
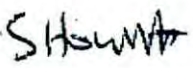



Guidance For The Management Of Bleeding In Patients Taking Anticoagulant, Anti-Platelet And Fibrinolytic Drugs

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Executive Sign-Off

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July 2023	January 2021	Warfarin risk factors for bleeding updated in line with reference - Beyth RJ, Quinn LM, Landefeld CS. Prospective evaluation of an index for predicting the risk of major bleeding in outpatients treated with warfarin. Am J Med. 1998;105:91–9. Reference also added.	Page 3, Section 2.1 Factors associated with an increased risk of bleeding on Warfarin Page 13, Section 3 - References
July 2023	January 2021	Warfarin flow chart title updated and flow content amended. Identified on index as 2.1.1.	Page 4, Section 2.1.1
May 2023	January 2021	Inclusion of edoxaban in section 2.3.	Page 7, Section 2.3
May 2023	January 2021	Removal edoxaban section 2.4 and subsequent reordering of sections.	Page 9, Section 2.4

* Changes marked should detail the section(s) of the document that have been amended, i.e. page number and section heading.

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Guidance For The Management Of Bleeding In Patients Taking Anticoagulant, Anti-Platelet And Fibrinolytic Drugs

1. Introduction

Around 1 to 1.5% of the population take anticoagulant drugs to prevent thrombosis. The main complication of all anticoagulants is bleeding. Major or life-threatening bleeding is seen in up to 2% of patients on anticoagulants each year.

Anticoagulation may result in excessive prolongation of clotting times with or without bleeding. It should also be noted that some anticoagulant drugs produce little or no prolongation of commonly used screening coagulation tests like the prothrombin time (PT) and activated partial thromboplastin time (APTT).

1.1. Guidance Application

This guidance is based on the available evidence and on relevant licensing of reversal agents. The guidance does not deal with the peri-operative management of patients on anticoagulants.

1.2. Aims

The main aims of this guidance are to prevent bleeding in patients who are over-anticoagulated on warfarin or an alternative coumarin and to treat bleeding in those taking warfarin or a direct oral anticoagulant (DOAC) e.g. dabigatran, edoxaban, apixaban or rivaroxaban in whom it has occurred. Guidance is also included on the management of patients receiving heparins, unfractionated and low molecular weight, fibrinolytic drugs and anti-platelet therapy.

1.3. Classification of Haemorrhage

Fatal

Death due to haemorrhage (Demonstrated at autopsy, radiologically or clinically obvious).

Major♥

Intracranial (Computerised Tomography (CT) or Magnetic Resonance Imaging (MRI))

Retroperitoneal (CT or MRI documented)

Intra-ocular (excludes conjunctival)

Spontaneous muscle haematoma associated with compartment syndrome

Pericardial

Non-traumatic intra-articular

Any invasive procedure to stop bleeding

Active bleeding from any orifice plus BP \leq 90mmHg systolic, or oliguria or \geq 20g/l fall in haemoglobin

Minor

Any other bleeding that would not influence your decision to anti-coagulate a patient.

