bjh guideline

Guideline on the management of bleeding in patients on antithrombotic agents

Mike Makris,[1,2] Joost J. Van Veen,[2] Campbell R. Tait,[3] Andrew D. Mumford[4] and Mike Laffan[5] on behalf of the British Committee for Standards in Haematology

[1]Department of Cardiovascular Science, University of Sheffield, Sheffield, [2]Sheffield Haemophilia and Thrombosis Centre, Sheffield Teaching Hospitals NHS Trust, Sheffield, [3]Department of Haematology, Glasgow Royal Infirmary, Glasgow, [4]Bristol Heart Institute, Bristol Royal Infirmary, University of Bristol, Bristol, and [5]Imperial College Academic Health Sciences Centre, Hammersmith Hospital, London, UK

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The guideline writing group was selected to be representative of UK-based medical experts. The MEDLINE and EMBASE databases were searched systematically for publications in English from 1966 to June 2011 and 1980 to June 2011 respectively, using the following strategy: Approved and proprietary names of the antithrombotic agents described in the guideline were combined with terms relating to antidote, reversal, haemorrhage, (activated) prothrombin complex concentrate, factor VIII inhibitor bypass activity (FEIBA), Beriplex, Octaplex, recombinant activated factor VII (rFVIIa), Novoseven, fresh frozen plasma, tranexamic acid, antifibrinolytic, platelet transfusion, and desmopressin. Identified papers were also searched for additional references. The writing group produced the draft guideline which was subsequently revised by consensus by members of the Haemostasis and Thrombosis task Force of the British Committee for Standards in Haematology (BCSH). The guideline was then reviewed by a sounding board of approximately 50 UK haematologists, the BCSH and the British Society for Haematology Committee and comments incorporated where appropriate. Criteria used to quote levels and grades of evidence are as outlined in: http://www.bcshguidelines.com/BCSH_PROCESS/EVIDENCE_LEVELS_AND_GRADES_OF_RECOMMENDATION/43_GRADE.html.

The objective of this document is to guide healthcare professionals on the management of patients receiving antithrombotic drugs who experience significant bleeding or who require emergency surgery or an invasive procedure. Guidance on reversal of vitamin K antagonists (VKAs; warfarin, phenprocoumon, acenocoumarol (sinthrome) and phenindione has been described previously (Keeling *et al*, 2011).

Antithrombotic drugs are used increasingly in patient groups at greater bleeding risk. Although major haemorrhage is infrequent, management can be difficult especially with antithrombotics for which there are no specific reversal agents. Bleeding during antithrombotic therapy is associated with high morbidity and mortality (Linkins *et al*, 2003; Eikelboom *et al*, 2006; Mannucci & Levi, 2007). Before any antithrombotic treatment is started, the risks and benefits should be carefully considered. In this guideline we consider the management of bleeding in patients on the more widely used antithrombotic agents including heparin, anti-IIa and anti-Xa inhibitors, oral VKAs, anti-platelet drugs as well as the fibrinolytic agents.

General measures to stop bleeding

Non-pharmacological measures

In many cases, simple non-pharmacological measures and stabilization of the patient whist the antithrombotic is eliminated are sufficient to treat or prevent bleeding (Table I). Plasmapheresis or haemofiltration may rapidly reduce the plasma concentration of antithrombotic drugs that are not highly protein bound. However, these techniques are often inaccessible in emergency settings outside highly specialized units.

General haemostatic agents

Specific antidotes are not always available to reverse antithrombotic drugs in emergencies. However, general prohaemostatic agents, listed in Table II may be useful in some circumstances.

Recombinant activated factor VII (rFVIIa, Novoseven®), prothrombin complex concentrates (PCC) and activated PCC [APCC; e.g. factor VIII inhibitor bypass activity (FEIBA)] are often considered as agents for reversal of the effect of antithrombotic drugs. However, off-label use of rFVIIa for

Correspondence: Dr Mike Makris, Department of Cardiovascular Science, Royal Hallamshire Hospital, Glossop Road, Sheffield, S10 2JF.
E-mail: m.makris@sheffield.ac.uk

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Table I. General non-pharmacological measures.

