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Review of Perioperative Anticoagulation in Urology

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Introduction

An increase in the elderly population with multiple complex co-morbidities, such as atrial fibrillation, stroke or myocardial infarction and on anticoagulation, poses a challenge for urologists managing patients, especially in the perioperative period. It is therefore important for all clinicians to have a clear understanding of the mechanisms of action of common anticoagulants and their pharmacokinetics and pharmacodynamics. This article outlines the various guidelines and recommendations for anticoagulant use in the perioperative period.

The question of when to stop and restart anticoagulation perioperatively can be challenging as excessive bleeding can lead to complications such as shock necessitating surgical control of haemostasis, blood transfusions or pose technical difficulties for the procedure being performed [1]. The two main factors which need to be taken into consideration are the individual risk of thrombosis and the risk of perioperative bleeding: essentially, weighing the risks against the benefits.

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When faced with a patient who is on anticoagulation, there are four broad options for managing this:

1) To defer surgery until antithrombotic agents are not needed

2) Stop antithrombotic agents prior to surgery and restart sometime after surgery which is usually done-e.g. TURP

3) Continue through the surgical procedure-e.g. Cystoscopy

4) Administer alternative antithrombotic agents that may still reduce the risk of thrombosis in the form of "bridging" for example using low weight molecular heparin when warfarin has been interrupted [2].

Anticoagulants-mechanism of action and half-life

Traditional anticoagulants in common usage include Vitamin K Antagonists (VKAs) such as warfarin, and unfractionated heparin. More recently, newly developed anticoagulants known as Direct Oral Anticoagulants (DOACs) such as rivaroxaban, apixaban, edoxaban and dabigatran have entered clinical practice.

1) Warfarin works by competitively inhibiting Vitamin K epoxide reductase complex 1 thereby reducing Vit K reserves and reducing the synthesis of clotting factors.

2) Unfractionated heparin binds to antithrombin and indirectly inhibits thrombin and Factor Xa.

3) DOACs such as apixaban, edoxaban, rivaroxaban directly inhibit Factor Xa.

4) Dabigatran is a direct thrombin inhibitor.

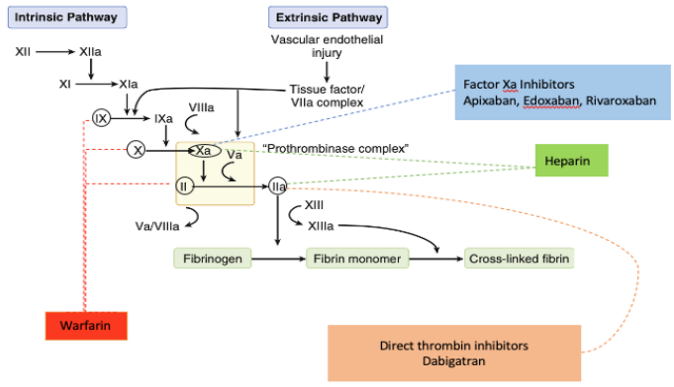

Figure 1: Classic coagulation cascade and the sites of action of anticoagulant agents.

Knowledge of the half-life and onset of action of each anticoagulant is pivotal in determining the duration of interruption. The half-life of DOACs is much shorter than older VKAs agents.

Table 1: Classic coagulation cascade and the sites of action of anticoagulant agents.

	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

Discussion

Various guidelines have been introduced with regards to the issue of interruption and resumption of antithrombotic agents. The American College of Cardiology (ACC) and the American Heart Association (ACS) guidelines provide 2 recommendations on the need for discontinuation and bridging:

1) Oral anticoagulants should not be interrupted for procedures with low bleeding risk.

2) All other patients should be managed by considering the procedure and patient factors [3].

