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CIRSE STANDARDS OF PRACTICE

CIRSE Standards of Practice on Peri-operative Anticoagulation Management During Interventional Radiology Procedures

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Abstract This CIRSE Standards of Practice document is aimed at interventional radiologists and provides best practices for peri-operative anticoagulation management during interventional radiology procedures.

Keywords Clinical practice · Vascular intervention · Periprocedural anticoagulation

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Introduction

Peri-procedural anticoagulation management for patients undergoing an interventional procedure is complex. The challenges stem from a continuously expanding list of procedures; a concurrent increase in the complexity of patients receiving anticoagulation, which are also ever increasing in type and number. There is a paucity of high-level evidence around peri-procedural management for patients on anticoagulation.

Two opposing risks decide the peri-procedural management of patients on anticoagulants; the risk of bleeding from the procedure versus the risk of thromboembolic events from stopping the anticoagulants. The risk of bleeding is based on the published data on bleeding risk for each procedure, as well as bleeding factors relating to the patient. Risk of thromboembolism is based on the clinical indication for anticoagulation and patient factors.

The problems observed around peri-procedural haematological management include risk of cancellations, overtreatment (with blood products) or exposing patients to undue risk, such as severe haemorrhage or recurrent thrombosis. Peri-operative coagulation management guidelines have been published over the years by various medical societies [1–7]. Despite this, current peri-procedural haematological practices remain variable [8].

Methodology

The CIRSE Standards of Practice Committee is tasked with producing practice-orientated documents that offer best practices for performing IR treatments, to both assist interventional radiologists in their daily practice and be

used as a reference for physicians from other medical specialties.

The CIRSE Standards of Practice Committee established a writing group for this document consisting of clinicians with internationally recognised expertise in interventional radiology and haematology. The writing group performed an in-depth literature search using electronic medical literature databases, including Medline (via PubMed) and The Cochrane Library. A critical review of peer-reviewed articles was performed with regard to the study methodology, results, and conclusions. This document has adopted similar published societies' guidelines to include recommendations to inform practice, such as the previously endorsed SIR anticoagulation guidelines. Conflicting or weak evidence was presented to the writing group members for review, and a 2-stage Delphi process to reach an 80% agreement was undertaken amongst the experts to agree a consensus recommendation.

A summary of key recommendations is provided in Table 1.

Peri-operative Assessment of Patients' Coagulation Status

a. Structured bleeding history

We recommend that all patients awaiting interventional procedures with risk of bleeding undergo a structured bleeding history as part of the pre-operative coagulation assessment.

Coagulation screening in the pre-operative setting will not provide accurate information on the haemostatic status and may miss common coagulation abnormalities such as von Willebrand's disease and platelet dysfunction [1, 9]. It is very unlikely that routine standard coagulation screening will have a significant pick up rate of unexpected coagulation abnormalities, particularly in younger patients and those without underlying risk factors. Traditional coagulation tests also do not assess the haemostatic role of endothelium, and other anticoagulant factors, counter balancing procoagulant factors, and thromboelastography (TEG) and rotational thromboelastography (ROTEM) may offer better information on the overall coagulation status of patients. Although TEG testing is commonly used in surgery, it has so far not been assessed for IR procedures.

The British Society for Haematology does not recommend indiscriminate coagulation screening prior to invasive procedures [9]. A systematic review of more than 12,000 procedures (including central vein cannulation, angiography, liver and kidney biopsy, bronchoscopy and paracentesis) has shown coagulation screening (prothrombin time (PT)/actiated partial thromboplastin time (aPTT)) to be ineffective in comparison with a structured bleeding history, and that peri-operative bleeding rates were similar

Table 1 Summary of key recommendations

Patients should be initially assessed using a structured bleeding history/questionnaire
Indiscriminate coagulation screens prior to an elective IR procedure will not post-procedural bleeding and is not recommended
If the structured bleeding history is negative, and the patient is not receiving antithrombotic treatment, no coagulation testing is indicated
If the structured bleeding history is positive, we recommend performing a coagulation assessment (platelet count, prothrombin time, activated partial thromboplastin time and Clauss fibrinogen) and discussion with a Haematologist with expertise in Thrombosis & haemostasis prior to the intervention
Coagulation laboratory assessment (platelet count, PT, aPTT, Clauss fibrinogen) is recommended for patients on anticoagulation or in the presence of other clinical conditions which may impair coagulation (e.g. renal ± liver disease) prior to a procedure with risk of bleeding
Patients on anticoagulants with *no increased risk* of thromboembolic events/complications undergoing elective IR procedure with a consider either continuing the anticoagulation or following the advice in Table 6 and 7 regarding holding the anticoagulation at the time of the procedure for low bleeding risk procedures
Patients on anticoagulants with *increased risk* of thromboembolic events/complications undergoing elective IR procedure with *low risk of bleeding* consider continuing anticoagulation but this will depend upon the specific procedure
Patients on anticoagulants with *increased risk* of thromboembolic events/complications and are undergoing elective IR procedure with *moderate/high risk of bleeding*, withholding anticoagulation and bridging therapy (if applicable) should be considered
Patients on anticoagulants requiring an *immediate emergency IR procedure* with *low risk of bleeding* consider proceeding and either omitting a dose or continuing anticoagulation
Patients on anticoagulants requiring an *immediate emergency IR procedure* with *moderate/high risk of bleeding* consider reversing anticoagulation and if at high risk of thrombosis, bridging therapy should be considered
For patients at risk of bleeding, attention should be given to pressure at puncture sites, supportive care and monitoring of vital signs
For patients on VKA anticoagulation and planned for an elective IR procedure, discontinuing anticoagulation is recommended over accelerated reversal with vitamin K

in patients with and without abnormal coagulation tests [9, 10]. An example of such a structured bleeding history questionnaire is the validated and comprehensive International Society on Thrombosis and Haemostasis (ISTH) Bleeding Assessment tool; however, this has not been validated to screen patients pre-operatively for bleeding risk [11]. An alternative and probably more practical tool for interventional radiologists is the HEMSTOP questionnaire (Table 2) [9, 12–14]. A positive bleeding questionnaire (≥ 2 points on the HEMSTOP questionnaire) should trigger discussion with a haematologist with expertise in thrombosis & haemostasis to fully assess the patient prior to the procedure.