Stop the antithrombotic drug
Document the timing and amount of the last drug dose and presence of pre-existing renal or hepatic impairment
Estimate the half-life and length of functional defect induced by the drug
Assess the source of bleeding
Request full blood count, prothrombin time, activated partial thromboplastin time, thrombin time, fibrinogen concentration, creatinine concentration
If available, request a specific laboratory test to measure the antithrombotic effect of the drug
Correct haemodynamic compromise with intravenous fluids and red cell transfusion
Apply mechanical pressure, if possible
Use endoscopic, radiological or surgical measures

Table II. Pharmacological and blood component pro-haemostatic therapies.

Tranexamic acid
Desmopressin
Fresh frozen plasma
Cryoprecipitate
Platelet transfusion
Fibrinogen concentrate
Prothrombin complex concentrate
Activated prothrombin complex concentrate
Recombinant factor VIIa

critical bleeding was associated with arterial thrombosis in 5·5% vs. 3·2% in placebo in all patient groups and 10·8% vs. 4·1% in placebo in patients >75 years (Levi *et al*, 2010). Efficacy of rFVIIa as a reversal agent has been demonstrated *in vitro*, in animal studies and single case reports, which are subject to publication bias. Reversal of the effect of antithrombotics is an unlicensed indication for rFVIIa (Sorour *et al*, 2010) but this agent is often considered as a last resort when all other measures have failed and the risks and benefits are carefully documented.

With the exception of the use of PCC to reverse warfarin and other VKAs, there is little evidence supporting the use of PCC and APCC as correction agents for other antithrombotics. PCC and APCC agents may increase thrombosis risk although this has not been evaluated in large-scale meta-analyses. PCC and APCC may be considered in settings of critical or refractory bleeding after thrombosis risk has been considered. The use of rFVIIa, PCC and APCC will be discussed in more detail in subsequent sections.

Fresh frozen plasma (FFP) may be a suitable reversal agent for warfarin or other VKA (if PCC is unavailable) and as a source of clotting factors in major haemorrhage. However, FFP has no proven efficacy as a reversal agent for antithrombotics other than warfarin, even those that cause prolonged prothrombin (PT) or activated partial thromboplastin (APTT) times by inhibiting coagulation factors (Crowther & Warkentin, 2009).

Specific measures

In the following sections, individual antithrombotics and options for reversal of the anticoagulant effect are discussed. With the exception of VKAs and unfractionated heparin (UFH), the evidence for individual approaches is often weak and limited to small case series and case reports. For some antithrombotics, clinical evidence to guide correction of the anticoagulant effect is absent and recommendations are based on theoretical considerations and animal studies.

Parenteral anticoagulants

Unfractionated heparin

The characteristics, monitoring and mechanisms of action of UFH were recently reviewed (Gray *et al*, 2008). At therapeutic intravenous (IV) doses, the plasma half-life of UFH is 45–90 min because of rapid cellular elimination. However, at higher doses, this mechanism becomes saturated and renal clearance results in a longer half-life (Hirsh *et al*, 2008). The pharmacokinetic clearance of UFH and pharmacodynamic effect varies between patients due to differences in plasma protein binding. UFH activity may be monitored with the APTT, activated clotting time (ACT) or thromboelastometric assays.

Given the short plasma half-life of UFH, treatment or prevention of bleeding can often be achieved by stopping UFH and general measures. UFH can be rapidly reversed with protamine sulphate, which is derived from fish sperm and forms a stable, inactive salt with heparin. Protamine dose may be calculated from the quantity of UFH administered in the 2 h prior to reversal using the assumption that 1 mg protamine neutralizes 80–100 units of UFH. For example, bleeding during an IV infusion of UFH 1250 units/h requires 25 mg protamine. Bleeding soon after a bolus dose of 5000 units requires 50 mg (Hirsh *et al*, 2008). The half-life of protamine is 7 min, which is shorter than UFH, thus, prolonged protamine administration may be necessary if UFH has been administered subcutaneously, causing entry into the circulation to be delayed (Hirsh *et al*, 2008). The reversal effect of protamine can be monitored by the APTT.