2. Medicines

2.1. Warfarin and other Coumarins

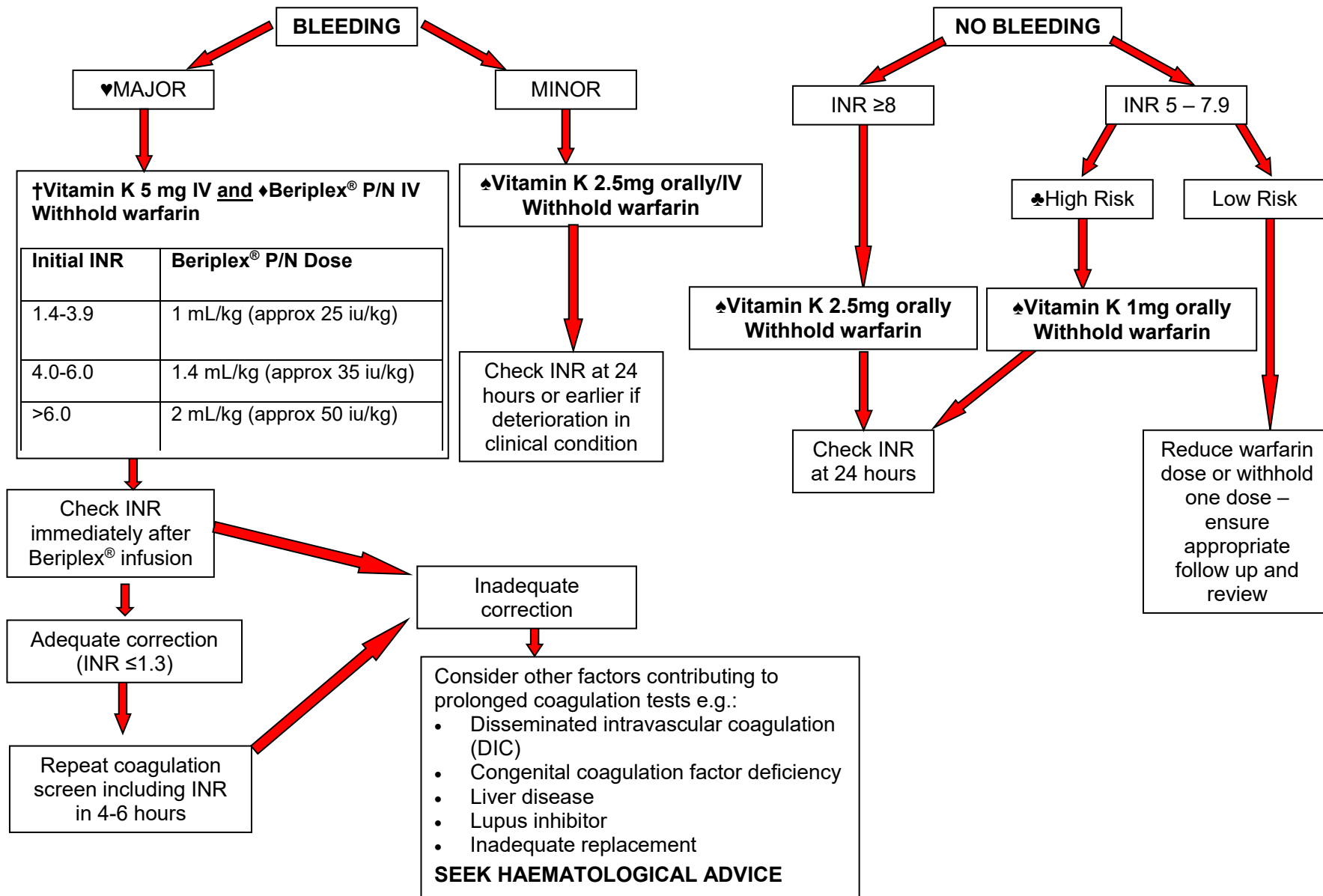
The reversal of warfarin and other coumarins is based on the immediate replacement of the depleted vitamin K dependent factors (II, VII, IX and X) and the reversal of warfarin activity by providing active vitamin K.

While there are randomised controlled studies to inform on the use of vitamin K, the recommendations on the use of the prothrombin complex concentrates which contain coagulation factors II, VII, IX and X (e.g. Beriplex®) are based on observational data and expert opinion.

This guidance is in keeping with the recommendations of the British Committee for Standards in Haematology (Keeling et al 2011).

The recommendations for partial reversal of anticoagulation in asymptomatic patients with INR values between 5 and 10 have been left in place despite the publication of a randomised controlled study which indicated little benefit in reversal for these patients in terms of the number of bleeding events which were prevented in comparison with a group who received placebo (Crowther et al 2009) – this remains under review.

2.1.1 Warfarin Reversal Flow Chart



Cautions in reversal of warfarin

◆ Beriplex® P/N contains heparin and is contraindicated in patients with heparin induced thrombocytopenia (present or previous).