Recommendation 1 Patients should be initially assessed using a structured bleeding history/questionnaire.

Recommendation 2 Indiscriminate blood coagulation screening prior to an elective IR procedure is not recommended.

Recommendation 3 If the structured bleeding history is negative, and the patient is not receiving antithrombotic treatment, no coagulation testing is indicated.

Recommendation 4 If the structured bleeding history is positive, we recommend performing a coagulation assessment (platelet count, prothrombin time (PT), aPTT and Clauss fibrinogen) and discussion with a haematologist with expertise in thrombosis & haemostasis prior to the intervention.

b. Laboratory coagulation assessment

A coagulation screen (full blood count, PT, aPTT and Clauss fibrinogen assay) is required for patients on vitamin K antagonists, as well as for patients with known increased bleeding risk, including liver and renal impairment, prior to an interventional procedure. The method of assessing the effect of anticoagulants will vary based on the type of anticoagulant and urgency of the procedure.

The prothrombin time (PT) and internal normalised ratio (INR) are functional assessments of the extrinsic and common coagulation pathway. The aPTT is a functional assessment of the intrinsic and common coagulation pathways, and thrombin time (TT) is a functional assessment of fibrinogen conversion to fibrin in the final common pathway. For ease of use and understanding, we have tabulated the commonly used coagulation parameter assessments (Table 3), which shows the normal ranges for each parameter as well as when it is indicated to request these. Table 4 demonstrates the effects of anticoagulants on coagulation tests and what additional tests may be required for the monitoring of certain anticoagulants. Viscoelastic methods are not recommended to assess peri-procedure bleeding risk [15].

Recommendation 5 Coagulation laboratory assessment (platelet count, PT, aPTT, Clauss fibrinogen) is recommended for patients on anticoagulation or in the presence of other clinical conditions which may impair coagulation (e.g. renal ± liver disease) prior to a procedure with risk of bleeding.

Types of Anticoagulants and Their Monitoring

Figure 1 details a simple summary of the most commonly used anticoagulants and how they affect the coagulation cascade.

a. *Heparins* are a heterogeneous group of linear polysaccharides with a primary function of increasing the activity of antithrombin (AT), the plasma serine protease inhibitor, 10,000-fold resulting in inactivation of clotting cascade factors Xa and thrombin (factor IIa). To a lesser degree, the heparin-AT complex also inhibits factors IXa, XIa, and XIIa.

Table 2 HEMSTOP Questionnaire [14]

1. Have you ever consulted a doctor or received treatment for prolonged or unusual bleeding (such as nosebleeds, minor wounds)?
2. Do you experience bruises/haematomas larger than 2 cm without trauma or severe bruising after minor trauma?
3. After a tooth extraction, have you ever experienced prolonged bleeding requiring medical/dental consultation?
4. Have you experienced excessive bleeding during or after surgery?
5. Is there anyone in your family who suffers from a coagulation disease (such as haemophilia, von Willebrand disease.)?
For females:
6. Have you ever consulted a doctor or received treatment for heavy or prolonged menstrual periods (contraceptive pill, iron, etc.)?
7. Did you experience prolonged or excessive bleeding after delivery?
HEMSTOP = Haematoma, Haemorrhage, Menorrhagia, Surgery, Tooth extraction, Obstetrics, Parents
HEMSTOP Questionnaire: Responses to the questions are either positive or negative. The questionnaire has demonstrated a sensitivity and specificity for the diagnosis of a bleeding disorder of 89.5% (when cut-off is set to 1 positive answer) and 98.6% (when cut-off set to 2 positive answers), respectively.

Table 3 Selected coagulation parameter assessments

Test	Normal value*	Indication for testing
Platelet count**	150,000–450,000 platelets/mL blood	Thrombocytopenia
		Disseminated Intravascular Coagulation (DIC)
PT/International normalised ratio (INR)	PT 9–12 s	*Vitamin K antagonists*
	INR 0.9–1.1	Liver disease, DIC, vitamin K deficiency
		Factor VII deficiency
		Prolonged with some direct oral anti-coagulants
aPTT	25–35 s	*Intravenous heparin therapy*
		von Willebrand disease
		Factor VIII, IX, XI and/or XII deficiency
		Presence of a lupus anticoagulant which may cause an in vitro prolongation of the aPTT but not a bleeding risk
		Liver disease, DIC, may be prolonged with direct oral anticoagulants or other therapeutic anticoagulants such as hirudin, or argatroban.
TT	12–14 s	Hypo- or dysfibrinogenaemia
		Thrombin inhibitors (unfractionated heparin or dabigatran)
Fibrinogen level	1.5–4.5 g/L	*Intravenous heparin therapy*
		Liver disease, DIC, major bleeding
ACT	80–120 s	Bedside blood clotting time assay.
		Intravenous heparin therapy