Protamine can cause severe allergic reactions including anaphylaxis, hypotension, bronchospasm and skin reactions in up to 10% of patients. Risk factors are previous exposure to protamine sulphate (including protamine-containing

insulin preparations), rate of administration, vasectomy and fish allergy (Porsche & Brenner, 1999). Protamine sulphate should be given slowly over >5 min (Crowther & Warkentin, 2008). Patients at risk may be pre-treated with corticosteroids and antihistamines. At higher doses, protamine may have significant anticoagulant and antiplatelet effects (Ammar & Fisher, 1997; Ni Ainle *et al*, 2009).

Recommendations

- **Stopping an UFH infusion and general haemostatic measures are often sufficient to stop or prevent bleeding (2C).**
- **Protamine sulphate (1 mg per 80–100 units UFH) will fully reverse UFH, but should be given slower than 5 mg/min to minimize the risk of adverse reactions.**
- **The maximum recommended dose of 50 mg protamine is sufficient to reverse UHF in most settings.**

Low molecular weight heparin

Low molecular weight heparins (LMWH) are derived from UFH through chemical or enzymatic depolymerization. The ratios of anti-Xa to anti-IIa activities vary between products depending on LMWH chain length. However the half-life of the anticoagulant activity of LMWH lasts approximately 4 h. The mechanism of action of LMWH and differences from UFH were recently reviewed (Gray *et al*, 2008). LMWH activity may be monitored with the anti-Xa test. Although LMWH may also prolong the APTT, this test should not be used to assess the extent of drug effect.

Protamine reverses approximately 60% of LMWH based on data from animal studies (Bang *et al*, 1991; Lindblad *et al*, 1987; Van Ryn-McKenna *et al*, 1990) and healthy human volunteers (Holst *et al*, 1994). The largest study using protamine in patients (Van Veen *et al*, 2011) described three patients requiring emergency surgery and 14 patients that were actively bleeding whilst receiving LMWH and who received protamine at doses suggested by the ACCP guidelines (Hirsh *et al*, 2008). Protamine prevented excessive bleeding in all the surgical patients and was effective in eight of 12 evaluable patients with active bleeding. Anti-Xa levels after protamine sulphate administration did not correlate with the likelihood of persistent bleeding (Van Veen *et al*, 2011).

Animal studies using rFVIIa for LMWH reversal show contradictory results (Chan *et al*, 2003; Lauritzen *et al*, 2008). Registry data indicate the successful use of rFVIIa in six patients with significant bleeding (Ingerslev *et al*, 2007), two of whom also received PCC but none of whom received protamine. Doses of rFVIIa varied between 20 and 120 μg/kg.

Recommendations

- **LMWH administration within 8 h of the time of requirement for correction of anticoagulation: give protamine sulphate (1 mg per 100 anti-Xa units of LMWH). If ineffective, consider further protamine sulphate 0·5 mg per 100 anti-Xa units (2C). Protamine sulphate should be given slower than 5 mg/min to minimize the risk of adverse reactions.**
- **LMWH administration greater than 8 h from the time of requirement for correction of anticoagulation: consider smaller doses of protamine (2C).**
- **Consider rFVIIa if there is continued life-threatening bleeding despite protamine sulphate and the time frame suggests there is residual effect from the LMWH contributing to bleeding. (2C).**

Danaparoid sodium

Danaparoid is a heparinoid consisting of a mixture of glycosaminoglycans with an anti-Xa/anti-IIa ratio > 20 (Hirsh, 1992). Danaparoid is excreted renally and has a plasma half-life of anti-Xa activity of approximately 24 h (Danhof *et al*, 1992). Danaparoid may be monitored by anti-Xa assay using a danaparoid standard. Major bleeding occurred in 8·1% of patients treated with danaparoid for heparin-induced thrombocytopenia (HIT) (Magnani & Gallus, 2006). Continued bleeding after cardiopulmonary bypass surgery (CPB) on danaparoid has been reported despite intensive blood product replacement (Schmahl *et al*, 1997; Westphal *et al*, 1997; Gitlin *et al*, 1998; Fernandes *et al*, 2000; Pamboukian *et al*, 2000). There is no specific antidote for danaparoid. However, plasmapheresis removes danaparoid effectively from the circulation (Schmahl *et al*, 1997). An *ex vivo* study showed partial restoration of thrombin generation when rFVIIa was added at supra-therapeutic doses to plasma spiked with danaparoid, but not with addition of APCC and FFP (Gatt *et al*, 2008).

