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# Guideline for stopping anticoagulants prior to urological procedures

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**Abstract**
There is a lack of clear evidence and guidelines on how to reverse anticoagulation prior to emergency and elective urological procedures. Our aim was to produce local hospital guidelines based on current evidence to simplify the perioperative process of stopping traditional and novel oral anticoagulants and antiplatelet therapy.

**Keywords**
Anticoagulation, antiplatelet, novel oral anticoagulant

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## Introduction

An anticoagulated patient poses well-known problems both in emergency and elective urological procedures. Whilst there is a need to minimise excessive bleeding by stopping anticoagulation, there is a fine balance to prevent risk of further thromboembolic events. Typically, anticoagulation with warfarin is necessary in patients with mechanical valves and/or atrial fibrillation (AF) to prevent venous thromboembolism.[1,2] Antiplatelets are used to prevent thrombus formation in patients with atherosclerosis.[1] New or novel oral anticoagulation agents (NOAC) are reportedly cheaper with a safer side effect profile; however, they cannot be monitored nor reversed, which causes major difficulties, including uncontrollable haemorrhage, and delays in surgery due to their irreversible nature particularly in emergency surgery.[1,3] This paper discusses anticoagulants, their mechanism of action and the introduction of local hospital guidelines for the safest method of stopping or reversing these prior to urological procedures.

## Anticoagulant agents

Haemostasis occurs due to the activation of the clotting cascade, which consists of an intrinsic and extrinsic pathway joining to form the common pathway.

When a vessel is injured, initial vasoconstriction occurs. Damage to the vessel wall causes activation of the extrinsic pathway culminating in the production of Factor VIIa. Exposure of collagen due to endothelial injury causes activation of the intrinsic pathway culminating in the production of Factor X-activating factor. These two factors both act on Factor Xa causing the conversion of prothrombin to thrombin. Platelets also adhere to the site of exposed collagen and are activated by thrombin to release adenosine diphosphate (ADP) and thromboxane A2, which attracts more platelets and results in the formation of a platelet plug. Thrombin also activates fibrinogen into fibrin leading to fibrin strands linking together, which help stabilise the platelet plug.[4] See Figure 1 and Table 1.

### *Warfarin*

Warfarin interferes with the synthesis of vitamin K-dependent clotting Factors II, VII, IX, and X. Its effect

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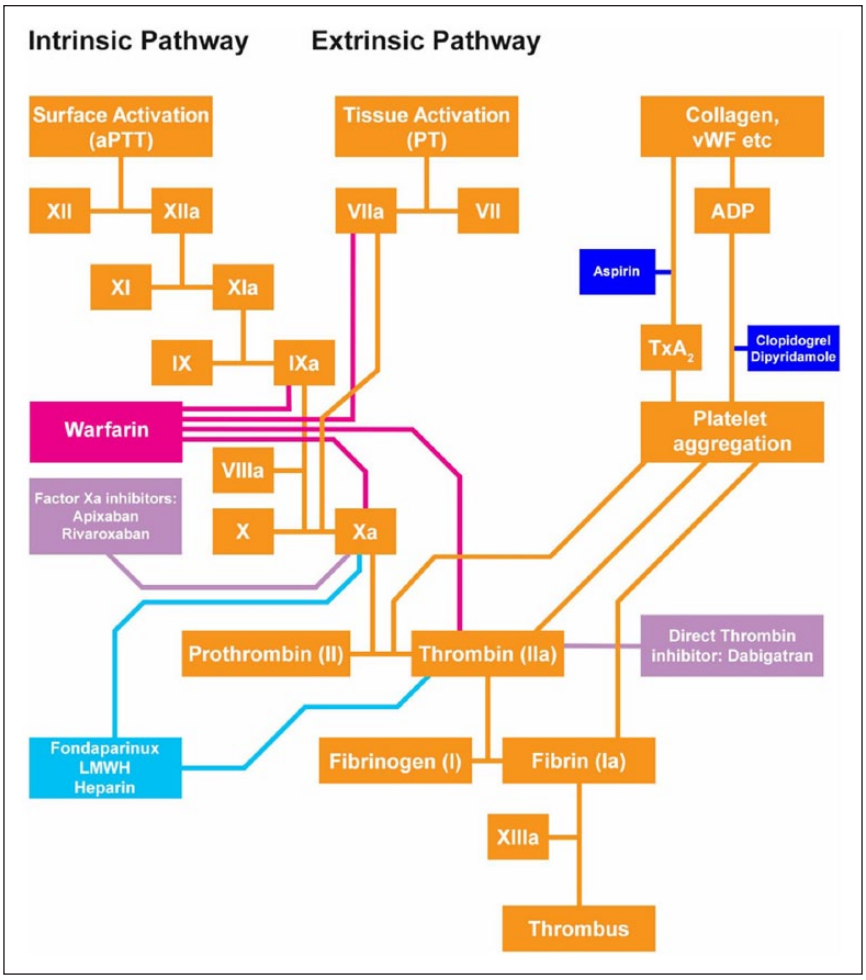