PT prothrombin time. INR (patient PT/control PT), *aPTT* activated partial thromboplastin time, *TT* thrombin time, *ACT* activated clotting time

*Values may vary and checking locally derived normal ranges is recommended

**The platelet count simply reflects the number of circulating platelets, not the platelet function

Table 4 Effect of commonly used anticoagulants on coagulation parameters

Agent	Prothrombin time (PT)	Activated partial thromboplastin time (aPTT)	Thrombin time	Therapeutic monitoring
Unfractionated Heparin	Normal (or prolonged at high doses)	Prolonged	Prolonged	aPTT (or anti-factor Xa levels)
LMWH	Normal	Normal (or prolonged at high doses)	Normal (or prolonged at high doses)	Anti-factor Xa levels
Warfarin	Prolonged	Normal or prolonged	Normal	INR
Apixaban*	Normal or prolonged	Normal or prolonged	Normal	Apixaban levels (anti-factor Xa based assay)
Rivaroxaban*	Normal or prolonged	Normal or prolonged	Normal	Rivaroxaban levels (anti-factor Xa based assay)
Dabigatran*	Normal (or prolonged at high doses)	Normal or prolonged	Prolonged	Dabigatran levels (Dilute thrombin time or ecarin clotting time-based assay)
Edoxaban*	Normal or prolonged	Normal or prolonged	Normal	Edoxaban levels (anti-factor Xa based assay)
Fondaparinux	Normal or prolonged	Normal or prolonged	Normal	Fondaparinux levels (anti-factor Xa based assay)
Argatroban	Normal (or prolonged at high doses)	Prolonged	Prolonged	aPTT

*PT and APTT sensitivity to direct oral anticoagulants (DOACs) will vary according to local laboratory reagents. INR (International Normalised Ratio) = (patient PT/mean normal PT)$^{\text{international sensitivity index}}$

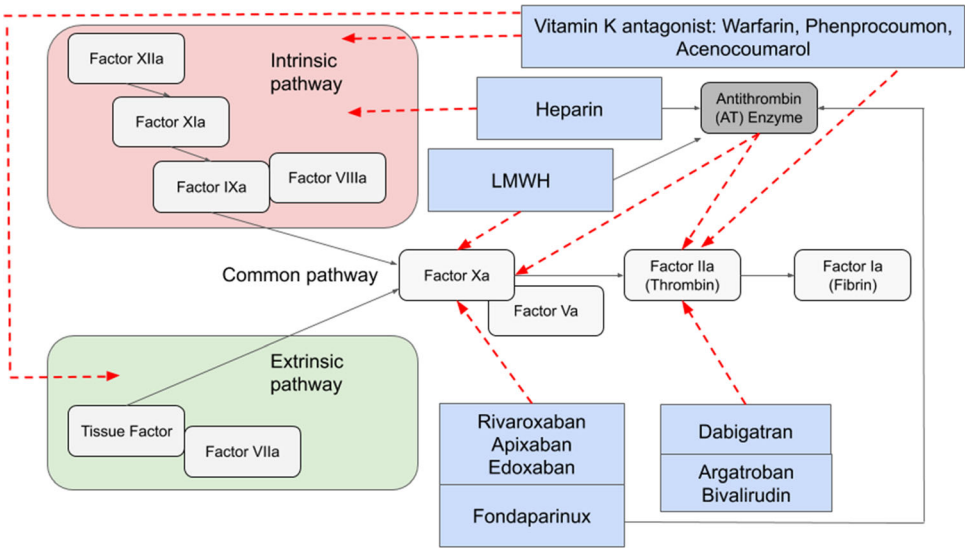


Fig. 1 Simplified summary of the most commonly used anticoagulants and how they affect the coagulation cascade. Red dotted line = Inhibition, Solid line = Activation

i. *Unfractionated Heparin (UFH)* has a short-half life and is cleared rapidly. Therapeutic response is monitored by aPTT, which is targeted at 1.5–2.5 times normal. In some cases, anti-factor Xa levels are used to monitor UFH. The half life of UFH varies from 23 to 168 min [16]. The platelet count should be monitored after the prolonged administration (> 4 days) of heparin for the possibility of heparin-induced thrombocytopenia.

ii. *Low Molecular Weight Heparin (LMWH)* (e.g. enoxaparin, dalteparin, tinzaparin, and nadroparin) is administered subcutaneously and have weight-adjusted doses (usually once or twice daily). LMWH has a much higher bioavailability than UFH (> 90% of the administered dose) and a predictable dose response. Drug levels do not usually need to be monitored but can be measured using an anti-factor Xa assay.

b. *Vitamin K antagonists (VKAs)* (e.g. warfarin, phenprocoumon, and acenocoumarol) are oral anticoagulants and are coumarin derivatives. They inhibit the gamma carboxylation of vitamin K-dependent clotting factors II, VII, IX, and X, and anticoagulant proteins C and S. Vitamin K antagonist effects can be assessed using PT but usually the INR test, which is derived from the PT, allows comparison with a patient's anticoagulant intensity between centres.

c. *Direct Oral-Anticoagulants (DOACs)* have emerged as an alternative to vitamin K antagonists. DOACs directly target the enzymatic activity of thrombin (factor IIa) or factor Xa. Currently available DOACs for use in Europe include dabigatran, apixaban, rivaroxaban, and edoxaban. These drugs have predictable pharmacokinetics and are easier to use than VKAs, due to the rapid onset of action (within approximately 2 h), short-half lives, and fewer drug and diet interactions [17, 18]. The current indications for DOACs, however, do not cover all the indications for VKAs (e.g. patients with mechanical heart valves or triple positive antiphospholipid syndrome).