Recommendations

- **There is no specific antidote for danaparoid. Management of bleeding should be through cessation of treatment and general haemostatic measures (2C)**
- **Plasmapheresis may be considered for critical bleeding.**

Fondaparinux

Fondaparinux is a synthetic pentasaccharide with indirect anti-Xa activity that achieves steady state antithrombotic activity after 3–4 d of use. The plasma half-life is 17–20 h with normal renal function and up to 72 h when creatinine clearance is <30 ml/min (Donat *et al*, 2002; Samama & Gerotziafas, 2003).

There is no specific antidote for fondaparinux. *In vitro* and *ex vivo* studies suggest that rFVIIa may enable at least partial correction as determined by global coagulation assays (Gatt *et al*, 2008; Desmurs-Clavel *et al*, 2009). A placebo

controlled study in healthy volunteers treated with therapeutic doses of fondaparinux and 90 μg/kg rFVIIa demonstrated correction of prolonged coagulation times and partial restoration of thrombin generation (Bijsterveld *et al*, 2002). Partial clinical efficacy of rFVIIa has been demonstrated in small case series (Dao *et al*, 2005; Huvers *et al*, 2005; Luporsi *et al*, 2011).

Recommendations

- **There is no specific antidote for fondaparinux. Management of bleeding should be through cessation of treatment and general haemostatic measures (2C).**
- **Recombinant FVIIa should be considered for critical bleeding (2C).**

Bivalirudin

Bivalirudin is a recombinant peptide thrombin inhibitor and is the only licensed hirudin in the UK. The lepirudin licence was recently withdrawn and so it is not considered in this guideline. Bivalirudin is cleared predominantly through proteolysis by thrombin (80%) and only 20% is excreted renally. The half-life is approximately 25 min, 1 h in severe renal impairment and 3·5 h in dialysis-dependent patients (Chew, 2002). Bivalirudin activity may be monitored by ACT or by APTT. The PT is minimally prolonged at therapeutic bivalirudin concentrations. The pharmacology and clinical applications of bivalirudin have been reviewed recently (Warkentin *et al*, 2008). Given the short plasma half-life of bivalirudin, cessation of treatment and general haemostatic measures are often sufficient for correction of the effect except when there is prolonged clearance due to renal impairment. An *in vivo* study showed that modified ultrafiltration after CPB surgery in patients with normal renal function reduced the half-life by 20% and reduced postoperative blood loss (Koster *et al*, 2008).

Recommendations

- **There is no specific antidote for bivalirudin. Management of bleeding should be through cessation of treatment and general haemostatic measures (2C).**
- **Exceptionally, haemodialysis, haemofiltration or plasmapheresis may be considered for critical bleeding (2C).**

Argatroban

Argatroban is a reversible direct thrombin inhibitor that is rapidly eliminated via the hepatic cytochrome P450 3A4/5 enzyme. The plasma half-life is 45 min. Argatroban is usually monitored by APTT ratio. However, argatroban also prolongs the PT, ACT and thrombin time.

There is no specific antidote for argatroban but given its short half-life, stopping the drug enables correction of the anticoagulation effect in most cases. Severe bleeding related to reduced elimination of argatroban after cardiac surgery was reported to be unresponsive to blood component treatments alone (Edwards *et al*, 2003; Gasparovic *et al*, 2004) and blood components in combination with rFVIIa (Malherbe *et al*, 2004; Genzen *et al*, 2010). Treatment with rFVIIa *ex vivo* restored abnormal thromboelastography parameters in blood samples from two patients treated with argatroban (Young *et al*, 2007). However, in an animal study of a different direct thrombin inhibitor (melagatran), rFVIIa had no effect on bleeding time whereas APCC reduced bleeding time (Elg *et al*, 2001). With yet another direct thrombin inhibitor, dabigatran, the drugs rVIIa, APCC and PCC exhibited activity in correcting the coagulopathy in animal models (Van Ryn *et al*, 2010a; Van Ryn *et al*, 2008). There are no data on the use of APCC in bleeding during argatroban treatment.

