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REVIEW

Direct Oral Anticoagulants: An Overview for the Interventional Radiologist

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Abstract The direct oral anticoagulants (DOACs) have emerged as a good alternative for the treatment of thromboembolic diseases, and their use in clinical practice is increasing rapidly. The DOACs act by blocking the activity of one single step in the coagulation cascade. These drugs act downstream in the common pathway of the coagulation cascade by directly antagonising the action of thrombin or factor Xa. The development of DOACs represents a paradigm shift from the oral vitamin K antagonists such as warfarin. This article aims to describe the properties of the currently available DOACs including pharmacology and dosing. We also address the strategies for periprocedural management and reversal of anticoagulation of patients treated with these agents.

Keywords Direct oral anticoagulants · Periprocedural · Anticoagulation · Bleeding

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Introduction

Oral anticoagulation is widely used for the prevention of stroke in patients with atrial fibrillation and the treatment of patients diagnosed with thromboembolic disorders such as deep venous thrombosis and pulmonary embolism [1, 2]. For more than 70 years, the vitamin K antagonists (VKAs) were the only available oral anticoagulant, and warfarin has been the most ubiquitous anticoagulant prescribed. Although experience with these agents is vast, the VKAs are limited by their narrow therapeutic index, high incidence of drug interactions and need for regular monitoring. This has prompted the development of the direct oral anticoagulants (DOACs). DOACs are anticoagulants that directly target the enzymatic activity of thrombin and factor Xa.

Each year, approximately 10% of patients on oral anticoagulants require treatment interruption for an invasive procedure [3]. The periprocedural management of these patients can be a complex and challenging process due to patient comorbidities and the range of interventional radiology techniques currently available. Although recommendations from the surgical literature can be helpful, they may not always be applicable to interventional techniques [4].

Several different terms have been used to describe this class of oral anticoagulants, including novel/new/non-vitamin K antagonist oral anticoagulants (NOACs), direct oral anticoagulants and target-specific oral anticoagulants. For the purpose of reaching a consensus on terminology, the International Society of Thrombosis and Haemostasis (ISTH) have proposed DOAC as the preferred acronym consistent with their official pharmacotherapeutic classification according to the World Health Organization [5].

The purpose of this review is (1) to provide an overview of the direct oral anticoagulants and (2) to outline

periprocedural management recommendations for elective and emergency procedures. In addition, we examine some of the challenges and controversies surrounding these new agents as well as the specific antidotes currently being developed.

The Coagulation Cascade

The coagulation cascade is a multi-step process that leads to the production of the primary clot stabilising molecule, fibrin. The formation of a clot at the site of injury involves four phases: exposure of tissue factor from the endothelium that leads to the initiation phase or binding of platelets to collagen; propagation or recruitment of platelets to the growing clot; amplification of the coagulation cascade and stabilisation or platelet–platelet interaction with fibrin deposition. The cascade consists of both the intrinsic and extrinsic pathways, which converge to form a common pathway. Inactive enzyme precursors and cofactors are converted into active components that catalyse the next reaction in the cascade. The first step in the final common pathway involves the activation of factor X to factor Xa. Factor Xa catalyses the activation of prothrombin (factor II) to thrombin (factor IIa). Thrombin catalyses the activation of fibrinogen to fibrin resulting in cross-linking and deposition of fibrin clots, the endpoint of the coagulation cascade.

The DOACs act by blocking the activity of one single step in the coagulation cascade. These drugs act downstream in the common pathway of the coagulation cascade by directly antagonising the action of thrombin or factor Xa (Fig. 1).

Direct Oral Anticoagulants

The direct oral anticoagulants can be broadly divided into two classes—the *direct thrombin inhibitors* (Dabigatran) and the *factor Xa inhibitors* (Rivaroxaban, Apixaban, Edoxaban). They are licensed for use for stroke prevention in AF, treatment of VTE, including deep venous thrombosis and pulmonary embolism and for postoperative thromboprophylaxis in patients having elective hip or knee arthroplasty (Table 1) [6].

The DOACs have a predictable anticoagulant response, making monitoring unnecessary in the majority of patients. Anticoagulation is achieved rapidly with peak plasma concentrations of 1–4 h following oral administration [9–12]. When compared with VKAs, the DOACs were associated with a 50% reduced risk of intracranial bleeding [13]. This reduction includes both subdural and intracerebral bleeds. Intracranial bleeds in patients treated with DOACs tend to be smaller compared to those treated with warfarin, which is thought to explain the lower case-fatality rate in the former [14, 15]. The pharmacological properties of DOACs are summarised in Table 2.

