Novel oral anticoagulants (NOACs) are increasingly replacing the use of warfarin in clinical practice. Their use has now also been extended to thromboprophylaxis in many orthopedic surgeries. This, in addition to an increasingly aging population with many complex comorbidities means that these medications will be ever more frequently encountered by urologists. Thus, a clear understanding of the mechanism of action of NOACs, their time to peak action and half-life is essential for the purpose of managing these patients perioperatively. This article demonstrates the patient and procedural variability that must be taken into account in the perioperative management of the anticoagulated patient. While the time to peak onset and half-life of NOACs can aid in determining the interval of interruption of anticoagulation, the risks of thrombosis and bleeding must be assessed before the decision to stop anticoagulation. This article takes into account the evidence available on NOACs in urological surgery in order to inform the perioperative management of these medications and to propose guidelines to aid in clinical decision making. In attempting this, we address the issue of the lack of high-level evidence surrounding NOACs in urological surgery given their relative novelty and the need for further research to better guide practice.

Key Words
Novel oral anticoagulant • Anticoagulation • Urology

Abstract
New oral anticoagulants (NOACs) are increasingly replacing the use of warfarin in clinical practice. Their use has now also been extended to thromboprophylaxis in many orthopedic surgeries. This, in addition to an increasingly aging population with many complex comorbidities means that these medications will be ever more frequently encountered by urologists. Thus, a clear understanding of the mechanism of action of NOACs, their time to peak action and half-life is essential for the purpose of managing these patients perioperatively. This article demonstrates the patient and procedural variability that must be taken into account in the perioperative management of the anticoagulated patient. While the time to peak onset and half-life of NOACs can aid in determining the interval of interruption of anticoagulation, the risks of thrombosis and bleeding must be assessed before the decision to stop anticoagulation. This article takes into account the evidence available on NOACs in urological surgery in order to inform the perioperative management of these medications and to propose guidelines to aid in clinical decision making. In attempting this, we address the issue of the lack of high-level evidence surrounding NOACs in urological surgery given their relative novelty and the need for further research to better guide practice.

Introduction
Novel oral anticoagulants (NOACs) were developed to address adverse events and difficulties achieving optimal anticoagulation on vitamin K antagonists (VKAs) such as warfarin due to their slow onset of action, long half-life, variable pharmacologic effects and multiple drug and food interactions (table 1) [1]. NOACs are increasingly being prescribed in clinical practice. As urological clinicians, we must understand their mechanism of action, safe timing of discontinuing preoperatively and recommencing postoperatively, any reversal agents, and time needed to return to therapeutic status. NOACs are either direct thrombin inhibitors (dabigatran) or factor Xa inhibitors (rivaroxaban, apixaban). The advantages of direct inhibitors are shorter half-life and onset of actions, however there are drawbacks such as high cost and lack of a specific antidote [1, 2]. NOACs do not require labo-
ratory monitoring to ensure efficacy which is particularly advantageous in comparison to VKAs which have a narrow therapeutic index and require monitoring of international normalized ratio or prothrombin time at variable intervals depending on patient cohort, drug interactions or medical co-morbidities [2]. The aim of the present narrative review is to discuss the pharmacokinetics of these NOACs and provide an overview of their perioperative management in urological surgery.

Methods

A literature search was undertaken using the PubMed, Embase and Cochrane databases. The following terms were entered into the search algorithm to identify peer-reviewed articles which related to NOACs and their use in urological surgery: “new oral anticoagulant” or “NOAC” and “urological surgery” or “anticoagulation in urological surgery”. Studies on adult patients published in English between 2008 and December 2016 were included. In addition, the reference list of retrieved publications was further screened for additional publications. Thirty studies published between 2008 and 2016 were retrieved, of which 10 were suitable for this narrative review based on clinical relevance and importance of content. This low volume of articles demonstrates the relative novelty of NOACs, especially in surgery, let alone the highly specialised field of urology. The pharmacokinetics and mechanism of action of NOAC was investigated. Inclusion criteria were articles regarding perioperative management of NOAC, urological management of NOAC, management of bleeding and thrombosis risk. Exclusion criteria were articles which did not reference NOACs, those that were not published in English and those which did not bear any relevance to the clinical use of NOACs.