i. *DOACs with Factor Xa Inhibitory effect* (e.g. rivaroxaban, apixaban, and edoxaban) are oral medications with different half lives and hence different frequency of dosing, as well as different renal/hepatic clearances. Levels can be measured using a chromogenic anti-factor Xa assays to measure the anticoagulant effect of these agents but are rarely needed.

ii. *DOACs with direct oral thrombin receptor inhibitors* (e.g. dabigatran) reversibly block the enzymatic function of thrombin. Drug level can be measured using a dilute thrombin time assay, or ecarin clotting time-based assay; however, these investigations to aid peri-procedural care are not based on results of large trials and are rarely needed.

d. *Other direct thrombin receptor inhibitors* (e.g. argatroban, natural, and synthetic hirudin) are agents that are used very infrequently and are beyond the scope of this document. Specialist advice should be sought for treatment of patients on these agents.

e. *Fondaparinux* is an indirect selective inhibitor of factor Xa, and a synthetic pentasaccharide. It is used in a similar fashion to LMWH, with once-daily dosing. If monitoring is needed, fondaparinux specific anti-Xa assays are required (if available).

Strategies for Peri-operative Anticoagulation Management

Peri-procedural management decisions need to be based on the assessment of competing risks; i.e. the risk of thromboembolic complications when the anticoagulant is stopped, versus the risk of bleeding during and after the procedure.

These risks vary depending on patient factors (e.g. age, comorbidities), type of anticoagulation (rapid versus slow offset and onset), procedure (low versus high bleeding risk), and circumstance (elective versus emergency). Thus, it is important, wherever possible, to discuss the plan for peri-operative anticoagulation with the patient and relevant clinical teams (e.g. experts in haemostasis and thrombosis for patients with previous venous thromboembolism, or experts in cardiology or cardiothoracic surgery for patients with metallic heart valves). Furthermore, it is essential that this plan is recorded clearly in the notes and discharge letter, for optimal patient outcomes.

The risk of bleeding has been stratified by various publications in many different ways often interchangeably, including; 'no clinically important risk', 'low risk', 'moderate risk', 'intermediate risk', and 'high risk'. This has been derived based on post-procedure bleeding rates in predominantly non-randomised and non-controlled studies, and retrospective reports from databases. Historically, procedures with > 2–4% major/clinically significant bleeding risk are considered moderate to high risk, while procedures with $< 2\%$ major/clinically significant bleeding rates were considered low-risk procedures [5, 6, 19, 20]. Similarly, for the purposes of this document, we have stratified the risks into 'Low Risk' versus 'Medium/High' risk. The 'No Risk' category was deemed superfluous and was omitted, as with no risk of bleeding there would be no alteration to patient anticoagulation. Moreover, the anticoagulation management for moderate/high risk bleeding procedures was no different from each other for the majority of procedures, and therefore did not require subcategorisation (Table 5).

Various bleeding prediction tools exist for patients on anticoagulation and have demonstrated modest discriminatory performance for peri-procedural bleeding making them noteworthy, for example the HAS-BLED score (Hypertension, Abnormal renal/liver function, Stroke, Bleeding History of Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly) [27–29], and BleedMAP [30], which predicts increased bleeding in patients with more than one of the identified risks (including history of bleeding, mechanical mitral valve, active cancer, and low platelets) [30]. However, these tools are currently not validated for predicting post-procedure bleeding in patients on anticoagulation.

On the other hand, those at increased risk of thromboembolic events/complications include patients with a history of stroke, a history of venous thromboembolic event, underlying active malignancy, mechanical heart valves, and valvular heart disease. Within this subset of patients, some patients are considered at a higher risk of developing thromboembolic complications including stroke, venous thromboembolism (VTE), and mechanical heart related thrombosis with an associated increased mortality rate [1, 7, 31]. These patients can be identified using several scoring systems and criteria (the exact details of which are beyond the scope of this document and have not been validated for periprocedural use). Table 6 provides a summary of the factors that increase patients' overall risk of thromboembolic events and should be considered for bridging therapy (below) as recommended by the British Society of Haematology [1].

Very high-risk patients, such as those with a deep vein thrombosis or pulmonary embolism in the preceding 30 days, should always be discussed with an expert in haemostasis and thrombosis.

The details on the timing of withholding and restarting anticoagulation are otherwise based on pharmacologic characteristics of the medication being held, and are described in Tables 7 and 8.

a. Anticoagulation management strategies for elective procedures (Fig. 2)

Recommendation 6 For patients on anticoagulants with no increased risk of thromboembolic events/complications undergoing an elective IR procedure, consider either continuing the anticoagulation or following the advice in Table 7 and 8 regarding holding the anticoagulation at the time of the procedure for low bleeding risk procedures.

Recommendation 7 For patients on anticoagulants with increased risk of thromboembolic events/complications undergoing an elective IR procedure with low risk of bleeding, consider continuing anticoagulation. However, this will depend on the specific procedure.

