiovascular indication. Usage of the terms “anticoagulant” and “antiplatelet” was also variable, leading to considerable ambiguity in reported results, particularly noted in the surgical literature. It is recommended that medications and dosages be clearly reported in the literature. While much needed, the development of an AC/AP resumption protocol (e.g. determining the most appropriate number of days to the resumption of AC/AP medications after low-, medium- and high- risk procedures) cannot be made based on the current urologic literature.

Section 7: Future research

The use of Clavien-Dindo classification in reporting of thromboembolic versus hemorrhagic risk in relationship to AC/AP and other comorbidities is recommended to inform the surgeon and patient as to the true risk of significant complications. The CROES study on percutaneous shockwave lithotripsy is the only high quality study of its kind in the current urologic literature, in classifying the hemorrhagic and other surgical complications from a large prospective database. Likewise, the true risk of minor complications should be detailed in a manner to facilitate informed decision making and consent. Determination of the earliest time interval to the resumption of AC/AP after high risk surgical procedures for high risk patients is needed from large prospective randomized trials.

Section 8: Recommendations for periprocedural management of AC\AP treatment for the Urologist

Certain operative site-related risks may incur a higher risk for hemorrhagic complications. Surgeons understand that the loss of tissue planes, exposed raw surface, mechanism of injury and extent of the procedure can add to the complexity of the
surgical process and increase the risk of perioperative hemorrhage. Contrariwise, knowledge of perioperative hemorrhage must take into account thromboembolic complications stratified by risk. The management of AC/AP often involves consideration of issues for which the urologist does not have expertise. In such cases, a multidisciplinary consensus approach is advised. Certainly, high risk procedures for high risk patients should prompt a multidisciplinary consensus approach. Perioperative planning is essential in all but urgent cases. For some patients, the urologic risk of major bleeding (complications graded Clavien-Dindo grade III and higher) may be outweighed by the higher risks of major adverse cardiac and cerebrovascular events. Minor Clavien-Dindo complications, including the use of transfusion blood products, may require an assumption of risk on the part of the surgeon for the patient at high risk of major adverse cardiac and cerebrovascular events complications from disruption of AC/AP. Parameters other than AC/AP usage are associated with an increased perioperative risk of bleeding as well as thrombosis in urologic patients and yet are often under recognized. Those include increasing age, renal insufficiency, a short delay between cardiac stenting and surgery, preoperative anemia, and high-risk surgery.

1. **For patients on clopidogrel or aspirin for secondary stroke prevention, especially for recent events, it is recommended to continue aspirin through the perioperative period.** For patients on AC for secondary stroke prevention, neurologic consultation is recommended to evaluate competing risks and determine the necessity for bridging therapy. The risk of hemorrhage from low risk procedures is outweighed by the risk of thromboembolic events in patients on AP/AC for secondary stroke prevention.

2. **Withdrawal of DAPT should NOT occur prior to urologic procedures within 12 months of drug eluding stent placement or within 3 months of bare metal stent placement, due to the high risk of major adverse cardiac and cerebrovascular events.** A multidisciplinary approach involving cardiology expertise is essential when urgent urologic procedures are required within these time frames. For procedures performed beyond these limits, discontinuation of the clopidogrel, prasugrel, or ticagrelor, and continuation of aspirin, is recommended if bleeding risks are acceptable.

3. **Patients with mechanical heart valves are at high risk for thrombotic complications and should be bridged as appropriate.** Expert cardiologic consultation regarding AC should be planned well ahead of any elective procedure and is strongly recommended in all complex management cases.

4. **For those patients with cardiac risk factors on low-dose aspirin alone, this can be continued in perioperative period without increased risk of major bleeding.**

5. **Patients taking low-dose aspirin without specific medical indications may be scheduled electively, discontinuing the AP drug until directed by the surgical team.**
6. Periprocedural Management of NOAC for patients with non-valvular atrial fibrillation is stratified by procedural risk of bleeding and the urgency of the procedure:

- For procedures with only a minor risk of bleeding, NOAC use does not have to be modified, similar to the management with warfarin or low molecular weight heparin.
- For urgent procedures: a delay of the procedure, if medically appropriate for 24 to 36 hours, allowing for expert consultation with cardiology/hematology/thrombosis services.
- For emergent procedures: if there is an increased risk of bleeding associated with this procedure, consultation with experts is strongly advised. Spinal/epidural anesthetics are contraindicated.
- Renal reduction procedures will require assessment of renal function post-procedure in order to determine the safety and dosing of NOAC.