**Figure 1.** Coagulation cascade and anticoagulant actions.
aPTT: activated partial thromboplastin time; PT: prothrombin time; vWF: von Willebrand factor; ADP: adenosine diphosphate; $TxA_2$: thromboxane A2; LMWH: low-molecular-weight heparin.

is monitored using the international normalised ratio (INR).[2,5] Warfarin is metabolised by the cytochrome p450 mechanism within the liver. Other drugs that also target this mechanism can lead to alterations in warfarin metabolism resulting in poor anticoagulation control.[5]

## *Heparin*

Unfractionated heparin (UFH) activates anti-thrombin III (ATIII) and accelerates the rate of inhibition of thrombin and Factor Xa. Heparin can be reversed using protamine. Problems with use of heparins are heparin-induced thrombocytopenia (HIT), which can occur 5–14 days following administration. Activated partial thromboplastin time is used to monitor the effectiveness of heparin.[5]

## *Low-molecular-weight heparins (LMWH) – enoxaparin, dalteparin*

These agents activate ATIII and subsequently inhibiting Factor Xa. LMWH can be partially reversed with protamine. LMWH are not typically monitored, but if necessary Factor Xa levels can be measured.[5]

## *NOACs*

These drugs were developed to overcome problems associated with warfarin, such as slow onset of action, numerous food and drug interactions, variable pharmacologic effects, frequent monitoring, and the need for bridging therapy.[3] Most of the NOACs are excreted renally, thus patients with impaired renal function can have raised plasma NOAC concentrations.[3,5] It is important to monitor the creatinine clearance of patients, as this will determine when these agents should be stopped perioperatively.

Whilst there are several NOAC available,[3] the most common are discussed below.

## *Dabigatran*

This is a specific direct thrombin inhibitor which reversibly binds and inactivates free and fibrin-bound thrombin,

**Table 1.** Anticoagulants and reversal agent.

| Anticoagulant | Mechanism of action | Half-life | Reversal agent |
|---|---|---|---|
| *Warfarin* | Interferes with vitamin K-dependent clotting – Factors II, VII, IX, and X | 36–42 hours | Vitamin K (oral/IV) |
| *Heparin* | Inhibits thrombin and Factor Xa | Dose dependent | Protamine |
| *Low-molecular-weight heparins (LMWH) – enoxaparin, dalteparin* | Inhibits Factor Xa | 3–4 hours | Protamine (60%–80% reversal) |
| *Dabigatran (NOAC)* | Direct thrombin inhibitor | 12–17 hours | Idarucizumab |
| *Rivaroxaban, (NOAC)* | Direct Factor Xa inhibitor | 5–9 hours (young)<br>11–13 hours (elderly) | *None currently licenced* |
| *Apixaban (NOAC)* | Direct Factor Xa inhibitor | 12 hours | *None currently licenced* |
| *Aspirin* | Antiplatelet agent | 13 hours | Platelet transfusion |
| Dipyridamole | Inhibits platelet aggregation | 7–10 hours | Platelet transfusion |
| *Clopidogrel* | Inhibits platelet aggregation | 7–10 hours | Platelet transfusion |