Dabigatran (Pradaxa®; Boehringer Ingelheim)

Dabigatran is a direct thrombin inhibitor administered as the prodrug, dabigatran etexilate. After oral administration, it is rapidly and completely absorbed and hydrolysed by a serum esterase converting it to dabigatran, which is the active form. Dabigatran reversibly blocks the enzymatic function of thrombin. Since thrombin plays a key role in the clotting cascade by converting fibrinogen to fibrin, its inhibition prevents the development of thrombus. Dabigatran reaches peak plasma concentration between 1 and 3 h following oral administration. This is followed by a rapid distribution/elimination phase with estimated half-lives of 8–10 and 14–17 h with single- and multiple-dose administrations, respectively [16]. Food does not affect the bioavailability of dabigatran but delays the time to peak plasma concentration by 2 h. Dabigatran is principally excreted by the kidneys [17]. Peak plasma concentration and elimination half-life are, therefore, significantly increased in patients with impaired renal function. The pharmacokinetic profile of dabigatran is not affected by gender, body weight, ethnic origin or moderate hepatic impairment. Terminal elimination half-life in healthy volunteers is 13 h compared to 15, 18 and 27 h in those with mild, moderate and severe renal impairment, respectively. [18] In healthy elderly subjects, concentrations are 40–60% higher than in younger subjects, a reflection of reduced renal clearance with increasing age [12]. The drug is contraindicated in patients with a creatinine clearance (CrCL) < 30 ml/min or severe hepatic impairment [19]. In patients presenting with major haemorrhage or with end-stage renal disease, dabigatran can be partly removed from the plasma by haemodialysis [20]. Dabigatran is not metabolised by cytochrome p450 isoenzymes, has no interaction with food and has a low potential for drug–drug interactions. Although it causes a linear elevation in prothrombin time (PT) and thrombin time as well as a non-linear elevation in activated partial thromboplastin time (aPTT) to a varying degree depending upon test conditions, their accuracy is insufficient to determine therapeutic levels [16]. The INR test is unreliable and misleading, and false positive elevations have been reported. Therefore, the INR test should not be used as a monitoring tool for therapeutic efficacy.

Rivaroxaban (Xarelto®; Bayer Healthcare)

Rivaroxaban is a highly selective direct factor Xa inhibitor, reversibly blocking the enzymatic function of factor Xa in the conversion of prothrombin to thrombin.