7. Perioperative management of atrial fibrillation in high risk surgical procedures requires that warfarin would be stopped five days before the surgical procedure and should be restarted 12 to 24 hours after surgery if the bleeding risk is acceptable. In patients with higher risk or thromboembolic events (e.g. mechanical valves) bridging anticoagulation with unfractionated heparin or low molecular weight heparin is recommended.[43] The NOACs, apixaban, dabigatran, or rivaroxaban, would be discontinued 2 to 5 days before elective surgery, the timing is dependent on the bleeding risk of the procedure (Table I). Rivaroxaban can increase acutely the risk of stroke if suspended; therefore, bridging with some other anticoagulant such as heparin is recommended, although longer periods of bridging may be needed.

8. Perioperative management of prosthetic valves should follow the American College of Cardiology /American Heart Association/Society for Cardiovascular Angiography and Interventions 2011 percutaneous coronary intervention Guidelines23 for the management in patients with valvular heart disease. Low risk of thrombosis (defined as those with a bileaflet mechanical AVR and no risk factors such as atrial fibrillation, previous thromboembolism, left ventricular dysfunction, hypercoagulable conditions, older generation thrombogenic valves, mechanical tricuspid valves or more than one mechanical valve) can stop warfarin 48 to 72 hours before the procedure and restarted within 24 hours after the procedure. Heparin is usually unnecessary. However, the INR should always be checked just prior to surgery to ensure that the INR is less than 1.5.
9. In patients at high risk of thrombosis (defined as those with any mechanical mitral valve replacement or a mechanical aortic valve with any risk factor) bridging should be started when the INR falls below 2.0 (typically 48 hours before surgery), and the dose adjusted to achieve an activated partial thromboplastin time two to three times the control. Unfractionated heparin is stopped four to six hours before the procedure and restarted as early after surgery as bleeding stability allows. Warfarin is resumed as soon as possible postoperatively, and unfractionated heparin is continued until the INR is in the therapeutic range for at least 48 hours.[108]

10. The American College Of Chest Physicians supports the use of three different bridging regimens for prosthetic valves:

- A high-dose (therapeutic-dose) heparin bridging (e.g., low molecular weight heparin such as enoxaparin 1 mg/kg bid or 1.5 mg/kg daily, dalteparin 100 IU/kg bid or 200 IU/kg daily, tinzaparin 175 IU/kg daily, or i.v. unfractionated heparin to attain an activated partial thromboplastin time [aPTT] 1.5 to 2 times the control aPTT).
- A low-dose (prophylactic-dose) heparin regimen (e.g., enoxaparin 30 mg bid or 40 mg daily, dalteparin 5,000 IU daily, unfractionated heparin 5,000-7,500 IU bid).
- An intermediate-dose regimen (e.g., enoxaparin 40 mg bid).[43]

Appropriate bridging strategies using low molecular weight heparin, or unfractionated heparin for the chronically anticoagulated surgical patient are associated with acceptable risks of major adverse cardiac and cerebrovascular events and bleeding.

11. AC/AP agents should be discontinued and/or reversed prior to shock wave lithotripsy. The timing of cessation and reinstitution of oral AC/AP should include an assessment of the risks of thrombotic complications versus bleeding using a coordinated multidisciplinary plan with stratification according to risks.

12. Ureteroscopy can be performed with continuing oral AC/AP therapy.

13. Oral AC/AP medications should be discontinued prior to percutaneous nephrolithotomy and patients bridged where deemed necessary. Timing of cessation and re-initiation of oral AC/AP with or without bridging therapy should involve multidisciplinary decision plan with stratification according to risks.

14. In appropriately selected patients, laser prostate surgery can be safely accomplished for the patient with a therapeutic INR who has a significant risk of thrombosis without the discontinuation of oral AC/AP.
15. **AC/AP in patients undergoing transurethral resection of the prostate is associated with an increased risk of bleeding complications which may continue throughout the perioperative period.** AC/AP should be carefully assessed and appropriately managed in patients undergoing transurethral resection; alternative treatment of the bladder outlet may be preferable.

16. **Prostate biopsy can be performed safely for the patient on low dose aspirin with a risk of minor bleeding approximately one third higher than controls.** For the patient who requires maintenance of AC based on higher risk of thromboembolic complications, small cohort studies suggest that this can be performed without significant risk of any major bleeding. Stopping AP agents before biopsy, when medical evaluation demonstrates a low risk of thromboembolic complications, is associated with a lower rate of minor complications.

17. **Higher risk urologic procedures, such as radical prostatectomy and partial nephrectomy, have been safely performed with bridging therapy in those with a higher risk of thromboembolic complications, albeit with an increased risk of bleeding.** When elective, deferral of surgery or multidisciplinary planning to coordinate perioperative AC/AP therapy with bridging will minimize both risks for surgical and thromboembolic complications.