IV: intravenous; NOAC: new oral anticoagulation agent.

leading to a reduction in fibrin clot formation and platelet aggregation.[3,5,6]

### *Rivaroxaban, apixaban*

These are direct Factor Xa inhibitors thus inhibiting the common pathway of coagulation. This results in a reduction in thrombin formation, reducing platelet activation and inhibiting clot formation.[3,5,6]

As these agents act differently to warfarin, the bleeding time and INR will often be normal.[3]

## Antiplatelet agents

### *Aspirin*

This is both an antiplatelet and anti-inflammatory agent. It irreversibly deactivates the cyclooxygenase enzymes (COX-1 and COX-2). Inhibition of COX-1 stops platelet generation of thromboxane $A_2$, preventing platelet aggregation.[1]

### *Dipyridamole*

This works by inhibiting platelet aggregation by reducing adenosine uptake into platelets and so reduces adenosine diphosphate (ADP)- and platelet activating factor (PAF) production.[1]

### *Clopidogrel*

This is an irreversible ADP inhibitor thus preventing platelet aggregation.[1]

## Recommendations for stopping anticoagulation

It is important to consider the type of patient and the type of surgery.

### *Type of patient*

High-risk patients include the following:

- Recent cardiac stent insertion or mechanical heart valves
- Recurrent venous thromboembolism
- Active cancer
- AF
- Recent stroke
- High $CHADS_2$ score 5–6 – The CHADS score is used to calculate the thrombosis risk for patients with AF, congestive heart failure, hypertension, age 75 years or greater, diabetes mellitus and prior stroke, transient ischaemic event, or thromboembolism.[1,5]

**Table 2.** Classification of procedures according to bleeding risk.[8]

| High-risk procedures | Moderate-risk procedures | Low risk procedures |
|---|---|---|
| Transurethral resection of prostate (TURP) | Transrectal ultrasound (TRUS) biopsy | Cystoscopy |
| Transurethral resection of bladder tumour (TURBT) | Bladder or ureteric biopsy | Ureteric stent insertion |
| Percutaneous nephrolithotomy (PCNL) | Suprapubic catheter (SPC) insertion | Ureteroscopy ± stone extraction |
| Extracorporeal shock wave lithotripsy (ESWL) | Inguinoscrotal surgery | Lasertripsy stone |
| Open/laparoscopic bladder or prostate surgery | Cystohydrodistension | Laser prostatectomy |
| Major renal surgery | Bladder neck incision | |
| | Transvaginal tape (TVT) | |
| | Ureteroscopy and laser ablation of upper tract urothelial cancers | |
| | Penile cancer surgery | |
| | Penile prosthesis | |
| | Urethral reconstruction | |

Current management for patients after simple angioplasty, bare metal stent and drug-eluting stent insertion is that dual antiplatelet therapy, i.e. aspirin and clopidogrel, prasugrel or ticagrelor, should be continued for two weeks, six weeks and at least 12 months, respectively. Particularly after stent deployment, only life-saving surgery should be performed, and both aspirin and clopidogrel should be continued perioperatively.[7] A multidisciplinary approach involving cardiology expertise is essential when urgent urological procedures are required within these time frames. Outside this critical period, antiplatelet agents should be discontinued 7–10 days preoperatively and resumed as soon as safely possible. There is no clear guideline on the usage of aspirin as a bridging therapy post-discontinuation of clopidogrel, and therefore this is not currently advised.

High-risk patients who have mechanical valves or AF, recent stroke, and are on warfarin can be started on bridging anticoagulation using LMWH or UFH. This should be started 24 to 48 hours after the last dose of warfarin when INR is less than 2. The last dose of LMWH should be 24 hours before the procedure and at half the daily dose. UFH has a shorter half-life, and so should be stopped four to six hours before surgery.[5,7] Caution should be shown in those with renal failure. LMWH must be either given in a reduced dose or withheld for longer than 24 hours before surgery. An INR of ≤1.5 is considered a ratio at which most surgical procedures are safe.[2] Resumption of LMWH can take place 24 hours postoperatively or when bleeding has almost completely settled. Warfarin can be restarted on day 1 postoperatively whilst continuing LMWH until the INR is within the target therapeutic range on two separate measurements.[1,5]

Patients at low risk for thrombosis in whom warfarin is being held before a procedure should have an INR of less than 1.5.[2,7] These patients can be started on a prophylactic dose of an LMWH 24–48 hours after cessation of warfarin.