Recommendation 8 For patients on anticoagulants with increased risk of thromboembolic events/complications undergoing an elective IR procedure with moderate/high risk of bleeding, withholding anticoagulation and bridging therapy (if applicable) should be considered.

b. Bridging

Bridging plans should be made in conjunction with a clinician with expertise in peri-operative bridging.

i. Patients with atrial fibrillation who are being anticoagulated to reduce their risk of stroke

Table 5 Bleeding risk stratification for common IR procedures [5, 6, 20–25]

	Blood parameters recommended for proceeding with procedure	
	Low risk of bleeding Hb: > 70 g/L (Asymptomatic) Platelet count: > 20 × 10^9/L INR: < 2.0 if on a vitamin K antagonist	Moderate/High risk of bleeding Hb: > 80 g/L Platelet count: > 50x 10^9/L INR: < 1.5 if on a vitamin K antagonist
Vascular interventions		
Vascular	*Venous procedures*	
	Venography	TIPSS
	PICC insertion	
	Uncomplicated central line insertion, tunnelled central line and ports, exchange, and removal	Complex Inferior vena cava filter removal (advanced technique)
	Inferior vena cava filter insertion/removal (Standard technique)	CNS interventions
	Venoplasty	
	Gonadal vein embolisation	
	Transjugular liver biopsy(patients presumed to have liver impairment)	
	Arterial procedures	
	Angiography ± angioplasty (PAD, mesenteric, carotid)	Aortic stent grafting
	Neuroangiography	
	Embolisation (fibroid, prostate, chemoembolization)	
	Dialysis access-related procedures	
	Dialysis access intervention (fistulogram ± fistuloplasty)	
Non-Vascular interventions		
	Superficial interventions: Biopsies/fine needle aspiration (breast, lymph nodes, thyroid). Abscess drainage	Percutaneous cholecystostomy, Gastrostomy and Gastro-jejunostomy
	Lymphocele drainage	Liver (transcutaneous), lung, and renal biopsies
	Gastrointestinal tract stenting (colon, oesophagus, and duodenum)*	Percutaneous transhepatic cholangeogram ± biliary stenting ± drainage
	Catheter exchanges/removal (genitourinary, biliary, abscess)*	Percutaneous nephrolithotomy and Nephrostomy
		Other deep intraabdominal,, thoracic chest wall, pleural or retroperitoneal biopsies/drainage
	Ultrasound guided diagnostic/therapeutic thoracentesis or paracentesis	Thermal ablation
Musculoskeletal interventions		
	Joint aspiration/injection	Vertebroplasty/kyphoplasty
	Facet joint block	Spinal biopsy
	Musculoskeletal extremity core biopsies	Lumbar puncture and Epidural Injections[+] (Complications including spinal canal haematoma carries devastating morbidity)

*Can be considered as very low risk of bleeding

[+]There are individualised platelet transfusion thresholds for each of these procedures (platelet count of ≥ 80 × 10 g/L should be used for placing/removing an epidural catheter and a count of ≥ 40 × 10 g/L for spinal anaesthesia and lumbar puncture [26]

The thrombosis versus bleeding risk on bridging patients with atrial fibrillation (AF) has been extensively examined. Evidence suggests bridging therapy is associated with an increased risk of major bleeding, with no difference in the risk of thromboembolic events [1, 32–34]. Thus, only AF patients at high risk of thrombosis should be recommended for bridging therapy with heparin [1, 6, 31] and other patients with AF can stop anticoagulation before procedures without bridging therapy (see Tables 7, 8 for information on when to stop).

ii. Patients who are anticoagulated for venous thromboembolism

For the first three months after a venous thromboembolism there is a significant increase in the risk of recurrent thrombosis. The risk is particularly high in the 30 days

Table 6 Patients with increased risk of thromboembolic events and to consider bridging therapy [1]

VTE	Patients with a VTE within previous 3 months
	Patients with a previous VTE whilst on therapeutic anticoagulation who now have a target INR of 3·5.
AF	Patients with a previous stroke/TIA in last 3 months.
	Mitral stenosis
	Patients with a previous stroke/TIA and 3 or more of the following risk factors:
	Congestive cardiac failure
	Hypertension (> 140/90 mmHg or on medication)
	Age > 75 years
	Diabetes mellitus
Valve replacement	MHV patients other than those with a bi-leaflet aortic valve and no other risk factors including:
	Congestive cardiac failure
	Hypertension (> 140/90 mmHg or on anti-hypertensive medication)
	Age > 75 years
	Diabetes mellitus
	Atrial fibrillation
	Prior stroke/TIA

Very high-risk patients such as those with a VTE in the preceding 30 days should always be discussed with a specialist in haemostasis and thrombosis

VTE Venous thromboembolic disease, *AF* atrial fibrillation, *MHV* mechanical heart valve, *TIA* transient ischaemic attack

after the initial diagnosis of a venous thromboembolism. For patients in the first 30 days after a venous thrombosis, advice should be sought from a specialist in haemostasis and thrombosis. Patients who are more than 30 days from their venous thromboembolism, but less than three months, should be considered for bridging if the procedure cannot be delayed.

iii. Patients who are anticoagulated who have metallic heart valves

These patients must be discussed with their usual cardiologist or cardiac surgeon. They may require bridging with unfractioned heparin (for those at high risk) or low molecular weight heparin.

iv. Bridging for patients at high risk of recurrent thrombosis who are anticoagulated with VKAs

VKAs should be stopped at 5 days prior to the procedure. Three days prior to the procedure, treatment dose LMWH should be administered, ideally in the morning so that the last dose can be given 24 h before surgery. The last dose of treatment dose LMWH should be given 24 h or more before the procedure [33].