Recommendations

- **There is no specific antidote for argatroban. Management of bleeding should be through cessation of treatment and general haemostatic measures (2C).**

Oral anticoagulants

Warfarin

Guidelines for the management of patients on warfarin experiencing major or non-major bleeding or over-anticoagulation were included in a recent BCSH guideline on oral anticoagulation with warfarin (Keeling *et al*, 2011). For completeness, these recommendations have been included below.

Recommendations

- **All hospitals managing patients on warfarin should stock a licensed four-factor PCC (1C).**
- **Emergency anticoagulation reversal in major bleeding should be with 25–50 U/kg four-factor PCC and 5 mg intravenous vitamin K (1B).**
- **Recombinant factor VIIa is not recommended for emergency anticoagulation reversal (1B).**
- **Fresh frozen plasma produces suboptimal anticoagulation reversal and should only be used if PCC is not available (1C).**
- **Anticoagulation reversal for non-major bleeding should be with 1–3 mg intravenous vitamin K (1B).**
- **Patients with an international normalized ratio (INR) > 5·0 but who are not bleeding should have 1–2 doses of warfarin withheld and their maintenance dose should be**

reduced (1B). The cause of the elevated INR should be investigated (1C).

- **Asymptomatic patients with an INR of $\geq$ 8·0 should receive 1–5 mg of oral vitamin K (1B). The INR should be rechecked the following day in case an additional dose of vitamin K is required.**
- **For surgery that requires reversal of warfarin and that can be delayed 6–12 h, the INR can be corrected by giving intravenous vitamin K. For surgery that requires reversal of warfarin and which cannot be delayed for vitamin K to have time to take effect, the INR can be corrected by giving PCC and intravenous vitamin K. PCC should not be used to enable elective or non-urgent surgery (2C).**

Other vitamin K antagonists

Whilst warfarin is the main coumarin used in the UK and North America, the VKA drugs phenprocoumon, acenocoumarol (sinthrome) and phenindione are also available and widely used in some countries. All drugs in this class reduce functional levels of the vitamin K-dependent clotting factors (II, VII, IX and X) but have different effective half-lives. Following discontinuation of treatment, the anticoagulant effect of phenprocoumon lasts the longest, and acenocoumarol the shortest. The principles of reversal of the anticoagulant effect with vitamin K and PCC are the same as for warfarin. However, further administration of vitamin K should be considered for correction of VKAs with longer half-lives.

Recommendations

- **Emergency reversal of the effect of phenprocoumon, acenocoumarol and phenindione should be with 5 mg intravenous vitamin K and 25–50 units/kg four-factor PCC.**
- **For less severe bleeding or for correction of over anticoagulation, 1–5 mg of oral vitamin K is sufficient.**

Direct oral thrombin inhibitors – dabigatran

The pro-drug dabigatran etexilate is rapidly hydrolysed to the active form dabigatran, a direct thrombin inhibitor. Following oral administration, plasma levels peak within 2–3 h. In individuals with normal renal function, the half-life is 13 h (range 11–22 h; van Ryn *et al*, 2010b). Dabigatran is 80% eliminated by the kidneys and has a prolonged plasma half-life in patients with renal impairment (plasma half-life 22–35 h with creatinine clearance < 30 ml/min). It is used for surgical thromboprophylaxis at a dose of 150–220 mg once daily and for stroke prevention in atrial fibrillation (AF) at a dose of 110 or 150 mg twice daily. In the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial of dabigatran in atrial fibrillation the annual risk of major bleeding was 2·71% and 3·11% with the 110 and 150 mg dabigatran doses, respectively, in comparison to 3·36% for patients treated with warfarin (Connolly *et al*, 2009). It must be appreciated, however, that both these figures are conservative as this pivotal trial excluded many real-life situations of patients with extreme body weights, significant renal impairment or multiple co-morbidities. A major advantage of dabigatran is that its use does not involve monitoring its concentration or effect but this is also a disadvantage because in a bleeding patient it is difficult to be sure of its concentration due to variable effect on the different standard coagulation tests (van Ryn *et al*, 2010b). A normal thrombin time and a normal APTT imply that a high level of dabigatran is unlikely in the patient.