18. **In general, the perioperative continuation of aspirin may be associated with a minor risk of increased bleeding, but the transfusion rate is not increased and the consequences of that bleeding are minor with the probable exception of transurethral resection of the prostate.**

**Section 9: Illustrative Cases**

**Scenario #1:** A 55-year-old male comes to you after his primary care physician has reported that he has a serially elevating PSA. The PSA is now measured at 5.8 ng/mL. He has a brother and father with prostate cancer. Comorbidities include the development of coronary artery syndrome treated with a drug eluding stent four months ago. His medications include a daily stain, aspirin, and clopidogrel. He is an avid runner and is in excellent physical shape. How do you address the apparent indication for prostate biopsy in light of these medications?

This man is at high risk of having prostate cancer. While consensus decision making should include the patient, the patient has a history of recent drug-eluting stent (<12 months) and he currently has no cardiovascular symptoms. Despite good cardiac performance, the presence of a recently deployed
cardiac stent makes the risk of an acute major adverse cardiac and cerebrovascular events extremely high if DAPT is stopped. The risk of DAPT discontinuation exceeds the benefit of a biopsy at this time. Rectal coil MRI is experimental, but would only be helpful in reassuring him if the MRI is normal. An MRI that is abnormal may markedly increase his anxiety. Here, the delay of a diagnostic biopsy is appropriate given his high risk of a stent thrombosis and a major cardiac event if DAPT are interrupted at this critical time. His biopsy should be deferred until 12 months have passed since insertion of the drug-eluting stent. At that point clopidogrel can be discontinued and the aspirin should be continued during the biopsy (and subsequent surgery, if required).

Scenario #2: A 75-year-old female presents to the emergency department with left flank pain. A non-contrast CT scan reveals an 8-mm stone within the left proximal ureter with significant hydronephrosis. The urinalysis shows microscopic hematuria with no sign of infection. The patient cannot tolerate oral intake due to nausea and her pain is severe and responsive to intravenous narcotics only. She has congestive heart failure in associated with a mechanical heart valve; her INR is therapeutic on warfarin.

Urologic assessment should include the urgency and timing of intervention versus the risk of a major complication of hemorrhage on therapeutic warfarin doses. Alternative procedures might include continued observation with the consideration of oral tamsulosin. However, the use of warfarin and tamsulosin has not been studied and their concurrent use should be with caution. From a cardiac standpoint, this patient currently has New York Heart Association class I symptoms and is euolemic without any signs or symptoms of decompensated congestive heart failure. Her cardiovascular risk is deemed to be low. However, her thrombotic risk is elevated due to the presence of a mechanical heart valve in mitral position. Continued narcotic support, extracorporeal shock wave lithotripsy, simple stent placement (with a documented therapeutic INR) or ureteroscopy with holmium:YAG laser lithotripsy may all be appropriate alternatives given the expertise of the urologist. Since the case is not emergent, it allows for the multidisciplinary management of her AC/AP, if needed. In this case, however, ureteroscopy is a good choice and does not require discontinuation of AC/AP agents.

Scenario #3: An 83-year-old male is referred with a history of a gross hematuria and high grade muscle invasive urothelial cancer diagnosed after a transurethral resection of a bladder tumor 6 months ago. His comorbidities include deep vein thrombosis developing post-resection and now managed with warfarin. He has adult-onset diabetes mellitus managed with daily insulin. He has completed three courses of neo-adjuvant chemotherapy and has opted for a radical cystectomy, an extended lymph node dissection and an ileal conduit. He denies any dyspnea on exertion, chest pain, orthopnea, but has mild lower extremity edema at the end of the day.
This is an urgent procedure due to his bleeding risks and risk of progression of his high grade muscle invasive urothelial cancer. This patient has compensated congestive heart failure with mild volume overload only clinically significant by mild edema. In perioperative planning, it would be advisable to increase his oral diuretics or transition him to intravenous diuretics to optimize his volume carefully addressing his renal function. As for the anticoagulation, this patient has a high risk for thromboembolic events due to active cancer and recent deep vein thrombosis. His bleeding risk is high, as is his perioperative morbidity and mortality. He needs to be bridged with heparin or low molecular weight heparin before surgery. He needs to stop oral anticoagulation, and start intravenous heparin or low molecular weight heparin adjusted for weight once the INR is below 2.0-2.5. The proposed procedure would need to be deferred until the INR is <1.5 and the heparin should be stopped six hours before the surgery, or last dose of low molecular weight heparin >12 hours before surgery, and they should be restarted soon after the procedure is completed unless the bleeding risk is too high. The resumption of warfarin should occur when the risk of perioperative bleeding has receded, typically within the first few days post-operatively if he has no transfusion requirement and is hemodynamically stable. Close multidisciplinary management of these surgical and medical conditions are required in combined high-risk patients.