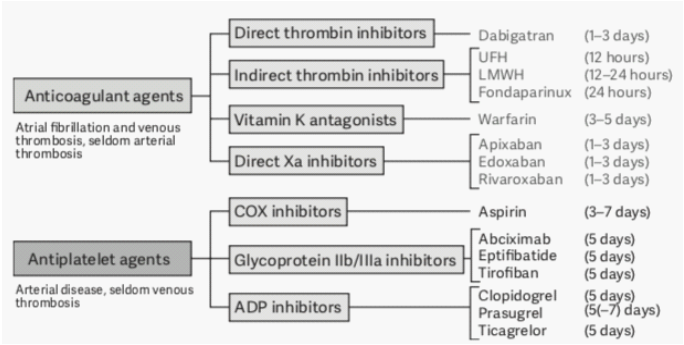

Figure 2: Commonly used antithrombotic agents in patients undergoing urologic surgery and the recommended period preoperative discontinuation [2].

The benefits of DOACs is that it can be stopped one-three days before surgery whereas other common antithrombotic agents such as warfarin needs to be stopped five days before and aspirin needs to be stopped for a longer time.

Table 2: The number of days that warfarin was routinely discontinued and recommenced post operatively for minor, major and endoscopic urological procedures in a cross-sectional study done by NF et al, [1].

Procedure	Cessation preoperatively (days)	Recommencement postoperatively (days)
Minor		
Circumcision	4.71 ± 1.58 (2-10)	2.24 ± 2.08 (1-10)
TRUS and biopsy	4.73 ± 1.51 (2-10)	2.58 ± 2.53 (I-14)
Mean	4.71 ± 1.52	2.41 ± 2.31
Endoscopic		
Cystoscopy and biopsy	4.70 ± 1.5 (2-10)	2.5 ± 3.38 (1-28)
TURP	4.80 ± 1.46 (2-10)	4.75 ± 4.70 (1-28)
TURBT	4.79 ± 1.44 (2-10)	4.08 ± 4.4 (1-28)
Urethrotomy	4.64 ± 1.27 (2-7)	2.63 ± 2.43 (1-14)
Diagnostic ureteroscopy	4.70 ± 1.37 (2-7)	2.09 ± 2.33 (1-14)
Ureteroscopy and stone fragmentation	4.85 ± 1.57 (2-10)	2.36 ± 2.24 (1-14)
Mean	4.74 ± 1.43	3.07 ± 3.52
Major		
Laparoscopic nephrectomy	4.90 ± 1.3 (3-10)	4.01 ± 3.40 (1-14)
Radical cystectomy	4.89 ± 1.35 (3-10)	4.82 ± 3.73 (1-14)
Open radical prostatectomy	4.86 ± 1.35 (2-10)	4.32 ± 3.46 (1-14)
Mean	4.88 ± 1.34	4.38 ± 3.53

The table shows that the procedure grade does not determine the duration warfarin is discontinued preoperatively as it is withheld five days before the procedure. NF et al suggest that restarting warfarin post operatively is dependent on the grade of procedure-three days for minor procedures; seven days for major procedures and four days for endoscopic procedures, with the exception of TURP and TURBT with six days [1].

The American Urology Association (AUA) recommend:

1) Low risk procedures such as laser prostate surgery and ureteroscopy, patients should remain on anticoagulant therapy.

2) High risk procedures such as extracorporeal shockwave lithotripsy, percutaneous nephrolithotomy and transurethral resection of the prostate, requires interruption of anticoagulant therapy.

3) Any major procedure (i.e. duration >45 minutes) is considered a high risk of bleeding, including renal biopsy [4].

Consequently, the American College of Surgeons Guidelines recommend discontinuation of DOACs 3 days prior to surgery to allow for approximately 5 to 6 half-lives of clearance to achieve minimal/no anticoagulant effect. AUA guidelines recommend that DOACs be discontinued between 2 and 5 days before an elective surgical procedure. ACC recommends discontinuation 2 days prior to surgery and longer for patients with decreased creatinine clearance [5].