Beriplex® P/N is also relatively contraindicated in patients with:

- 1) An increased risk of thrombosis.
- 2) Angina pectoris and after recent myocardial infarction.

Maximum single dose of Beriplex® is 5000 international units (IU).

Adhere to the product SmPC for administration. In all clinical situations an assessment of the likely risks and benefits of administration needs to be made.

In disseminated intravascular coagulation, prothrombin complex-preparations (e.g. Beriplex® P/N) may only be administered after termination of the consumptive state.

† Intravenous vitamin K may rarely cause anaphylaxis. Administration should be;

- By slow IV bolus
- Withheld in patients with a history of previous severe allergic reaction to vitamin K.

♠ Oral Vitamin K – preparation for injection (10mg/mL) Konakion® (Roche). Dose may be diluted, to mask taste, in a small amount of diluting juice/water after drawing up in an oral syringe.

♣ Standard risk patients do not require INR reversal at INR 5 – 7.9 but correction should be considered in “high risk” patients whose risk of bleeding is approximately 15 fold higher.

Factors associated with an increased risk of bleeding on Warfarin include:

- Age ≥65
- History of stroke
- History of GI bleeding
- Recent MI
- Anaemia with Hct <0.30
- Serum creatinine >132 µmol/l
- Diabetes Mellitus.

2.2. Dabigatran (Pradaxa®)

Dabigatran is a direct thrombin inhibitor. It is indicated in the prophylaxis of major orthopaedic surgery, for the acute management and long term prevention of recurrence of venous thromboembolism and for the prevention of cardioembolic events in patients with atrial fibrillation with risk factors for thrombosis. The reversal of dabigatran activity is achieved using idarucizumab (Praxbind®) which is a monoclonal antibody that is directed against the dabigatran molecule.

Indication

Idarucizumab (Praxbind®) is licensed for use in adults (≥ 18 years old) who have taken dabigatran in the last 48 hours, presenting with life/limb-threatening bleeding or requiring emergency surgery. The decision to use idarucizumab (Praxbind®) should be made by the physician-in-charge at Speciality Trainee Registrar (STR) grade or higher following risk, benefit consideration. For major haemorrhage classification see [page 2](#). For emergency surgery, the Thrombin Clotting Time (TCT) should be sent to the laboratory immediately. A normal TCT excludes the presence of dabigatran and so the need for idarucizumab (Praxbind®).

Dose and Method of Administration

Fixed dose of idarucizumab (Praxbind®) 5g in 100mLs (2 vials) as a bolus injection, over 10 minutes. Each vial contains 2.5g/50mL idarucizumab (Praxbind®). No dose adjustment is required in renal or hepatic impairment.

Monitoring

Monitoring for efficacy is clinical. It is recommended to send PT, APTT, fibrinogen, and Thrombin Clotting Time (TCT) pre and 30 minutes post idarucizumab (Praxbind®). A second dose of idarucizumab can be considered after at least 4 hours if on-going coagulopathic bleeding due to dabigatran is suspected. A normal TCT after idarucizumab (Praxbind®) excludes the presence of dabigatran / need for idarucizumab (Praxbind®). If the TCT is prolonged, further investigation is required and if proven, hypofibrinogenemia should be corrected before a second dose of idarucizumab (Praxbind®) is considered.

Contraindications

Previous severe or life-threatening reaction to idarucizumab (Praxbind®).

Caution

The safety and efficacy of idarucizumab (Praxbind®) is not established for children below age of 18, in pregnancy or lactation. There is a potential thrombotic risk from idarucizumab (Praxbind®) and/or from reversing dabigatran in prothrombotic patients. There is limited data on re-exposure to idarucizumab (Praxbind®).

Restarting Dabigatran

When clinically stable with adequate haemostasis, dabigatran can be restarted after 24 hours. Other antithrombotics can be started at any time. If re-starting dabigatran is to be delayed then mechanical or pharmacological thromboprophylaxis for venous thromboembolism (VTE) should be considered.