Clotting Cascade

The clotting cascade is the term used to describe the physiological process of fibrin formation to form a clot. This happens through a series of events mediated by clotting factors (fig. 1). VKAs like warfarin inhibit the formation of vitamin K dependant clotting factors [3]. The anticoagulant effect can therefore be reversed by administering vitamin K or allowing warfarin to be cleared from the body [4]. NOACs are divided into 2 groups by their mechanism of action. Dabigatran acts by directly inhibiting thrombin which is the enzyme responsible for converting fibrinogen to fibrin, resulting in the inability to form a clot [3]. The other arm of NOACs is the factor Xa inhibitors which act by preventing the conversion of prothrombin to thrombin [3].

Fig. 1. Common pathway of clotting cascade.

![Common Pathway](image)

Table 1. Half-life and onset of action of warfarin vs. NOACs

|                  | Warfarin | Dabigatran | Rivaroxaban | Apixaban |
|------------------|----------|------------|-------------|----------|
| Half-life, hour  | 40       | 14–17      | 5–9         | 10–14    |
| Peak onset of action, hour | 120–168 | 2         | 2–4         | 1–4      |
| Renal clearance, % | negligible | 80     | 35          | 27       |

Table 2. CHADS<sub>2</sub>-VASc score

| Risk factors                          | Score |
|---------------------------------------|-------|
| Congestive heart failure              | 1     |
| Hypertension                          | 1     |
| Age ≥ 75 years                        | 2     |
| Age 65–74 years                       | 1     |
| Diabetes mellitus                     | 1     |
| Stroke/TIA/thromboembolism            | 2     |
| Vascular disease                      | 1     |
| Sex (female)                          | 1     |

TIA = Transient ischemic attack.
Indications for NOACs

These drugs now have a wide array of indications such as primary prevention of venous thromboembolism (VTE) and stroke in atrial fibrillation as well as treatment of deep VTE and pulmonary embolism, and more recently as thromboprophylaxis for patients undergoing total hip or knee arthroplasty [1]. Therefore, as the indications for their use expand, there will be an increase in the number of urological patients on this form of anticoagulation. In North America periprocedural management of patients on oral anticoagulation, including VKAs, affects 250,000 people per year [4]. Management of these patients can be challenging. The increased risk of bleeding predisposes to technically difficult cases, blood transfusions and need for re-operation. In addition, part of the patient cohort may be at a very high risk for VTE in the absence of oral anticoagulation [4]. Aside from patient factors affecting the risk of thromboembolism, surgery itself is a recognised risk factor for VTE [4].

Consideration of Thrombotic Risk

The decision to stop or continue anticoagulation perioperatively may be straightforward but more often involves a consideration of the procedural risk of bleeding and the patients’ level of risk for a thromboembolic event in the absence of anticoagulation [3, 5].

The individual patient risk for VTE depends on the indication for anticoagulant therapy. For instance, mechanical heart valves, atrial fibrillation or previous VTE are the 3 most common indications for chronic anticoagulation [4]. In the case of mechanical heart valves the risk of thromboembolism varies depending firstly on the placement of the valve – mitral valves have almost twice the risk of thromboembolism of aortic valves [4]. Secondly, thromboembolic risk varies with the type of valve, which is, in order of decreasing thrombogenicity – caged ball valves, tilting disc valves or bileaflet valves [4].

The congestive heart failure, hypertension, age, diabetes mellitus, stroke/transient ischemic attack/thromboembolism, vascular disease, sex (CHADS2-VASc) score, developed by the American College of Cardiology, American Heart Association and European Society of Cardiology, can be used to assess thromboembolic and stroke risk in patients with non-valvular atrial fibrillation (table 2) [5]. The CHADS2-VASc takes into account a number of patient comorbid factors as outlined in the table below and gives the patient a score out of 10 [5]. The higher the score, the greater the thromboembolic risk is [4, 5].

VTE can also be graded depending on whether the VTE was provoked or unprovoked, the length of time since the VTE developed and whether the patient in question has had a solitary VTE or a number of recurrences [4].