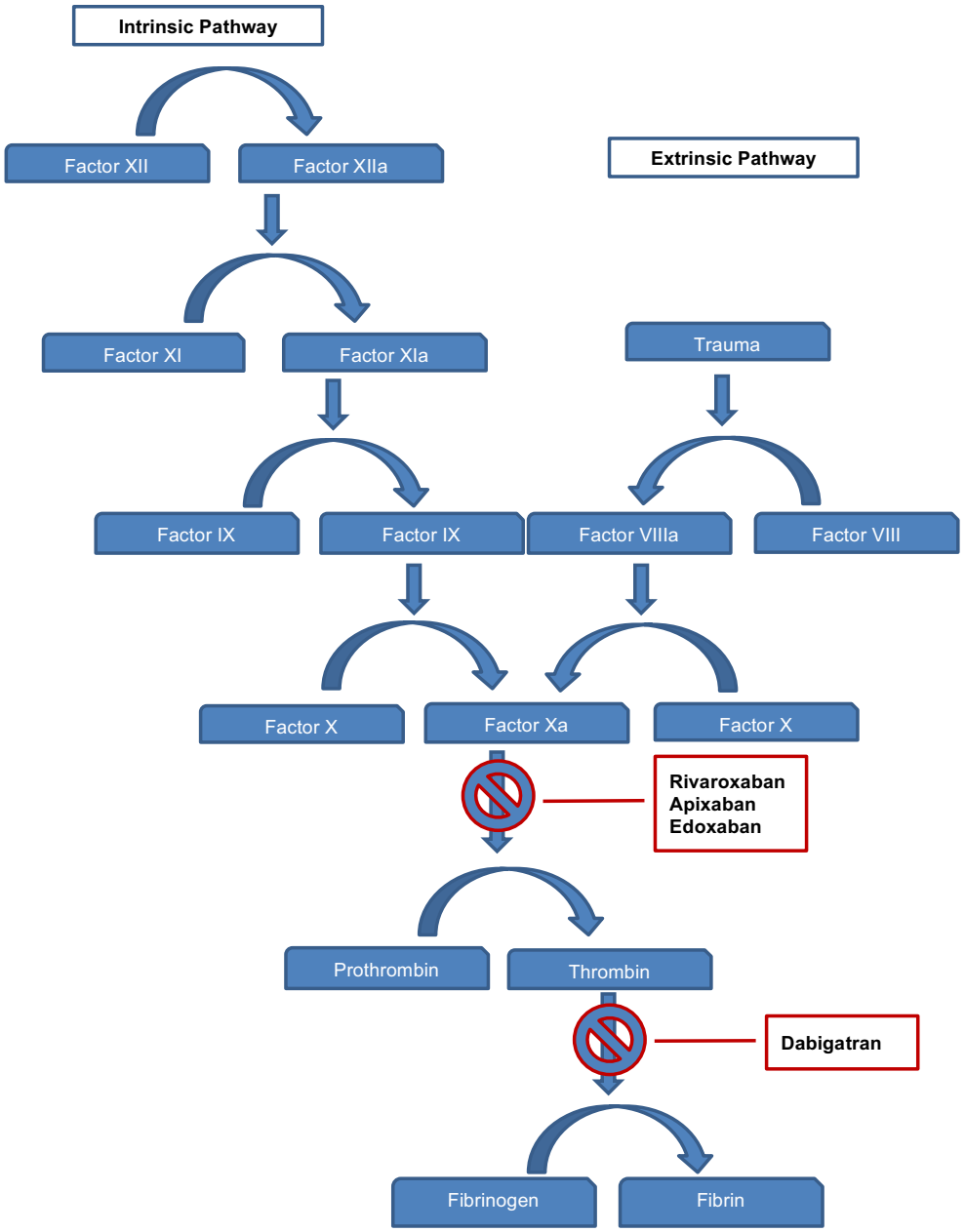

Fig. 1 Coagulation cascade highlighting the biological targets of the direct oral anticoagulants

Table 1 Licensed indications of DOACs

Indication	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Stroke prevention in non-valvular AF [7]	Yes	Yes	Yes	Yes
Acute VTE treatment	Yes	Yes	Yes	Yes
VTE prophylaxis in orthopaedic surgery [8]	Yes	Yes	Yes	No
Acute coronary syndrome	No	No (US)	No	No

It has a rapid onset of action with maximal inhibition of factor Xa within 2–4 h after ingestion. Absorption of rivaroxaban is dependent on the site of its release in the gastrointestinal tract. Rivaroxaban must be administered with food to increase its absorption, the other DOACs can be administered without regard to food [21]. Approximately 95% of the drug is protein-bound making dialysis ineffective in reversing the action of the drug.

Table 2 Pharmacological properties of DOACs

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Mechanism of action	Direct thrombin inhibitor	Factor Xa inhibitor	Factor Xa inhibitor	Factor Xa inhibitor
Time to maximum effect	1–3 h (delayed by food)	2–4 h	3–4 h	1–3 h
Bioavailability (%)	6.5	80–90 (increased by food)	30–90	62%
Half-life	8–17 h	5–13 h	8–15 h	10–14 h
Protein binding (%)	35	92–95	87	40–59
Renal elimination (%)	80	33	30	35
Use in severe renal failure	Contraindicated if CrCl < 30 ml/min	Dose reduction if CrCl 15–30 ml/min Contraindicated if CrCl < 15 ml/min	Can be used	Dose reduction if CrCl 15–50 ml/min Contraindicated if CrCl < 15 ml/min
Use in severe hepatic failure	Not recommended	Contraindicated	Contraindicated	Not recommended
Hepatic metabolism (%)	20	66	70	65
Prophylactic dose	110–220 mg once daily	10 mg once daily	2.5 mg twice daily	30 mg once daily
Therapeutic dose	150 mg twice daily	20 mg once daily 15 mg once daily for renal impairment	10 mg twice daily for 7 days then 5 mg twice daily	60 mg once daily 30 mg once daily for renal impairment

The elimination half-life of the drug is 5–13 h in patients with normal renal function [22, 23]. One-third of the active drug is excreted via the renal system. A dose reduction is recommended in patients with moderate renal impairment. Rivaroxaban is not recommended in patients with CrCl < 15 ml/min. Rivaroxaban is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk including Child Pugh B and C cirrhotic patients. Patients with moderate renal failure taking renal doses of rivaroxaban appear to have lower rates of fatal bleeding compared to patients taking warfarin [24]. Women on rivaroxaban have a higher rate of menorrhagia compared with women taking VKAs [25].