## *Type of surgery*

Procedures can be classified into high or low risk depending on the risk of bleeding. See Table 2.

Procedures such as spinal anaesthesia, epidural anaesthesia, and lumbar puncture may require complete haemostatic function, and fall under the 'high risk of bleeding' category.[8] A systematic review performed by the American Urological Association (AUA) and International Consultation on Urological Disease (ICUD)[7] examined the outcomes of urological studies reporting on bleeding and thromboembolic outcomes where anticoagulation was continued or stopped perioperatively.

High-risk procedures in high-risk patients should prompt a multidisciplinary consensus approach.[7] Current guidance varies for high-risk surgeries and discontinuation of anticoagulation. Patients on aspirin or bridging therapy

can undergo radical prostatectomy and partial nephrectomy, although there is an increased risk of bleeding. Patients undergoing transurethral resection of the prostate (TURP) should not continue on anticoagulant or antiplatelet therapy due to increased risk of bleeding.[7]

Patients requiring percutaneous nephrolithotomy (PCNL) should have traditional oral anticoagulants and antiplatelet therapy stopped with associated bridging therapy. NOAC should be discontinued 72 hours before, although this is dependent upon the patient's creatinine clearance.[7] Specifically if the patient's creatinine clearance is 30–50 ml/min, dabigatran should be omitted 96 hours before, or if creatinine clearance is >50 ml/min, dabigatran can be stopped 72 hours before the procedure. Patients on apixaban and rivaroxaban in whom the creatinine clearance is >30 ml/min should stop treatment 72 hours before the procedure.[3,9]

Patients requiring urgent surgery and on NOAC should have their procedures delayed 24 to 36 hours to allow for discussion with cardiology and haematology experts.[7] Currently there is still debate as to the benefit of bridging therapy in patients on NOAC as acute discontinuation can acutely increase the risk of stroke whilst bridging with heparin leads to a significantly higher periprocedural bleeding rate (without lower thromboembolic rate).[7,10] Patients receiving treatment with NOAC, when surgery is imminent but the timing is unpredictable (e.g. organ transplantation), can be switched to warfarin because its effects can be rapidly and reliably reversed.[11]

Prostate biopsy can be performed safely for the patient on low-dose aspirin with a minor risk of bleeding.[7]

For patients undergoing low-risk procedures such as holmium laser enucleation of the prostate or ureteroscopy, traditional oral anticoagulants and antiplatelets can be continued (if INR is within range),[7] although it is recommended to take the last dose of NOAC 48 hours before the elective procedure in patients with normal kidney function. If the creatinine clearance is >50 ml/min, dabigatran should be stopped at least 48 hours prior. If creatinine clearance is >30 ml/min, rivaroxaban and apixaban should be stopped at least 48 hours and 24 hours respectively prior to surgery.[3,9]

## Postoperative care

### *Excessive bleeding*

Typically if this is warfarin induced, administration of vitamin K can promptly reverse the effect within 24–48 hours. Fresh frozen plasma can also be used but caution must be taken in those with cardiac and renal failure due to fluid overload. Prothrombin complex concentrates can be used in patients in whom there is a risk of fluid overload.[11] In cases where UFH or LMWH has been used, protamine can completely reverse the action of UFH and can partially reverse the action of LMWH.[7] Idarucizumab can reverse dabigatran; however, there are no other licenced reversal agents for rivaroxaban or apixaban.[12] If there is significant bleeding, local haemostatic measures, fluid replacement, blood and platelet transfusion, fresh frozen plasma, prothrombin complex, charcoal haemoperfusion, and dialysis can be considered but urgent haematological advice is required.[1,7,9,10]