If bridging LMWH/UFH therapy is to be given after the procedure, it should be started at least 48 h afterwards in patients at high risk of bleeding and 6–12 h afterwards when the risk is not high. Post-operative resumption of anticoagulation should be done when haemostasis is achieved. If treatment dose anticoagulation is to be withheld for more than 6–12 h after a procedure, consideration should be given to administering prophylactic dose low molecular weight heparin in the interim.

Patients with a low bleeding risk can usually resume maintenance dose warfarin 12–24 h after the procedure with advice to have an INR performed after 1 week.

Patients with a high bleeding risk can usually resume warfarin within 24–72 after the procedure. Consideration should be given to formally re-load such patients and stop bridging LMWH when the INR is within the target range for 2 consecutive days.

c. Anticoagulation management strategies for emergency procedures (Fig. 3)

Recommendation 9 For patients on anticoagulants requiring an immediate emergency IR procedure with low risk of bleeding, consider proceeding and either omitting a dose or continuing anticoagulation.

Recommendation 10 For patients on anticoagulants requiring an immediate emergency IR procedure with moderate/high risk of bleeding, consider reversing anticoagulation. If at high risk of thrombosis, bridging therapy should be considered.

Recommendation 11 For patients at risk of bleeding, attention should be given to pressure at puncture sites, supportive care and monitoring of vital signs.

d. Reversal of anticoagulation:

Table 7 Guidance on when to stop and restart anticoagulation for procedures with low risk of bleeding

Procedures with low risk of bleeding			
	Discontinue	Hold duration prior to procedure	Restart time (h)**
Heparins			
Unfractionated Heparin	Yes	4 h	6
LMWH (prophylactic)	Possible to continue	12 h	6
LMWH (Therapeutic)	Yes	24 h	6–12
Vitamin K Antagonists			
Warfarin	Either continue and check INR one week before with VKA dose adjustment to ensure it is in range or hold prior to procedure at discretion of the physician undertaking the procedure. If warfarin is continued then check INR day of procedure to ensure it is within range and if warfarin is discontinued then check INR day of procedure to check it is < 2	3–5 days + (INR Check)	12–24
Phenprocoumon		15–20 days + (INR Check)	
Acenocoumarol		2–3 days + (INR Check)	
Thrombin Inhibitors			
Dabigatran	Either continue or omit the dose prior to procedure at discretion of physician undertaking procedure	1–2 days	6
Bivalirudin	Yes	4 h	6
Argatroban	Yes	4 h	6
Desirudin	Yes	2 h (IV). 10–12 h (SC)	24
Factor Xa Inhibitors			
Apixaban	Either continue or omit the dose prior to procedure at discretion of physician undertaking procedure	1–2 days	6
Rivaroxaban		2 days (CrCl > 50)	6
		2–4 days (CrCl < 50)	
Edoxaban		1–2 days	6
Fondaparinux	Possible to continue	36 h	6–12
Fondaparinux (therapeutic)	Yes	48 h	6–12

SC subcutaneous, *IV* intravenous, *CrCl* creatinine clearance, *LMWH* low molecular weight heparin

Prior to considering reversal of anticoagulation, baseline information on type, dose, frequency, timing of last dose, and indication of anticoagulants is required, as well as on other medication affecting bleeding such as antiplatelet drugs. Laboratory tests should be requested, including full blood count (FBC), coagulation status (PT, aPTT, TT and fibrinogen), renal function and liver function. Discussion with a specialist in haemostasis and thrombosis regarding additional coagulation samples for drug-specific tests may be required [1, 35].

Reversal of anticoagulation should be reserved for anticoagulated patients requiring emergency procedures or with life-threatening bleeding [1, 36–38]. In the elective setting, the focus should be on timely discontinuation of an anticoagulant taking into account the clinical context (Tables 7, 8) [9].

Recommendation 12 For patients on VKA anticoagulation and planned for an elective IR procedure, discontinuing anticoagulation is recommended over accelerated reversal with vitamin K [9].

In the emergency setting, discontinuation of the anticoagulant and supportive care for those who are actively bleeding is the first management step. Supportive treatment includes haemodynamic monitoring and volume resuscitation, if indicated, with intravenous fluids or blood as per haematological guidelines [37]. Reversal of anticoagulation should be discussed with a specialist experienced in the reversal of anticoagulation.

i. Unfractionated heparin and low molecular weight heparin

UFH has a short-half life and stopping the infusion is often all that is necessary. UFH can be fully reversed with

Table 8 Guidance on when to stop and restart anticoagulation for procedures with medium/high risk of bleeding

Procedures with medium/high risk of bleeding			
	Discontinue	Hold duration prior to procedure	Restart time after procedure (h)**
Heparins			
Unfractionated Heparin	Yes	4 h	24
LMWH (prophylactic)	Yes	6–12 h	6–12
LMWH (Therapeutic)	Yes	24 h	24–72
Vitamin K Antagonists			
Warfarin	Discontinue VKA prior to procedure and on day of procedure check INR < 1.5 prior to commencing procedure	5 days + (INR Check)	12–24
Phenprocoumon		15–20 days + (INR Check)	
Acenocoumarol		3 days + (INR Check)	
Thrombin Inhibitors			
Dabigatran	Yes	2–3 days (CrCl > 50) 3–5 days (CrCl < 50)	48–72
Bivalirudin	Yes	4 h	48–72
Argatroban	Yes	4 h	48–72
Desirudin	Yes	2 h (IV). 10–12 h (SC)	48–72
Factor Xa Inhibitors			
Apixaban	Yes	1–2 days (CrCl > 50). 3–5 days (CrCl < 50)	48–72
Rivaroxaban	Yes	1–2 days (CrCl > 50) 3–5 days (CrCl < 50)	48–72
Edoxaban	Yes	3–4 days	48–72
Fondaparinux (prophylactic)	Yes	36 h	6–12
Fondaparinux (therapeutic)	Yes	48 h	6–12

SC subcutaneous, *IV* intravenous, *CrCl* creatinine clearance, *LMWH* low molecular weight heparin

*Consider bridging therapy in patients with increased risk of thromboembolic events

**Restart time assumes post-procedure haemostasis has been achieved at the discretion of the physician undertaking the procedure

protamine sulphate (1 mg per 80–100 units UFH; maximum dose 50 mg) [39].