Prescribing Information (UK): [Praxbind](#)[®] idarucizumab 2.5g/50mL. Solution for injection/infusion.

2.3. Rivaroxaban (Xarelto[®]), Apixaban (Eliquis[®]) and Edoxaban (Lixiana[®])

Rivaroxaban, apixaban and edoxaban are direct inhibitors of activated factor X (Xa). Rivaroxaban and apixaban are licensed for the prevention of thrombosis in major orthopaedic surgery. All three are licensed for the acute management and long term prevention of recurrence of venous thromboembolism and for the prevention of cardioembolic events in patients with non-valvular atrial fibrillation with risk factors for thrombosis. Rivaroxaban is also licensed in the management of stable coronary artery disease and peripheral vascular disease and also for the management of post Acute Coronary Syndrome (ACS) in combination with anti-platelet therapy. Reversal of Xa inhibitors is achieved using andexanet alfa (Ondexxya[®]), a site inactivated decoy molecule without protease activity.

Indication

Andexanet alfa (Ondexxya[®]) is indicated for the rapid reversal of rivaroxaban and apixaban in adults (≥18 years old) who have taken either drug in the last 48 hours, presenting with major, life or limb-threatening bleeding. The decision to use andexanet alfa (Ondexxya[®]) should be made by the physician-in-charge at STR grade or higher following risk benefit consideration. For major haemorrhage classification see [page 2](#). The use of andexanet alfa (Ondexxya[®]) to reverse anticoagulation with rivaroxaban or apixaban to facilitate urgent surgery is not currently licensed.

Andexanet alfa (Ondexxya[®]) is also approved in NHS Grampian for reversal of edoxaban in patients with life-threatening or uncontrolled bleeding. **Please note this is off label/unlicensed use and treatment should only be prescribed after discussion with the on call Consultant Haematologist.**

Dose and mode of administration

Patients who had apixaban ≤5mg, edoxaban ≤30mg or rivaroxaban ≤10mg, or who had apixaban >5mg, edoxaban >30mg or rivaroxaban >10mg more than 8 hours previously, should be given low dose andexanet alfa (Ondexxya[®]) 400mg intravenous (IV) bolus (30mg/minute) then 480mg as an IV infusion over two hours (4mg/minute).

Patients who had apixaban >5mg, edoxaban >30mg or rivaroxaban >10mg within the preceding 8 hours or at an unknown time, should be given high dose andexanet alfa (Ondexxya[®]) 800mg IV bolus (30mg/minute) then 960mg as an IV infusion over two hours (8mg/minute).

Refer to Summary Dosing tables below.

Dosing regimens

	Initial intravenous bolus	Continuous intravenous infusion	Total number of 200 mg vials needed
Low dose	400mg at a target rate of 30mg/min	4mg/min for 120 minutes (480mg)	5
High dose	800mg at a target rate of 30mg/min	8mg/min for 120 minutes (960mg)	9

Summary of dosing for reversal for Xa inhibitors

FXa inhibitor	Last dose	Timing of last dose before Andexanet alfa initiation	
		< 8 hours or unknown	≥ 8 hours
Apixaban	≤ 5mg	Low dose	Low dose
	> 5mg/Unknown	High dose	
Edoxaban	≤ 30mg	Low dose	Low dose
	> 30mg/Unknown	High dose	
Rivaroxaban	≤10mg	Low dose	Low dose
	> 10mg/Unknown	High dose	

Monitoring

Monitoring for efficacy is clinical. It is recommend to send 2 citrate coagulation tubes and requesting PT, APTT, and fibrinogen along with a request for anticoagulant drug levels (specifying the appropriate anti-coagulant), pre and 30 minutes post-andexanet alfa (Ondexxya®). The drug levels will only require to be performed urgently in the event of perceived on-going coagulopathic bleeding. Measurement of Xa inhibitors following administration of andexanet alfa (Ondexxya®) is not reliable and will tend to overestimate residual anticoagulant levels.