### *Recommencing anticoagulation*

Prophylactic anticoagulation therapy can be resumed once haemostasis is secured.[11] In patients receiving bridging therapy, heparin at a therapeutic dose should be withheld for 48 hours after the procedure though this can be restarted earlier if risk of post-procedural bleeding is low.[11] Patients can be recommenced on warfarin 12 to 24 hours postoperatively, provided bleeding risk is acceptable and there is no substantial risk of delayed bleeding or reoperation.[7,11] Antiplatelet agents, including aspirin and clopidogrel, can be reinitiated within 24 hours. Prasugrel or ticagrelor should be re-initiated with caution as they have a rapid onset of action, potent antiplatelet inhibition, and the lack of agents to reverse their effects.[11]

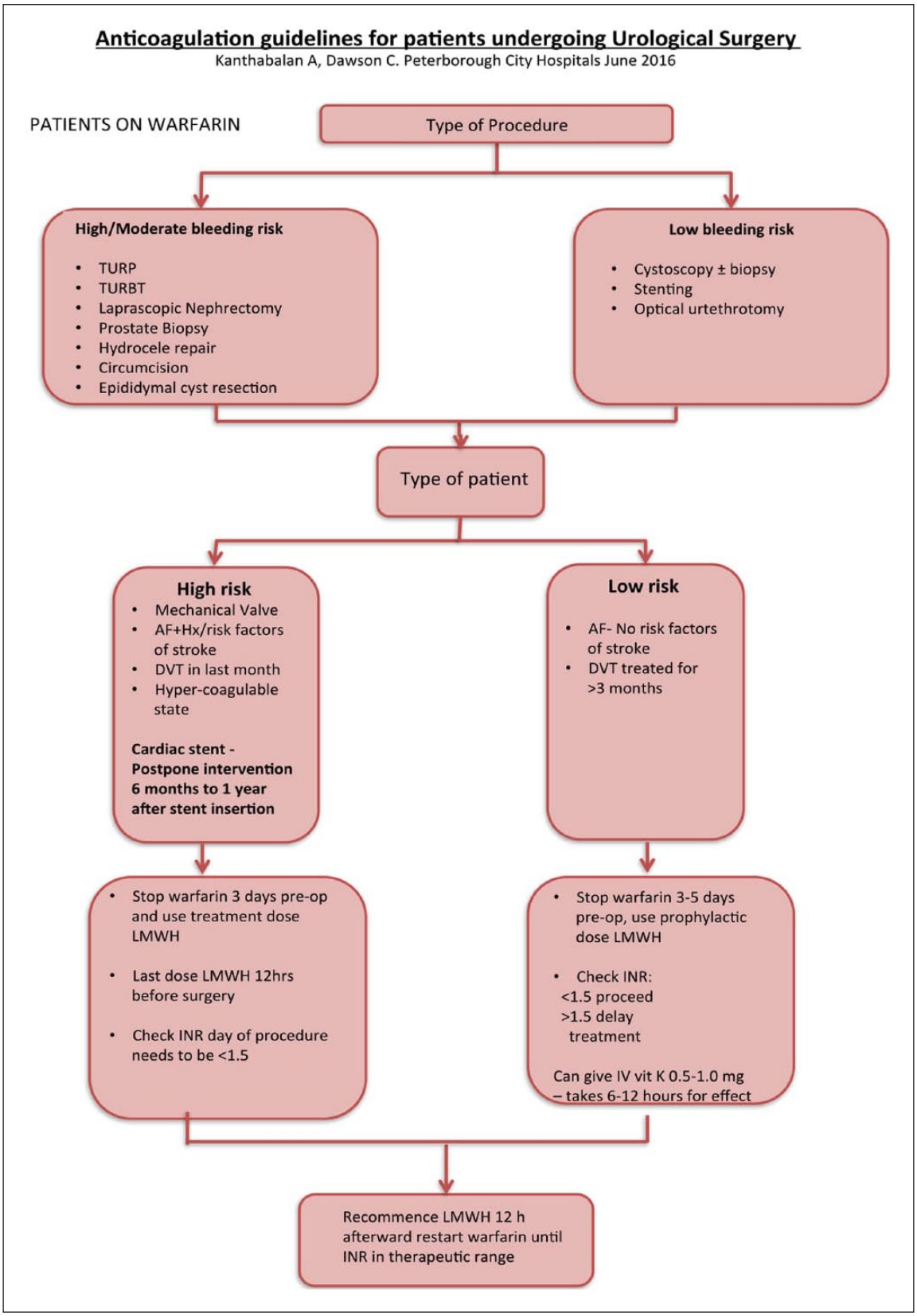
Patients on NOAC can restart therapy six to eight hours postoperatively as long as there is immediate and complete haemostasis;[10] however, this should be delayed for at least 48 hours after high-risk procedures as full anticoagulation occurs shortly after administration and there are no reliable reversal agents.[11] The same applies after atraumatic spinal/epidural anaesthesia or clean lumbar puncture (i.e. non-bloody tap).[10]