LMWH can be partially reversed by protamine (1 mg per 80–100 units UFH; maximum dose 50 mg). If LMWH was given more than 8 h prior to the procedure then lower doses of protamine should be considered [39].

ii. Vitamin K antagonists

With VKAs, INR testing will indicate the degree of anticoagulation and provide information on how to proceed. Intravenous vitamin K (5–10 mg depending upon locally agreed protocols), will usually reverse the effects of vitamin K antagonists within 6 to 8 h. If more rapid reversal is necessary, due to acute bleeding or requirement for emergency surgery, then prothrombin complex concentrate (PCC) can be given in addition to intravenous vitamin K (5–10 mg). PCC normalises the INR within a few minutes of administration. Fresh frozen plasma (FFP) should only be used if PCC is not available, as it has been shown to be inferior for rapid INR reversal and effective haemostasis in patients needing reversal for urgent surgical or invasive procedures [36, 40–42]. Further doses of vitamin K may be necessary in the following days [43].

iii. Direct oral-anticoagulants

Oral-activated charcoal can be administered if direct oral-anticoagulants were taken within the last 2–3 h; however, this treatment is often very poorly tolerated and may require a nasogastric tube. In emergency procedures requiring vascular access, closure devices can also be used to minimise the bleeding risks.

The evidence to support the use of anti-fibrinolytic drugs such as tranexamic acid (TXA; a fibrinolysis inhibitor which inhibits the binding of plasminogen to fibrin) in trauma, post-partum haemorrhage and during surgery is well established. In these settings, the risk of thrombosis is similar between TXA and placebo [44, 45]. The evidence is more limited for using TXA to reduce bleeding risks for

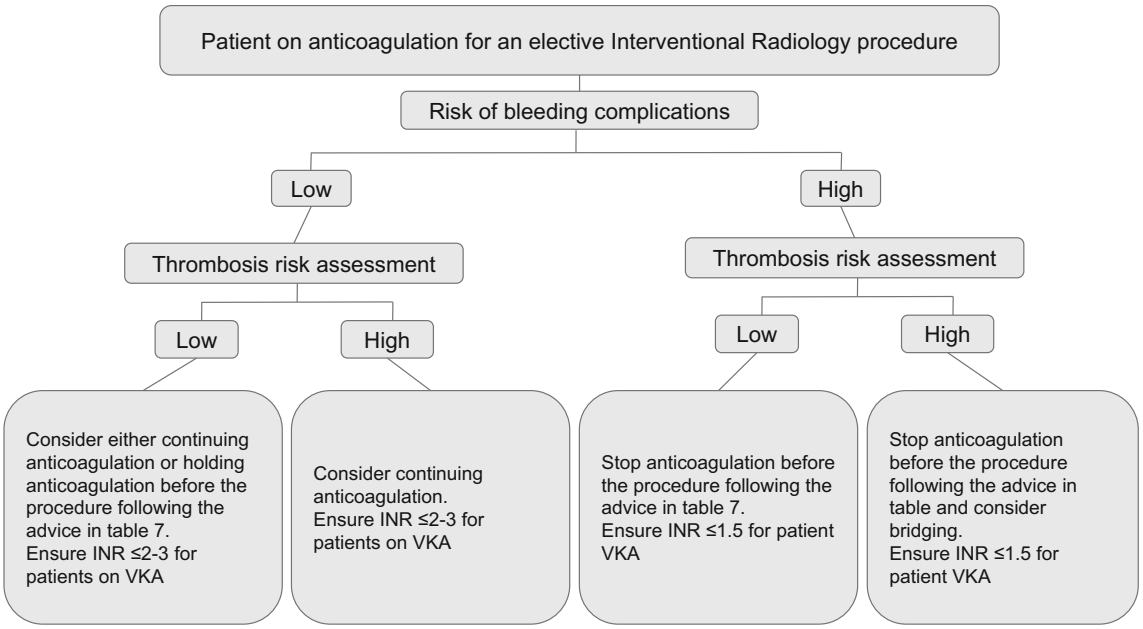
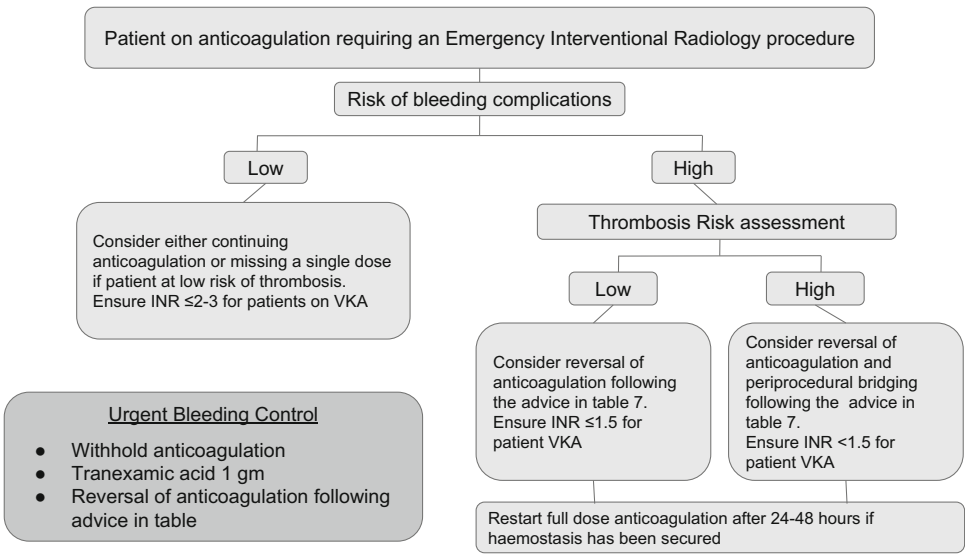