Contraindications

Previous severe or life-threatening reaction to andexanet alfa (Ondexxya®).

Caution

The safety and efficacy of andexanet alfa (Ondexxya®) is not established for children below age of 18, pregnancy or lactation. There is a potential thrombotic risk from andexanet alfa (Ondexxya®) and/or from reversing rivaroxaban or apixaban in prothrombotic patients. There is limited data on re-exposure to andexanet alfa (Ondexxya®).

Restarting anticoagulation with rivaroxaban and apixaban

When clinically stable with adequate haemostasis, anticoagulation can be re-commenced. Clinical review of the risk, benefit of and the timing of re-starting anticoagulation should be carried out by the clinical team in charge of the patient. In the period before re-commencing therapeutic anticoagulation prophylaxis by mechanical and pharmacological means should be considered.

Prescribing Information (UK): Rivaroxaban ([Xarelto®](#)) Apixaban ([Eliquis®](#)), Edoxaban ([Lixiana®](#)), Andexanet Alfa ([Ondexxya®](#))

2.4. Heparins Unfractionated (UFH) and Low molecular weight (LMWH)

Unfractionated heparin (UFH) and low molecular weight heparins (LMWH) are the most commonly used parenteral anticoagulants in current clinical practice. Both are used in prophylaxis and the acute treatment of thrombotic events. UFH may be given as a bolus dose for both prophylaxis and treatment and may also be given as a continuous infusion for treatment of acute events. LMWH are almost always given by subcutaneous route whether in prophylactic or treatment doses. Protamine sulfate is a cationic peptide that binds to and stabilises heparins neutralising their anticoagulant effect.

Indication and monitoring.

Protamine sulfate is licensed for the reversal of heparins before surgery; after renal dialysis; after open-heart surgery; if excessive bleeding occurs and when an overdose has inadvertently been given.

Neutralisation of unfractionated heparin (UFH):

1mg of protamine sulfate will usually neutralise at least 100 IU of mucous heparin. The dose of protamine sulfate should be reduced if more than 15 minutes have elapsed since intravenous injection.

For example, if 30-60 minutes have elapsed since heparin was injected intravenously, 0.5-0.75mg protamine sulfate per 100 units of mucous heparin is recommended. If two hours or more have elapsed, 0.25-0.375mg per 100 units of mucous heparin should be administered.

If the patient is receiving an intravenous infusion of heparin, the infusion should be stopped and 25-50mg of protamine sulfate given by slow intravenous injection.

If heparin was administered subcutaneously, 1mg protamine sulfate should be given per 100 units of mucous heparin - 25-50mg by slow intravenous injection and the balance by intravenous infusion over 8-16 hours.

Monitoring

Patients should be carefully monitored using either the APTT or a calibrated anti-Xa assay 15 minutes post protamine bolus administration. Further doses may be needed because protamine is cleared from the blood more rapidly than heparin.

Neutralisation of low molecular weight (LMW) heparins:

A dose of 1mg per 100 units is usually recommended but the manufacturer's own guidelines should be consulted.

The anti-Xa activity of LMW heparins may not be completely reversible with protamine sulfate and may persist for up to 24 hours after administration.

The longer half-life of LMW heparins (approximately twice that of UF heparin) should also be borne in mind when estimating the dose of protamine sulfate required in relation to the time which has elapsed since the last heparin dose.

Theoretically, the dose of protamine sulfate should be halved when one half-life (4 hours) has elapsed since the last LMW heparin dose. Intermittent injections or continuous infusion of protamine sulfate have been recommended for the neutralisation of LMW heparin following subcutaneous administration, as there may be continuing absorption from the subcutaneous depot.

Monitoring

Patients should be carefully monitored. Further doses may be needed because protamine is cleared from the blood more rapidly than heparin, especially low molecular weight heparin.

Contraindication

Previous allergic reaction to protamine sulphate.

Caution

Previous exposure to protamine sulphate.
Males with infertility and post-vasectomy.