In the most recent American College of Chest Physicians (ACCP) guidelines on antithrombotic therapy they suggest a low, intermediate or high risk stratification system based on the factors influencing thrombotic risk in the three most common indications for anticoagulation as outlined above (table 3) [6]. However, this is not a validated risk stratification system, and currently none exist for the estimation of thromboembolic risk during the perioperative period [7]. Schemes like the ACCP are however very useful for the clinician to understand their patients level of risk to manage their perioperative anticoagulation appropriately [4, 5].

| Risk level | Indication for VKA |
|------------|--------------------|
| Mechanical heart valve | CHADS2 score > 5 recent (< 3 month) stroke or TIA rheumatic heart disease |
| Atrial fibrillation | CHADS2 score 3–4 VTE within past 3–12 months non-severe thrombophilia recurrent VTE active cancer (< 6 months or palliative) |
| VTE | CHADS2 score 0–2 VTE > 12 months |

AF = Atrial fibrillation; TIA = transient ischemic attack; HTN = hypertension; DM = diabetes mellitus; CCF = congestive cardiac failure.

Table 3. ACCP risk stratification for thrombosis
Table 4. HAS-BLED score

| Clinical characteristic              | Points awarded |
|-------------------------------------|----------------|
| Hypertension (uncontrolled)         | 1              |
| Abnormal liver function             | 1              |
| Abnormal renal function             | 1              |
| Stroke                              | 1              |
| Bleeding (history of bleeding or anemia) | 1        |
| Labile INRs                         | 1              |
| Elderly (Age > 65 years)            | 1              |
| Drugs (AP or NSAID)                 | 1              |
| Alcohol (> 8 units/week)            | 1              |

INR = International normalized ratio; AR = aspirin; AP = antiplatelets; NSAIDs = nonsteroidal anti-inflammatory drugs.

Finally, when discussing thrombotic risk in relation to perioperative management of anticoagulation, the thrombotic risk imbued by the surgery itself must not be overlooked. In fact, it is estimated that surgery could theoretically increase the risk of VTE 100 fold and it may also increase the risk of arterial thromboembolic disease [4]. Whether a patient needs to be managed conservatively or aggressively in terms of perioperative anticoagulation depends on their risk of thromboembolism and therefore while suggested guidelines have been developed, at present the decision whether and when to stop NOACs is predominantly a clinical decision [4].

Consideration of Bleeding Risk

The other consideration is the risk of bleeding as a result of anticoagulation. This can be due to both patient factors excluding anticoagulation but also depends on the type of procedure being carried out. Parameters except anticoagulation which are associated with an increased periprocedural bleeding risk are hypertensive patients, those with abnormal renal or liver function, increasing age (< 65 years), history of a previous stroke, predisposition to bleeding, labile international normalized ratio and drug or alcohol use [7].

The hypertension, abnormal liver function, abnormal renal function, stroke, bleeding history, labile international normalized ratios, elderly, drugs, alcohol (HAS-BLED) score is a useful tool to identify those patients who may have an increased risk of bleeding (table 4). It was developed to measure bleeding risk in patients with atrial fibrillation to guide prescription of anticoagulation [8]. A score > 3 indicates an increased bleeding risk and prompts caution in prescribing anticoagulation [8]. The HAS-BLED score can also be applied to predict individualised perioperative bleeding risk in terms of patient factors [5].

The procedural risk of bleeding must also be considered when dealing with patients on NOAC therapy. For this purpose, procedures are divided into low and high bleeding risk categories. Low bleeding risk procedures are those which have a 2-day risk of a major bleeding of 0–2%, high bleeding risk procedures are those which carry a 2-day risk of a major bleeding of 2–4% [4]. There is no distinct stratification for bleeding risk in urological procedures. Therefore clinical judgement must play a large role in determining the procedural risk of bleeding. The American Urological Association (AUA) have identified some procedures pertaining specifically to urology which they consider to be high or low risk for bleeding [5].