Apixaban (Eliquis®; Bristol-Myers Squibb)

Apixaban is a potent, reversible, direct and highly selective active site inhibitor of factor Xa. It has a rapid onset of action of approximately 3 h [26]. Plasma protein binding is approximately 87%. Apixaban has a plasma elimination half-life of 12 h and has to be administered in a twice-daily dosing regimen. It has an elimination profile similar to that of Rivaroxaban (70% hepatic and 30% renal) [26]. As a result of factor Xa inhibition, apixaban may prolong clotting tests such as prothrombin time (PT), INR and activated partial thromboplastin time (aPTT). Often however, these tests are normal with apixaban.

Edoxaban (Lixiana®; Daiichi Sankyo)

Edoxaban is a highly selective, direct and reversible direct factor Xa inhibitor [27]. It was only approved for use in the UK in July 2015. The pharmacokinetics of edoxaban is characterised by rapid absorption (1–3 h) and a half-life of approximately 10–14 h [11, 28]. Renal clearance accounts for approximately 35% of the administered dose. Metabolism and biliary/intestinal excretion account for the remaining clearance. The absolute bioavailability is approximately 62%. It is only minimally dependent upon the CYP3A4 metabolism and therefore, is not subject to the same drug interactions as the other factor Xa inhibitors. Edoxaban has a small and unpredictable effect on routine clotting tests.

Elective or Planned Procedures

Invasive image-guided procedures that carry a bleeding risk require temporary discontinuation of a DOAC. Periprocedural management of DOACs involve addressing several key clinical questions. For elective procedures, the physician should consider if the procedure could be delayed. In the majority of cases, bridging therapy with heparin is unnecessary due to the predictable anticoagulant response of DOACs. Nevertheless, pre-procedure management should take into account patient characteristics

Table 3 Classification of procedures based on risk of bleeding (adapted from Society of Interventional Radiology Standards of Practice Consensus Guidelines)

	Category 1 Low risk of bleeding	Category 2 Moderate bleeding risk	Category 3 Significant bleeding risk
Vascular	Dialysis access intervention	Angiography and arterial interventions up to 7 F access	TIPSS
	Venography	Chemoembolisation	Arterial interventions with ≥ 7 F access
	Central line removal	Uterine fibroid embolization	
	Vena cava filter placement	Transjugular liver biopsy	
	Peripherally inserted central venous catheter placement	Tunnelled central venous catheter	
		Port device placement	
		Venous interventions	
Non-vascular	Drainage catheter exchange	Intra-abdominal/intrathoracic or retroperitoneal drainage/biopsy	Renal biopsy
	Thoracocentesis	Lung biopsy	Biliary intervention
	Paracentesis	Transabdominal liver biopsy	Nephrostomy tube placement
	Superficial aspiration and biopsy (thyroid/lymph node)	Gastrostomy tube	Complex radiofrequency ablation
	Superficial abscess drainage	Percutaneous cholecystostomy	
		Spine procedures (vertebroplasty, lumbar puncture, facet blocks)	
		Radiofrequency ablation	

such as renal function, age and past history of bleeding complications, as well as procedural factors, specifically risk of bleeding (Table 3).

Approximately 25% of patients treated with DOACs may require temporary cessation of the drug due to invasive interventions [29, 30]. The European Heart Rhythm Association (EHRA) and other groups have published guidelines for the management of direct oral anticoagulants during elective procedures [31–33]. The EHRA recommends classifying procedures into three categories:

(a) For interventions with 'no clinically important bleeding risk', the procedure can be performed at trough plasma concentration of the DOAC (i.e. 12 or 24 h after the last dose depending on either twice daily or once daily dosing, respectively).
(b) For interventions with a 'low risk of bleeding' and normal renal function, the EHRA recommends DOAC discontinuation at least 24 h before the procedure. The interval increases proportionately with an increase in the degree of renal impairment.
(c) For interventions with a 'high risk of bleeding', DOACs should be stopped at least 48 h before a procedure. This recommendation includes dabigatran, providing the CrCl is greater than 50 mls/min. In patients with impaired renal function, that interval becomes wider the more severe the degree of renal impairment and may be up to 5 days prior to planned intervention.