There are no published clinical trials or other high quality evidence addressing the management of bleeding on dabigatran. Van Ryn *et al* (2009) showed *in vitro* that activated charcoal was able to bind virtually all the dabigatran etexilate and dabigatran suspended in water, and it would be reasonable to recommend that activated charcoal is given orally to bleeding patients if they have had a dose of the drug within 2 h to prevent further absorption (van Ryn *et al*, 2010b). In view of the relatively short dabigatran half-life, minor bleeding should be managed by withholding further doses of the drug and using standard measures, such as direct pressure, simple surgical intervention and fluid replacement.

In an emergency, dabigatran plasma clearance would be expected to be accelerated using haemodialysis or haemofiltration because it has relatively low plasma protein binding at 35%. Supportive evidence is provided by the fact that haemodialysis effectively reduces the plasma level of dabigatran in patients with end stage renal disease (Stangier *et al*, 2010; van Ryn *et al*, 2010b). Van Ryn *et al* (2010c) also showed that charcoal haemoperfusion using the commercially available Gambro Adsorba Cartridge (containing activated carbon in the form of charcoal) was able to remove *c.* 85% of dabigatran suspended in bovine blood and circulating in an *in vitro* system. Only very limited reports on the use of these techniques in bleeding patients on dabigatran are available and the evidence for their support remains preliminary (Warkentin *et al*, 2012). Furthermore, their rapid deployment in settings outside intensive care units is likely to be challenging.

No antidote is available for use in patients with major or life-threatening bleeding on dabigatran. In the absence of this, rFVIIa, PCC and APCC have been investigated *in vitro*, *ex vivo* and in animal models. In a rat tail bleeding time model, rFVIIa and FEIBA (Van Ryn *et al*, 2008), and in a rabbit trauma model Beriplex (a four-factor PCC) were effective in correcting the coagulopathy (Van Ryn *et al*, 2010a). In an *in vitro* experiment using the calibrated automated thrombogram, rFVIIa failed to correct the suppressed thrombin generation induced by dabigatran in spiked platelet-rich plasma samples (Perzborn & Harwardt, 2007). In experiments on healthy volunteers, rFVIIa failed to correct the reduced thrombin generation of melagatran, another direct thrombin inhibitor (Wolzt *et al*, 2004), and more recently

this failure was also observed with a PCC (Eerenberg *et al*, 2011; Levi *et al*, 2011). At present the data on rFVIIa and APCC is preliminary and inconclusive and not based on bleeding humans, nevertheless until new knowledge becomes available it is reasonable to try these products in patients with life-threatening bleeding on dabigatran, having made a risk-benefit decision on an individual basis.

Recommendations

- **There is no specific antidote for dabigatran. Management of bleeding should be through cessation of treatment and general haemostatic measures (2C).**
- **In bleeding patients who have taken a dose of dabigatran in the last 2 h, consider oral activated charcoal to prevent further absorption (2C).**
- **If rapidly deployable, haemodialysis, haemofiltration and charcoal haemoperfusion offer the possibility of enhanced clearance of the active drug (2C).**
- **In situations with ongoing life-threatening bleeding PCC, APCC and rFVIIa should be considered (2C).**

Direct oral Xa inhibitors – Rivaroxaban and Apixaban

A number of direct oral factor Xa inhibitors are in development but so far only two have been licensed for thromboprophylaxis and/or treatment of venous thromboembolism and stroke prevention in AF. Following an oral dose, both rivaroxaban and apixaban reach a peak at 3 h and have half-lives of 7–9 and 9–14 h respectively, in patients with normal renal function. In both cases, 75% are metabolized by the liver and 25% are excreted unchanged by the kidneys. In the ROCKET AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) trial, the annual risk of major bleeding was 3·6% for 20 mg once daily rivaroxaban and 3·4% for warfarin (Patel *et al*, 2011). In the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial, which compared apixaban 5 mg twice daily with warfarin in AF, the annual risks of major bleeding were 2·13% and 3·09%, respectively (Granger *et al*, 2011). As these clinical trials restricted recruitment of some patient groups, such as at the extreme of body weight, significant renal impairment and multiple comorbidities, the real risk of bleeding experienced in clinical practice is likely to be higher.