The recommendations stated by Keeling et al suggests that warfarin can be stopped five days before elective surgery to ensure haemostasis has been returned to normal. The International Normalised Ratio (INR) needs to be determined before the surgery to allow the administration of phytonmenadione if INR >1.5. If there is adequate haemostasis post operatively, warfarin can be restarted on the evening of the surgery or the next day as the onset of action of warfarin is slow. They recommend bridging with treatment dose heparin in:

- Patients with Venous-Thromboembolism (VTE) within previous 3 months
- Previous VTE whilst on therapeutic anticoagulation who have a target INR of 3.5
- Patients with previous stroke/TIA in the last 3 months with risk factors such as congestive cardiac failure, hypertension, age >75 years and diabetes mellitus
- Patients with mechanical heart valves except those with bi-leaflet aortic valve

The last dose of LMWH should be given 24hours before surgery and the last dose must be halved for high risk surgery. They also recommend that post-operative bridging should be started at least 48 hours after high bleeding risk surgery.

Moreover, they highlight the importance of calculating the half-life of DOACs taking into account the renal function and high/low risk procedures to determine when to discontinue DOACs. In patients with normal renal functions undergoing low risk procedures, DOACs should be stopped 24 hours before the procedure. In case of high risk procedures, DOACs should be stopped 48 hours before. This table summaries when individual DOACs needs to be stopped in patients with impaired renal function.

Table 3: When DOACs needs to be stopped in patients with impaired renal function.

Renal function (CrCl, ml/min)	Estimated half-life (h)	Low bleeding risk (h)	High bleeding risk(h)
Dabigatran			
>80	13	24	48
50-80	15	24-48	48-72
30-50	18	48-72	96
Rivaroxaban			
>30	9	34	48
<30		48	72
Apixaban			
>30	8	24	48
<30		48	72
Edoxaban			
>30	10-14	24	48
<30		48	72

Anticoagulation can be restarted 6-12 hours post-procedure in low risk procedures, only if haemostasis has been fully achieved. In case of high risk procedures and patients with high risk of bleeding, DOACs should not be introduced until 48 hours post procedure. It may also be appropriate to consider prophylactic doses of anticoagulation before re-introducing DOACs.

Aspirin can be continued for most invasive procedures but if the bleeding risk is high, aspirin should be stopped three days preoperatively and seven days postoperatively. Patients taking dual antiplatelet due to coronary artery stent or recent acute coronary syndrome should continue anticoagulation in low risk bleeding procedures. However, in similar patients undergoing high bleeding risk procedures, should have their procedure delayed. If this is not possible then aspirin should be continued and clopidogrel should be stopped 5 days preoperative [6].

A study by Dimitripoulos et al compared the anticoagulation guidelines for perioperative anticoagulation issues by four associations-European association of Urology (EAU), American Urology Association (AUA), American College of Chest Physicians (ACCP) and European Society of Cardiology/Anaesthesiology (ESC/ESA) and found significant variation. With regards to DOACs for example, EAU recommends stopping anticoagulants 1-3 days prior, with no bridging and restarting when bleeding is no longer a risk which is usually 4 days post op; the AUA recommends discontinuing 2-5 days before surgery and bridging with heparin for rivaroxaban and there are no guidelines given by ACCP. Furthermore, ESC/ESA recommend stopping DOACS 2-3 times their biological half -lives and in cases of high-risk procedures, stopping DOACs 4-5 times their half-lives. ESC does not recommend bridging due to the relatively short half-life of DOACs [4].

A study by Beckmann et al assessed 32 patients receiving DOACs who were planned for radical prostatectomy, the method used was to stop DOACs 48 hrs before the elective procedure without any bridging modalities and anticoagulant therapy was recommenced on post op day 3. The patients were followed up to check for any complications such as rebleeding. They found

that following an uneventful intraoperative and postoperative period, DOACs can be restarted safely on the third day. It is uncertain whether the same period of interruption of anticoagulation can be used for other major urological procedures such as radical cystectomy or nephrectomy; however, the article states that DOACs can be safely restarted on the third post-operative day for other major urological procedures [7]. An article by Lopez et al reviewed the available literature and the European guidelines on the use of perioperative anticoagulant in urological procedures. Their findings are summarised in (Table 4) [8].