The Society of Interventional Radiology (SIR) and EHRA differ in the nomenclature used for stratifying bleeding risks. The procedures classified into "no clinically important bleeding risk" and "low risk of bleeding" under EHRA guidelines may be interchangeable with procedures classified under 'low bleeding risk" and "moderate bleeding risk", respectively, under SIR guidelines for the purpose of drawing up local policy guidelines.

Figure 2 illustrates an example of periprocedural management of DOAC interruption taking into consideration bleeding risk and renal function [34].

Emergency Procedures

The approach to management of a patient receiving DOACs prior to an emergency procedure differs from that of an elective setting. The lack of a widely available antidote to DOACs makes planning for emergency interventions particularly challenging. In deciding whether a procedure should be delayed, the increased risk of bleeding should be weighed against the urgency of the intervention.

The time interval between administration of the last dose and the procedure must be noted. All DOACs are partially eliminated via the kidneys. Therefore, assessment of renal function is important to estimate their clearance from the body. If a patient has acute kidney injury, drug clearance may be prolonged and anticoagulant effect may persist longer than anticipated. The RE-LY (Randomized Evaluation of Longterm Anticoagulation) Trial

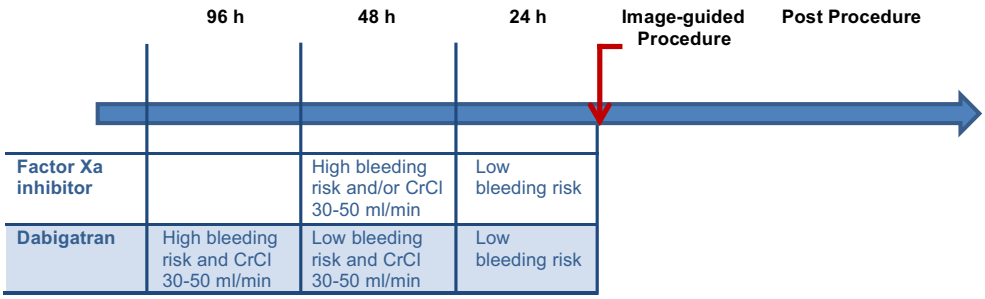

Fig. 2 Periprocedural management of patients treated with DOAC—when to stop the DOAC in relation to time of planned procedure

randomized 18,113 patients with atrial fibrillation to receive either dabigatran or warfarin. Although the rate of gastrointestinal haemorrhage was significantly increased with the higher 150 mg dose, analysis of data from the FDA Mini-Sentinel database showed that the bleeding rate in patients treated with dabigatran requiring urgent surgery was not higher when compared with those in VKA-treated patients [29].

If an emergency intervention is necessary, the DOAC must be discontinued to mitigate the risk of bleeding. Ideally, any intervention should be delayed until at least 24 h after the last dose. If a procedure cannot be delayed, reversal of the anticoagulant may be considered. Routine standard coagulation tests such as prothrombin time (PT) and activated partial thromboplastin time (aPTT) may not exclude the presence of clinically relevant concentrations of the drug [35]. Specific diluted thrombin time test (Hemoclot®) for dabigatran and anti-factor Xa assays calibrated for each specific anti-factor Xa drug are now available in the market [36]. However, many hospitals will be unable to access these tests outside normal working hours.

Managing Bleeding Complications

Minor bleeding can be problematic with any form of anticoagulation, and temporary drug withdrawal may be the only measure necessary due to their short half-lives [37].

Major bleeding can be defined as symptomatic bleeding in a critical organ, for example, gastrointestinal, retroperitoneal, intracranial, pericardial or intramuscular with compartment syndrome. Major or life-threatening bleeding should be managed by immediate withdrawal of the drug followed by general measures including haemodynamic monitoring and aggressive resuscitation with fluid and blood products. Invasive interventions (Interventional Radiology or surgery) should be considered to definitively control the source of bleeding. A proposed algorithm for the management of DOAC-associated bleeding is provided in Fig. 3.