As these drugs show high plasma protein binding they would not be expected to be dialysable. For minor bleeding, in view of the short half-life, supportive measures, such as direct pressure, minor surgical intervention and fluid replacement, should be tried.

No antidote is available for use in patients with major or life-threatening bleeding on rivaroxaban or apixaban. In the absence of this, rFVIIa and PCC have been investigated *in vitro*, *ex vivo*, and in animal models. In an *in vitro* study using the calibrated thrombogram with platelet-rich plasma spiked with rivaroxaban, the suppressed thrombin generation could be partially reversed with rFVIIa (Perzborn & Harwardt, 2007). In a different *in vitro* system using spiked whole blood and employing rotational thromboelastometry (ROTEM), only a modest correction was obtained following the addition of rFVIIa or PCC to the samples (Olesen *et al*, 2009). In a baboon animal model the effects of rivaroxaban on the bleeding time and coagulation tests could be partially reversed with both rFVIIa and the APCC (Gruber *et al*, 2008). In a rabbit model both PCC and rFVIIa were able to partially improve the laboratory parameters but did not reverse rivaroxaban-induced bleeding (Godier *et al*, 2012). In a controlled clinical trial in healthy volunteers, PCC was able to correct the prolonged prothrombin time and restore the suppressed thrombin generation induced by rivaroxaban (Eerenberg *et al*, 2011; Levi *et al*, 2011). Although so far most of the available data regarding reversal of effect are for rivaroxaban, in view of the common mode of action, similar results would be expected for apixaban but this remains to be proven. In an *in vitro* study of fibrin permeability and fibrin network structure, FEIBA® was able to only partially correct the defect induced by apixaban (Blomback *et al*, 2011).

In the absence of an antidote, based on animal studies results, PCC, rFVIIa and APCC may be tried after carefully balancing the risks and benefits associated with the use of these products.

Recommendations

- **There is no specific antidote for rivaroxaban. Management of bleeding should be through cessation of treatment and general haemostatic measures (2C).**
- **In situations with ongoing life-threatening bleeding, PCC, APCC and rFVIIa should be considered (2C).**

Anti-platelet drugs

Anti-platelet drugs have short plasma half-lives but may have a prolonged biological effect because of irreversible platelet inhibition (Table III). As there are no specific reversal agents, the treatment or prevention of bleeding requires general haemostatic measures, cessation of anti-platelet treatment or reversal of the effect of co-prescribed antithrombotics. However, many patients who are prescribed anti-platelet drugs are at high risk of arterial thrombosis. Therefore the safety of anti-thrombotic drug withdrawal and pro-haemostatic interventions should be considered carefully through a multi-disciplinary risk assessment. If anti-platelet agents are withdrawn they should be re-instated as soon as possible after haemostasis is secured (Howard-Alpe *et al*, 2007; Bhala *et al*, 2011; Korte *et al*, 2011). Platelet transfusion may be considered for emergency reversal of the anti-platelet effect but may confer a risk of arterial thrombosis.

Table III. The elimination half-life of antithrombotic drugs.

Drug	Elimination half-life	Time to normal platelet function/ coagulation activity after drug discontinuation
Heparins		
UFH	1–2 h	
LMWH	3–7 h	
Heparinoids		
Danaparoid	24 h	
Bivalirudin	25 min	
Argatroban	30–35 min	
Fondaparinux	17–20 h	
Antiplatelet drugs		
NSAIDs		24 h
Aspirin		5–7 d
Clopidogrel		5–7 d
Prasugrel		5–7 d
Ticagrelor		3–5 d
Tirofiban		4–8 h
Eptifibatide		4–8 h
Abciximab		24–48 h
Dipyridamole		24 h
Oral anticoagulants		
Warfarin	4–5 d	3–4 d
Rivaroxaban prophylaxis [> 30 ml/min CC]	7–9 h	
Rivaroxaban treatment [> 30 ml/min CC]	7–11 h	
Dabigatran [> 80 ml/min CC] (prophylaxis or treatment)	12–17 h	
Dabigatran [50–80 ml/min CC]	15 h	
Dabigatran [30–50 ml/min CC]	18 h	
Apixaban prophylaxis	12 h	
Fibrinolytic drugs		
Alteplase, anistreplase reteplase, streptokinase	4–24 min	24–48 h