*Emergency.* In the case of patients presenting with significant bleeding, this can be managed as for patients who have excessive bleeding postoperatively. Haematological opinion is advised.

## Recommended guidelines

Given our review of current clinical evidence and recommendations, it was felt that the best method of deciding when and in whom anticoagulation needed to be stopped was by first splitting different anticoagulation methods: warfarin vs. NOAC; then dividing procedures into two groups: high and moderate risk vs. low risk; and then further dividing patients into high risk vs. low risk. Patients on low-dose aspirin may continue this perioperatively and those on clopidogrel should stop this one week before any procedure and liaison with haematology/cardiology to discuss need of bridging therapy.

Figure 2 shows a flow diagram of suggested guidelines.[2,3,9,13–16]


Anticoagulation guidelines for patients undergoing Urological Surgery
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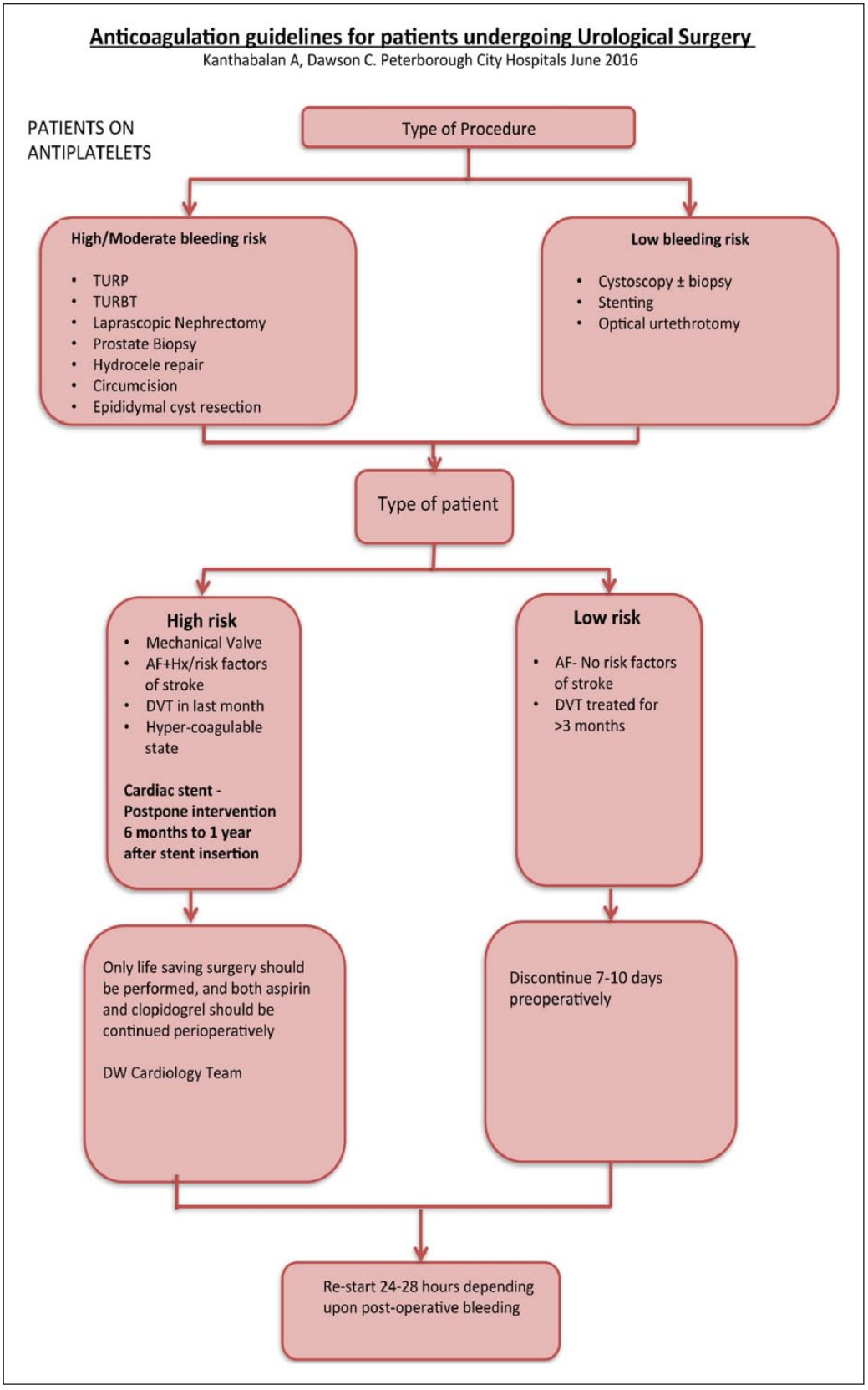
PATIENTS ON WARFARIN
Type of Procedure
High/Moderate bleeding risk
TURP
TURBT
Laprascopic Nephrectomy
Prostate Biopsy
Hydrocele repair
Circumcision
Epididymal cyst resection
Low bleeding risk
Cystoscopy ± biopsy
Stenting
Optical urtethrotomy
Type of patient
High risk
Mechanical Valve
AF+Hx/risk factors of stroke
DVT in last month
Hyper-coagulable state
Cardiac stent - Postpone intervention 6 months to 1 year after stent insertion
Low risk
AF- No risk factors of stroke
DVT treated for >3 months
Stop warfarin 3 days pre-op and use treatment dose LMWH
Last dose LMWH 12hrs before surgery
Check INR day of procedure needs to be <1.5
Stop warfarin 3-5 days pre-op, use prophylactic dose LMWH
Check INR:
<1.5 proceed
>1.5 delay treatment
Can give IV vit K 0.5-1.0 mg – takes 6-12 hours for effect
Recommence LMWH 12 h afterward restart warfarin until INR in therapeutic range