If DOAC ingestion occurred within the last 2 h, physicians may consider the use of oral activated charcoal. This is administered as a tablet or suspension at a dose of 1 g/kg body weight up to a maximum of 100 g and it acts by adsorbing the drug and reducing its absorption. Haemodialysis may be considered for dabigatran patients, particularly if they have impaired renal function. Haemodialysis is not effective in the removal of the direct Xa inhibitors due to their extensive protein binding. The time of last intake of DOAC should be determined and the half-life estimated from measurement of serum creatinine and calculation of the CrCl. Activated and non-activated prothrombin complex concentrates (PCCs) for DOAC reversal may be considered. The evidence supporting their use has been poor and limited to in vitro studies, animal models and healthy human volunteers [38–42]. Inactive 4-Factor PCCs (KCentra®) 50U/kg or active PCCs (aPCC; FEIBA®) 80U/kg are reasonable options for the reversal of direct Xa inhibitors and direct thrombin inhibitors, respectively.

Vitamin K or protamine sulphate has no effect on DOAC-associated bleeding. There are no clinical data on the efficacy of antifibrinolytics on DOAC-associated bleeding. Fresh frozen plasma does not reverse the anticoagulant effect of DOACs to any appreciable degree and should not be used for DOAC reversal. There is also no evidence to support the use of recombinant Factor VIIa; indeed, administration of this component alone was associated with a significant increase in the incidence of fatal thromboembolic complication [43].

Restarting DOACs Post-procedure

With adequate haemostasis, treatment with DOACs can potentially be resumed 24 h following low-bleed risk procedures, although some investigators have suggested recommencing DOAC treatment as soon as 6–8 h after a minor procedure [44–46]. Procedures with higher-bleeding risk should recommence DOAC therapy at 48–72 h after the procedure [47]. Based on data from the RE-LY study, patients who require a period of immobilisation post-procedure may benefit from low-molecular-weight heparin (LMWH) cover for the first 48 h prior to restarting DOACs [48].