The AUA guidelines also add that for procedures of a minor risk of bleeding, NOAC doses do not need to be changed or held [7]. High risk procedures which require interruption of anticoagulant therapy are laser prostate surgery and ureteroscopy [5]. The AUA guidelines also add that for procedures of a minor risk of bleeding, NOAC doses do not need to be changed or held [7]. High risk procedures which require interruption of anticoagulant therapy are extracorporeal shockwave lithotripsy, percutaneous nephrolithotomy and transurethral resection of the prostate [5]. In addition, Spyropoulos et al. [4] suggest that any major procedure (i.e. duration > 45 minutes) is considered a high risk of bleeding, alongside biopsy of the kidney. The general consensus appears to be that most urological procedures fall into the high bleeding risk category and therefore in-

Table 5. HASHTI algorithm

| HASHTI algorithm                      | Low | High |
|---------------------------------------|-----|------|
| 1 Hold further doses of anticoagulant |     |      |
| 2 Antidote if available               |     |      |
| 3 Supportive treatment (volume resuscitation, inotropes) |     |      |
| 4 Hemostatic measures (local or surgical, tranexamic acid) |     |      |
| 5 Transfusion (red cell concentrates, platelets, fresh frozen plasma) |     |      |
| 6 Investigate source of bleeding      |     |      |

Table 6. AUA guidelines on interruption of NOACs preoperatively

| Anticoagulation | Surgical bleeding risk |
|-----------------|------------------------|
| Dubigatran      | 2 days                 | 3 days               |
| Rivaroxiban     | 2 days                 | 3 days               |
| Apixibian       | 2 days                 | 3 days               |
individual patient risk needs to be taken into consideration depending on the type of procedure carried out and the urgency of this procedure [1, 5, 7]. The lack of distinct guidelines about perioperative NOAC therapy is congruent with the AUA’s finding that high level evidence does not exist to address the issue of NOACs in urological surgery [7].

Furthermore, when perioperative bleeding risk is being considered in patients on anticoagulant therapy it is imperative to have a strategy for dealing with hemorrhage. The American Society of Hematology has devised guidelines for the management of anticoagulant associated bleeding, known as the hold anticoagulation, antidote, supportive treatment, hemostatic measures, transfusion, investigate (HASHTI) algorithm (table 5) [5]. The lack of antidotes to NOACs that are present for VKA complicates the management of NOAC associated bleeding [1]. There is currently a reversal agent for dabigatran, a monoclonal antibody idarucizumab and there may be a reversal agent available for rivaroxaban in the near future [5, 9]. Some benefit is also seen with hemodialysis of patients on dabigatran which removes up to 60% of dabigatran [1]. However current emergent management of NOAC associated bleeding is predominately as per the HASHTI guidelines and consultation with experts, with the caveat that fresh frozen plasma is not useful in NOAC associated bleeding and concentrates of coagulation factors should be used instead [5, 7, 10]. Fortunately, the relatively short half-lives of the NOACs mean that anticoagulant effects are reasonably short-lived [1].

**Interval of Interruption**

It is important to consider the timing of interruption of anticoagulant therapy [2]. The half-life of NOACs is much shorter than older VKAs (table 1) and therefore these agents do not need to be stopped as far in advance of surgery [2]. Additionally, while bridging was previously commonplace in patients on warfarin therapy, it is now not recommended, especially in those patients treated with NOACs [2]. AUA guidelines recommend that NOACs be discontinued between 2 and 5 days before an elective surgical procedure and base the timing of interruption on the bleeding risk of the surgical procedure (table 6) [1].

The European Heart Rhythm Association have since come up with more detailed guidelines on stopping anticoagulation prior to a surgical procedure which consider the renal function of the patient on NOAC therapy (table 7) [10].

The lack of an antidote is particularly concerning when dealing with NOACs in emergent surgery. Some assays can detect the level of residual drug, however, these are not generally useful and current recommendations advise waiting the appropriate amount of time for the drug to be excreted and consultation with experts [1, 7].

The existing guidelines only serve to demonstrate further how the perioperative management of patient of NOAC therapy needs to be highly individualised.