Table 4: The general recommendations for stopping and restarting anticoagulant agents [8].

Typeof surgery	Type of treatment	Suspension	Bridge therapy	Reintroduction
Elective	Antiplatelet	According to half life	Only high risk-with Tirofiban	4th postoperative day
	Anticoagulant	According to half life	Only high risk-low molecular weight heparin (LMWH)	4th postoperative day
Urgent	Antiplatelet	Unable to reverse		
	Anticoagulant	Reversal methods include: -Vitamin K -Prothrombin complex		

A study by Douketis et al., devised a simple standardised perioperative DOAC interruption and resumption strategy based on the pharmacokinetics. The Perioperative Anticoagulant Use for Surgery Evaluation (PAUSE) cohort consisted of 3007 participants taking DOACs. In low-bleeding risk procedures, DOAC was stopped for one day and in high-bleeding risk procedures stopped for two days. It was resumed a day after a low-risk bleeding procedure and two-three days after a high-bleeding risk procedure. The patients were followed up for 30 days after the operation to assess if patients developed major bleeding and arterial thromboembolism including ischemic stroke, systemic embolism and transient ischemic attack. To deem the protocol safe, the aim was to achieve a <2% rate of major bleeding and arterial thromboembolism (Table 5).

Table 5: The percentage of patients who developed thromboembolism and bleeding following the standardised perioperative interruption of DOACs.

Outcome		Apixaban	Dabigatran	Rivaroxaban
Low-risk bleeding procedure	Major bleeding (%)	1.35	0.9	1.85
	Arterial thromboembolism (%)	0.16	0.6	0.37
High-risk bleeding procedure	Major bleeding (%)	2.96	-	2.95

The true incidence of major bleeding was lower than 2% and arterial thromboembolism was lower than 1.5% for each DOAC. The study shows that using the above protocol for perioperative interruption is safe. The study concludes by stating that a perioperative management without heparin bridging is associated with lower rates of bleeding and thromboembolism [9].

In conclusion, the guidelines on perioperative anticoagulants in urology are uncertain and unclear. We currently lack any specific guidelines for the interruption of anticoagulant therapy in urological procedures, partly due to the variability of both the patient and the urological procedures. The recommencement of anticoagulant is challenging and depends on individual cases particularly the clinical condition of the patient, nature of the surgery (high or low risk, elective or emergency), thromboembolic risk and haemostasis of the patient [9,10]. Taking into account the different guidelines, this is what we recommend:

Take home message/recommendation

1. Warfarin should be omitted five days before an elective procedure. If there is adequate haemostasis post operatively, warfarin can be restarted on the evening of the surgery or the next day. Bridging with low weight molecular heparin or unfractionated heparin should be considered for people who have high risk of recurrent VTE, mechanical heart valve and previous stroke/TIA in the last three months. Bridging should be started at least 48 hours after the procedure.
2. DOACs should be stopped 24 hours before a low risk procedure in patients with normal renal function. It should be restarted between 6-12 hours post-procedure if haemostasis is achieved.
3. DOACs should be stopped 48 hours before a high risk procedure in patients with normal renal function and should be recommenced 48 hours post-procedure if haemostasis is achieved.
4. The interruption of DOACs depends on the half life for patients with deranged renal function.
5. Aspirin can be continued for most invasive procedures but needs to be stopped three days prior and seven days post procedure in high bleeding risk procedures.
6. In patients with dual antiplatelet, the procedure should ideally be postponed. However, if surgery cannot be deferred, aspirin should be continued and clopidogrel should be stopped five days pre-op.

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