Fig. 2 Flowchart detailing anticoagulation management strategies for elective procedures

Fig. 3 Flowchart detailing anticoagulation management strategies for emergency procedures



patients taking DOACs who are undergoing interventional procedures. However, given their favourable side-effect profile (with no significant increase in thrombotic risk), efficacy in other clinical settings and low cost, it is reasonable to consider their use [1, 35].

Specific antidotes for DOACs are now available. In 2015, idarucizumab (Praxbind), a humanised monoclonal antibiotic fragment antidote for dabigatran, was approved for use in Europe. It is capable of reversing anticoagulation by binding dabigatran with higher affinity than the dabigatran is able to bind to thrombin [42].

More recently in 2019, andexanet alfa, a recombinant modified factor Xa protein has been licensed by the European Medicines Agency as an antidote to reverse the anticoagulant effects of rivaroxaban and apixaban for use in life-threatening or uncontrolled bleeding [46]. While it may also have effects for other anticoagulants which inhibit factor Xa (such as edoxaban and LMWH) the European Medicines Agency do not consider there to be sufficient evidence for this. It is only licenced for bleeding patients where urgent reversal of apixaban or rivaroxaban is required, and is not licensed for emergency surgery or interventional procedures.

When a specific antidote is not available (or licensed), PCC may be considered off-label. The thrombotic risk of administering PCC must be considered. For patients taking

Table 9 Reversal of anticoagulants before emergency surgery

Drug names	Reversal agents
Heparins	
Unfractionated Heparin	Protamine Sulphate (1 mg per 100 units of factor Xa inhibition; maximum dose 50 mg). Consider a reduced dose of protamine for reversal of low molecular weight heparins if given more than 8 h previously
Enoxaparin/Lovenox®	
Dalteparin/Fragmin®	
Tinzaparin/Innohep®	
Nadroparin/Fraxoparine®	
Vit K antagonists	
Warfarin/Coumadin®	Vitamin K (IV 5–10 mg)
Phenprocoumon	4-PCC**
Acenocoumarol	
DOAC	
Direct thrombin Inhibitors	
Dabigatran/Pradaxa®	Idarucizumab (Praxbind) if thrombin time prolonged.
Factor Xa Inhibitors	If idaracizumab not available consider:
	Tranexamic acid
	4-PCC*
Apixaban/Eliquis®	Tranexamic acid
Rivaroxaban/Xarelto®	4-PCC*
	Andexanet alfa (Andexxa) was licensed in 2019 by the European Medicines Agency for life-threatening or uncontrolled bleeding but not for emergency surgery or procedures
Edoxaban/Savaysa®	Tranexamic acid
	4-PCC*
Other direct anticoagulants	
Direct Thrombin Inhibitors	
Argatroban	Discuss with a specialist in reversal of anticoagulation
Bivalirudin	
Desirudin	
Indirect Factor Xa Inhibitors	
Fondaparinux	Discuss with a specialist in reversal of anticoagulation

4-PCC Four factor prothrombin complex concentrate

*Fresh frozen plasma (FFP) can be considered in the absence of 4-PCC, however, is considered inferior

Discussion with a specialist in haemostasis and thrombosis is recommended before the use of PCC

dabigatran, haemodialysis can be considered. This is rarely practical outside intensive care of renal medicine units. A 4-hour session of haemodialysis results in approximately 50% dabigatran clearance [47]. There is no role for dialysis in rivaroxaban and apixaban related bleeding due to their high protein binding [38, 48].

iv. Other anticoagulants

Patients who are taking other anticoagulants who require emergency surgery should be discussed with a specialist experienced in the reversal of anticoagulation.

Table 9 is a summary of common anticoagulants and their respective reversal agents for emergency surgery.

Conclusion

Peri-procedural anticoagulation management can be is complex due to the multiple factors involved as well as the paucity of good quality evidence available with regards to the optimal approach. It is, thus, important to highlight that the recommendations provided within this document are not meant to be authoritative but rather a user friendly and pragmatic tool to help with the day to day clinical decision making of the interventional practitioner.

This document's main aim is to help the interventionists by attempting to simplify the complex and often confusing topic of peri-procedural anticoagulation management by stratifying patients into groups: elective versus emergency

patients, low versus moderate/high procedural bleeding risk, and low versus high thromboembolic risk, as well as, providing management pathways/flow charts to aid the interventionist to come to the optimal management plan for each individual patient without undue delay.

Wherever possible, the plan for peri-operative anticoagulation needs to be discussed with the patient and their clinical teams and recorded clearly in the notes and discharge letter, for optimal patient outcomes.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

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