**Recommending NOACs**

AUA guidelines do not have a definitive conclusion about recommencing NOAC therapy postoperatively [7]. Wilson et al. [1] advise that re-initiation of NOAC therapy postoperatively depends on a number of factors including the nature of the surgery, the thromboembolic risk and the hemostasis of the patient. The conclusion can then be drawn that ensuring hemostasis intra-operatively is critical in ensuring that there is no unnecessary increased thrombotic risk incurred by interruption of anticoagulation and to reduce major bleeding complications once a NOAC has been reintroduced. Wilson et al. [1] suggest that with good hemostasis, anticoagulation can be recommenced at a reduced dose on the evening of the surgical procedure. Spyropoulos et al. [4] postulate a

### Table 7. European Heart Rhythm Association recommendations on interruption of NOAC therapy

| Creatinine clearance, ml/min | Direct thrombin inhibitors | Factor Xa inhibitors |
|-----------------------------|---------------------------|---------------------|
|                             | Low bleeding risk         | High bleeding risk  |
|                             | ≥ 24 hours                | ≥ 24 hours          |
|                             | ≥ 36 hours                | ≥ 72 hours          |
|                             | ≥ 48 hours                | ≥ 96 hours          |
| ≤ 15                        | not indicated for use     | not indicated for use |
| ≤ 50                        | not indicated for use     | not indicated for use |
| ≥ 80                        | ≥ 24 hours                | ≥ 48 hours          |
| ≥ 50–80                     | ≥ 24 hours                | ≥ 48 hours          |
| ≥ 30–50                     | ≥ 24 hours                | ≥ 48 hours          |
| < 15                        | not indicated for use     | not indicated for use |
| ≥ 80                        | ≥ 24 hours                | ≥ 48 hours          |
| ≥ 50–80                     | ≥ 24 hours                | ≥ 48 hours          |
| ≥ 30–50                     | ≥ 24 hours                | ≥ 48 hours          |
| < 15                        | not indicated for use     | not indicated for use |
| ≥ 24 hours                  | ≥ 48 hours                | ≥ 96 hours          |
| ≥ 36 hours                  | not indicated for use     | ≥ 96 hours          |
| ≥ 48 hours                  | not indicated for use     | ≥ 96 hours          |
| not indicated for use       | not indicated for use     | not indicated for use |

NOACs in Urological Surgery  

Curr Urol 2017;11:169–174  

173
NOACs in Urological Surgery (Implications of Renal Clearance)

Many direct inhibitors of thrombin are excreted by the kidneys and therefore their use is not recommended in patients with severe renal insufficiency [1, 10]. This is particularly concerning in a urological setting as many of the emergent patient cohort will have impaired renal function secondary to obstructive uropathy and therefore will have delayed excretion of the drug and longer duration of anticoagulant effect [1, 10]. In addition to this, some urological procedures such as partial or radical nephrectomies can cause renal impairment and so it must be noted that dose adjustment of NOACs postoperatively may be required.

Conclusion

The evidence base for perioperative management of NOACs in urological surgery is small and predominantly anecdotal. The decision to discontinue anticoagulation in non-urgent or elective surgery is therefore very much a clinical one. The 2 main factors which need to be considered when making this decision are the individual patient’s risk of thrombosis and the risk of perioperative bleeding. Like most surgical procedures, the risks must be weighed against the benefits and an appropriate decision regarding anticoagulation made. This approach and its necessary considerations may go a long way to explain why we currently lack any specific guidelines for the interruption of anticoagulant therapy in urological procedures.

The other issue in the perioperative management of anticoagulation, specifically NOACs, is the interval of its interruption. Here, guidelines can be more specific however careful consideration of patient factors is involved such as creatinine clearance, particularly in the case of dabigatran. The reintroduction of a NOAC postoperatively is firmly governed by the patients hemostasis and therefore is, once again, a clinical decision.

There are not and it seems there cannot be any specific guidelines regarding the management of NOACs perioperatively in urological surgery. This is in part due to the variability of both the patient and the urological procedures. Further research is required to improve our understanding of NOACs in urological surgery and to increase clinician confidence in dealing with these agents. Only then can we have realistic, accessible guidelines which can be used to increase the positive outcomes for patients and reduce inter-clinician variability.

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