*(Figure 2 Continued)*

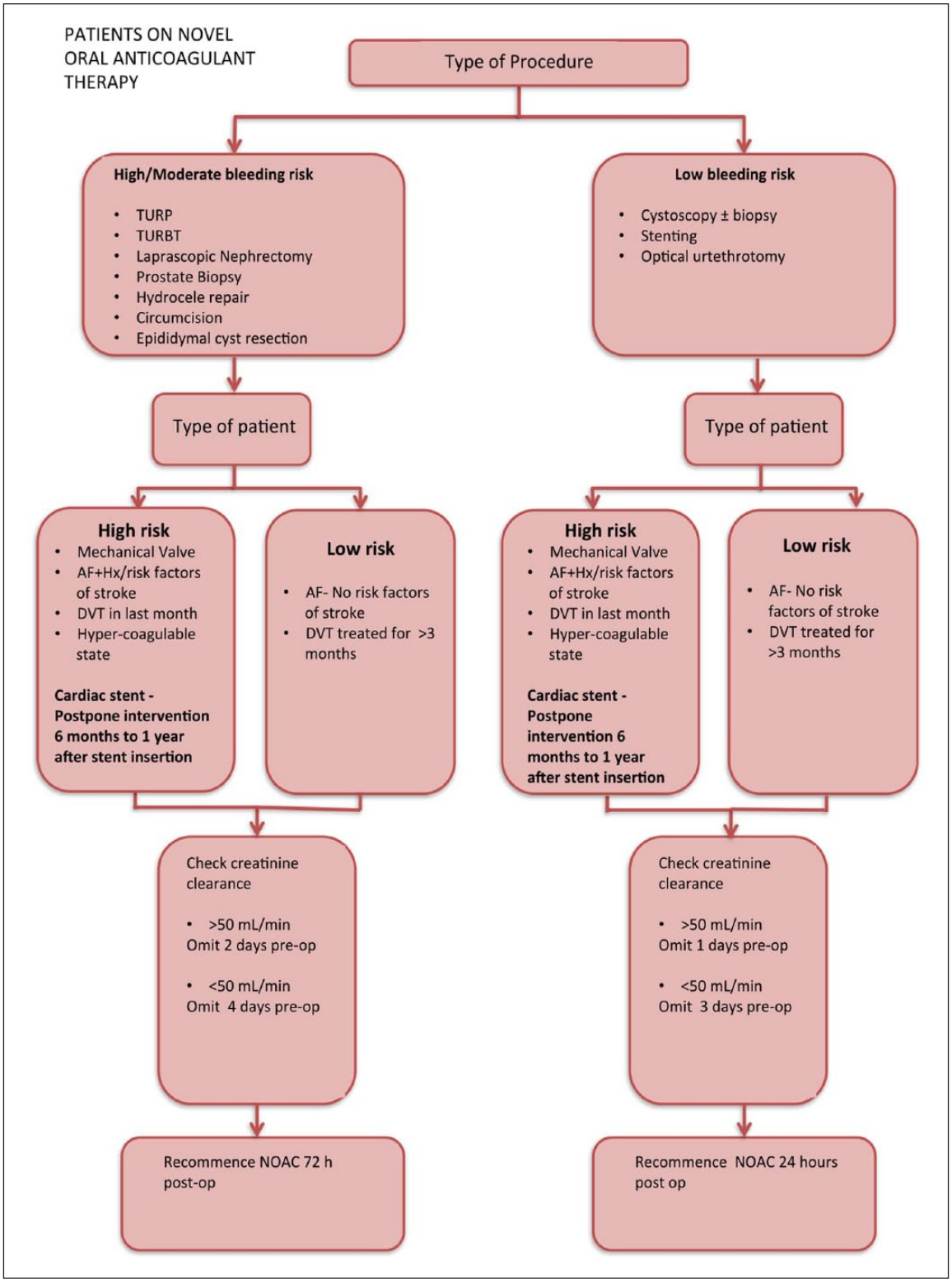



**Figure 2.** Anticoagulation guidelines for patients undergoing urological surgery.
TURP: transurethral resection of the prostate; TURBT: transurethral resection of bladder tumour; AF: atrial fibrillation; Hx: history; DVT: deep vein thrombosis; LMWH: low-molecular-weight heparins; INR: international normalised ratio; IV: intravenous.

## Discussion

This paper discusses anticoagulants and provides guidance as to when they should be stopped prior to urological surgery.

The key issue with providing this guideline is lack of robust studies comparing anticoagulants vs. antiplatelets vs. NOAC in differing urological procedures with a low, moderate and high bleeding risk.

This is understandable due to the difficulties in collecting data on large groups of patients who fulfil the above criteria (method of anticoagulation and undergoing different urological procedures). The other issue when examining anticoagulation is that much of the current literature reports on how to prevent venous thromboembolism perioperatively as opposed to stopping anticoagulation agents to prevent significant bleeding.

The production of our guidelines is an attempt to simplify perioperative control of anticoagulation.

### Conflicting interests

The Authors declare that there is no conflict of interest.

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### Ethical approval

Not applicable.

### Informed consent

Not applicable.

### Guarantor

AK.

### Contributorship

AK and CD researched literature and conceived the study. AK was involved in guideline development and the first draft of the manuscript. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

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