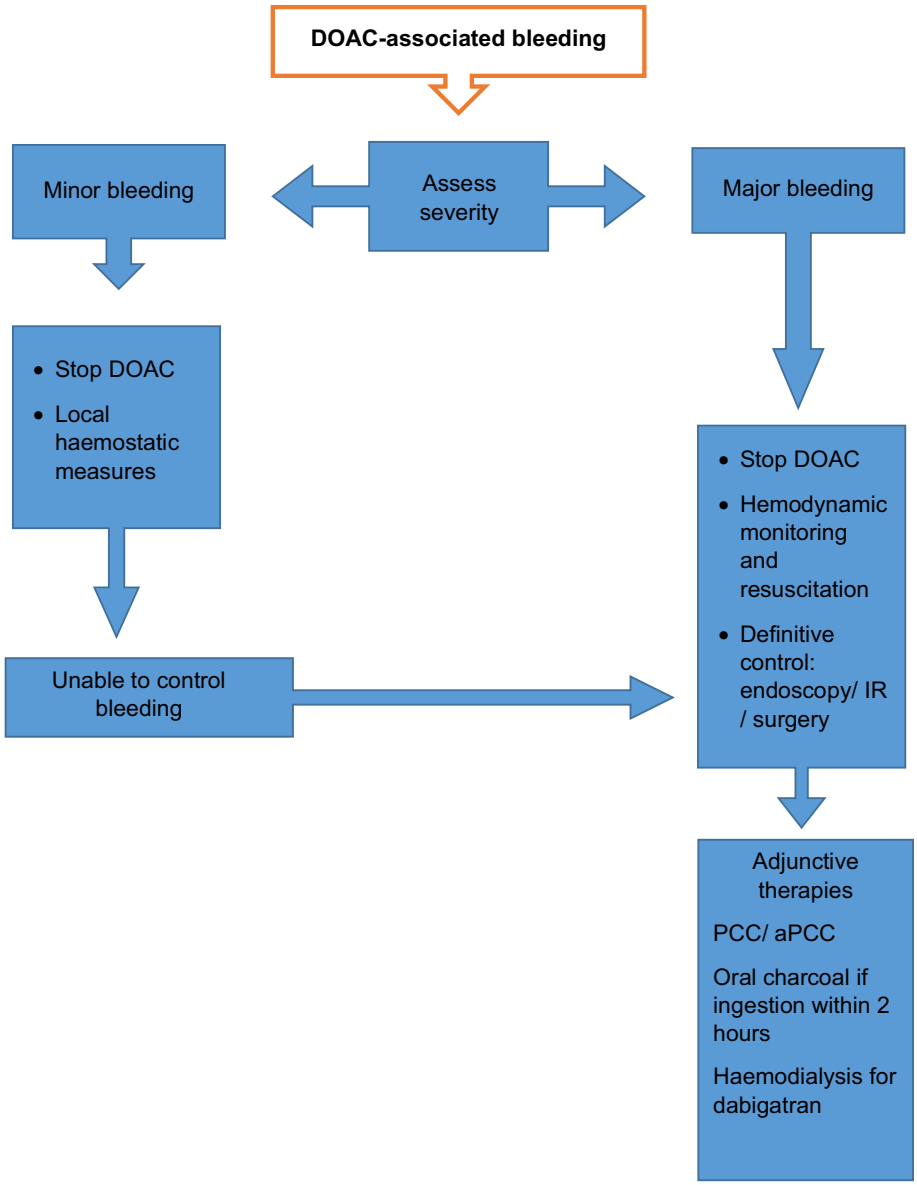

Fig. 3 Proposed algorithm for management of DOAC-associated bleeding

Antidotes for DOACs

Antidotes to DOACs for use in emergency situations are in various stages of development. Although all anticoagulants can produce bleeding, the outcomes of major bleeds with DOACs are no worse than those with VKAs even in the absence of clinically available antidotes [49]. Idarucizumab (Praxbind®) is a humanised monoclonal antibody fragment (Fab) that binds to dabigatran with higher affinity than the binding affinity of dabigatran to thrombin, and thereby neutralises its anticoagulant effect. It is administered 5 g IV and is available in the UK, being licensed for use in the United States and Europe. Andexanet alfa (PRT 064445), the antidote for the oral factor Xa inhibitors, is a modified recombinant form of factors Xa that binds directly to the factor Xa inhibitors rivaroxaban, and apixaban is undergoing phase III investigation [50]. Aripazine (PER977, Ciraparantag), a small molecule reported to reverse the anticoagulant effect of all of the DOACs, is at an earlier stage of development [51].

Challenges and Controversies

There remain several unresolved issues with DOAC use. The cost of DOACs is far higher than warfarin limiting access in many healthcare systems. The safety profile of DOACs has been subject to scrutiny due to the lack of a widely available specific antidote. With shorter half-lives than warfarin, adherence to DOACs is essential. There is

currently insufficient information about dosing of the DOACs in patients at extremes of body weight. Recent guidelines from the ISTH recommend avoiding DOACs in patients with a body mass index (BMI) above 40 [52].

Bleeding with the DOACs seems to be organ-bed specific [53]. The risk of gastrointestinal bleeding is higher with dabigatran at the 150 mg BD dose and with rivaroxaban and edoxaban at the 20 mg and 60 mg QDS doses, respectively. The risk also appears to be dose-dependent for both dabigatran and edoxaban. The reason behind this increase in risk remains unclear. It has been suggested that presence of the unabsorbed drug in the gastrointestinal tract could incite bleeding from ulcers, polyps or other lesions. [9, 17, 54, 55] The COMPASS study (Rivaroxaban for the Prevention of Major Cardiovascular Events) is evaluating the potential for concomitant administration of a proton pump inhibitor in reducing the risk of upper gastrointestinal haemorrhage.

Conclusion

The development and increasing use of the direct oral anticoagulants has changed the therapeutic landscape of anticoagulation and revolutionised our approach towards prevention and treatment of thromboembolism [56]. The principal advantages of these agents include their rapid onset and offset of action, predictable and stable pharmacokinetics and fixed dosing requirements precluding routine monitoring. The periprocedural management of patients being treated with DOACs remains a challenge, and it is of critical importance for Interventional Radiologists to familiarise themselves with this class of drugs in order to ensure their safe and effective use in specific clinical situations.

Compliance with Ethical Standards

Conflict of interest On behalf of all authors, the corresponding author declares that they have no conflicts of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed Consent Does not apply.

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