Re-starting treatment with heparins

Patients who have been receiving heparin will remain at risk of thrombosis after the bleeding episode. Re-introduction of heparin would require a balanced opinion on the risks and benefits of doing so and consideration of the doses employed.

Prescribing Information (UK): [Heparin \(unfractionated\)](#) and [Protamine Sulphate](#).

2.5. Fibrinolytic Drugs

There are several drugs (alteplase, streptokinase, urokinase) that are used for fibrinolysis in the context of ischaemic stroke, acute coronary syndromes and for the lysis of pulmonary emboli and rarely Deep Vein Thrombosis (DVT). These drugs in general have a short half-life ranging from 5 to around 20 minutes but the effects on coagulation may be more prolonged especially where there has been significant depletion of coagulation factors and fibrinogen. Fibrinolytic drugs are cleared by hepatic and renal mechanisms.

Indication and monitoring

The recommendations for the management of bleeding in patients who are undergoing or who have undergone fibrinolysis within 48 hours are as suggested by the current British Committee for Standards in Haematology (BCSH) guidance.

Stop infusion of fibrinolytic drugs and other antithrombotic drugs.

Administer Fresh Frozen Plasma (FFP) 12mL/kg by intravenous infusion.

Administer tranexamic acid 1g three times daily by intravenous infusion.

If there is depletion of fibrinogen, indicated by a claus fibrinogen level of <1.5g/L, administer cryoprecipitate or fibrinogen concentrate.

Further therapy should be guided by results of coagulation tests.

Caution and contraindication

Allergic reactions to any of the proposed agents used in reversal process.

Prescribing Information (UK): www.medicines.org.uk.

2.6. Antiplatelet therapy

There is widespread use of anti-platelet therapy in the acute and chronic management of a range of arterial disorders. This includes the use of oral preparations aspirin, prasugrel, clopidogrel, ticagrelor and dipyridamole. In addition eptifibatide, tirofiban and abciximab are used during coronary interventions. There are no specific antidotes for any of these drugs and because of their mechanism of action, bleeding can complicate their use for some time after administration. The outcomes of the PATCH study suggest that there is not a role for platelet transfusion in patients with anti-platelet therapy associated bleeding. As such the recommendations for the management of bleeding in these patients is based on other interventions to minimise the effect of drugs that might worsen bleeding and general pro-haemostatic drugs that might improve the situation.

The duration of the anti-platelet effect of these drugs is given below. This may help in decision making.

Aspirin	5-7 days
Clopidogrel	5-7 days
Prasugrel	5-7 days
Ticagrelor	3-5 days
Dipyridamole	24 hours
Tirofiban	4-8 hours
Eptifibatide	4-8 hours
Abciximab	24-48 hours

Treatment

Withhold or reverse any concurrently administered anticoagulant that is being used following the protocol for these above. Consider the use of tranexamic acid. Platelet transfusion can be considered but there is little evidence for a benefit in this and it may potentially worsen outcomes (based on the PATCH study).

Caution and contraindication

See above for each individual drug or group of drugs.
Prescribing Information (UK): www.medicines.org.uk.

3. References

Pollack et al. [Idarucizumab for Dabigatran Reversal – Full Cohort Analysis](#). N Eng J Med 2017;377:431-441

Connolly et al [Full Study Report of Andexanet Alfa for Bleeding Associated with Factor Xa Inhibitors](#) N Eng J Med 2019;380:1326-1335

Baharoglu, M.I. et al [Platelet transfusion versus standard care after acute stroke due to spontaneous cerebral haemorrhage associated with antiplatelet therapy \(PATCH\): a randomised, open-label, phase 3 trial](#). The Lancet 2016 (10038) pp2605-2613

Beyth RJ, Quinn LM, Landefeld CS. Prospective evaluation of an index for predicting the risk of major bleeding in outpatients treated with warfarin. Am J Med. 1998;105:91–9.

SmPC www.medicines.org.uk/emc/