Scenario #4: A developmentally challenged 45-year-old female presents with gross hematuria, sebaceum adenoma of the face and retinal hemangiomas. A CT urogram reveals multiple left solid renal tumors ranging in size from 3- to 5-cm.

The patient presents a classic presentation of tuberous sclerosis which is associated with an increased risk of thrombotic complications. The option of complex renal surgery planned to remove the multiple renal tumors, likely malignant, is likewise associated with high risk of perioperative bleeding. Alternative treatment might include minimally invasive procedures; there is little data on which procedure is associated with lower bleeding risk. Tuberous sclerosis can affect the heart (rhabdomyomas) and sometimes the patient can have congestive heart failure. Since the clinical information and interrogation of the patient can be challenging, an echocardiogram could be useful as part of her preoperative evaluation.

She clearly has an elevated hemorrhagic risk so careful deep vein thrombosis prophylaxis using mechanical compression and possibly low doses of heparin (if tolerated) are possibly the best approach before surgery to decrease her thrombotic risk. If the patient develops more hematuria, continuing the mechanical compression and possibly the insertion of a temporary inferior vena caval filter would be considered.
# Appendix A – Abbreviations Used in Report

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>AC</td>
<td>anticoagulant/anticoagulation medications: inclusive of coumarins, heparin, NOAC (see text)</td>
</tr>
<tr>
<td>AP</td>
<td>antiplatelet medications: inclusive of aspirin, clopidogrel, ticagrelor, ticlopidine, dipyridamole</td>
</tr>
<tr>
<td>DAPT</td>
<td>Dual antiplatelet therapy</td>
</tr>
<tr>
<td>INR</td>
<td>international normalized ratio</td>
</tr>
<tr>
<td>NOAC</td>
<td>novel oral anticoagulant</td>
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</table>
Figure 1: Simplified coagulation cascade with mechanism of action of selected anticoagulants.
Table 1: Anticoagulant agents: suggested perioperative management. Modified from Ortel TL\textsuperscript{9}

<table>
<thead>
<tr>
<th>Anticoagulant Therapy</th>
<th>Time to Maximum Effect</th>
<th>Low Bleeding Risk Surgery*</th>
<th>High Bleeding Risk Surgery**</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin (racemic)</td>
<td>5-7 d for a therapeutic IRN</td>
<td></td>
<td></td>
<td>Circulating vitamin K dependent factors (II, VII, IX, X)</td>
</tr>
<tr>
<td>Unfractionated Heparin</td>
<td>Immediate IV; within 6 h SQ</td>
<td></td>
<td></td>
<td>Renal clearance; Effective reversal with protamine</td>
</tr>
<tr>
<td>Low-molecular Weight Heparin</td>
<td>3-5 h</td>
<td></td>
<td></td>
<td>Renal clearance; partial reversal</td>
</tr>
<tr>
<td>Drug</td>
<td>Half-life</td>
<td>Last dose:</td>
<td>Last dose:</td>
<td>Notes</td>
</tr>
<tr>
<td>------------</td>
<td>-----------</td>
<td>------------</td>
<td>------------</td>
<td>------------------------------</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>2 h</td>
<td>2 d before surgery</td>
<td>3 d before surgery</td>
<td>Renal clearance; not reversed by protamine</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>1.25-3 h</td>
<td>2 d before surgery</td>
<td>3 d before surgery</td>
<td>Nonreversible; 80% renal clearance</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>2-4 h</td>
<td>2 d before surgery</td>
<td>3 d before surgery</td>
<td>Nonreversible; 66% renal clearance</td>
</tr>
<tr>
<td>Apixaban</td>
<td>1-3 h</td>
<td>2 d before surgery</td>
<td>3 d before surgery</td>
<td>Nonreversible; 25% renal</td>
</tr>
</tbody>
</table>
The intensity of the anticoagulation regimen depends on the preoperative risk stratification.
If the surgical bleeding risk is low, the periprocedural recommendation would be to continue dual antiplatelet therapy or aspirin alone.
References


2. World Health Organization Cardiovascular Diseases.


108. Bonow, R.O., et al., 2008 focused update incorporated into the ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to revise the 1998 guidelines for the management of patients with valvular heart disease). Endorsed by the Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and