For drugs where the antithrombotic effect does not depend on their plasma concentration, time to normalization of platelet function or coagulation is shown.

UFH, unfractionated heparin; LMWH, low molecular weight heparin; NSAIDs, non-steroid anti-inflammatory drugs; CC, creatinine clearance.

Aspirin

Aspirin inhibits platelet activation by inactivating platelet cyclooxygenase. Aspirin has a rapid onset of action after oral administration (<1 h but 3–4 h with enteric-coated preparations) and has a plasma half-life of *c.* 20 min. However, laboratory evidence of platelet inhibition may persist for 4 d because the effects of aspirin on individual platelets is irreversible (Li *et al*, 2012).

Aspirin increases the risk of surgical bleeding 1·5-fold, but does not increase the severity of bleeding for most procedures. Given that 10% of acute cardiovascular events are preceded by aspirin withdrawal and the average time interval from withdrawal to acute stroke and acute coronary syndrome are 14·3 and 8·5 d respectively, aspirin is not usually withdrawn before surgery (Burger *et al*, 2005). Several studies have demonstrated a lack of haematoma following neuroaxial anaesthesia while on low dose aspirin (Horlocker *et al*, 2003; Burger *et al*, 2005).

Desmopressin reduced the bleeding time in healthy aspirin-treated volunteers (Mannucci *et al*, 1986). However, desmopressin is relatively contraindicated in patients with cardiovascular disease and there is no evidence to support efficacy in this patient group. Similarly, rFVIIa reverses abnormal thrombin generation in platelet-rich plasma from aspirin-treated volunteers (Altman *et al*, 2006) but this agent has not been studied systematically in patients receiving aspirin.

Mixing aspirin-treated platelets *ex vivo* with 30–50% untreated donor platelets restored abnormal platelet aggregation responses (Vilahur *et al*, 2007; Li *et al*, 2012). In practice, infusion of 2–3 adult doses of donor platelets is usually effective for emergency reversal of the effect of aspirin in adults. There are no specific reversal agents for aspirin.

$P2Y_{12}$ antagonists

The $P2Y_{12}$ antagonists include the pro-drugs clopidogrel and prasugrel and the active drug ticagrelor. Clopidogrel may show a delayed onset of platelet inhibition of 4–8 h because it requires activation by two-stage hepatic metabolism. Prasugrel, which requires one-stage activation, and ticagrelor exert anti-platelet effect within 2–4 h. The active metabolites of clopidogrel and prasugrel have short plasma half-lives (*c.* 0·5 and *c.* 7 h respectively), although as they are irreversible $P2Y_{12}$ antagonists, the duration of platelet inhibition may be 5–7 d (Weber *et al*, 2001; Price *et al*, 2011) or longer (Li *et al*, 2012). Ticagrelor is a potent $P2Y_{12}$ antagonist that has a plasma half-life of 8–12 h and is more reversible than clopidogrel and prasugrel. However, the anti-platelet effect of ticagrelor may persist for 3–5 d (Nawarskas & Snowden, 2011). All the $P2Y_{12}$ antagonists are eliminated by hepatic inactivation (Giorgi *et al*, 2011).

Desmopressin shortened the bleeding time in healthy volunteers after exposure to clopidogrel (Mannucci *et al*, 1986; Leithauser *et al*, 2008) but safety concerns in patients with cardiovascular disease usually prevent use. Mixing platelets treated with P2Y12 antagonists *ex vivo* with untreated donor platelets restored abnormal platelet aggregation responses although a higher proportion of donor platelets was required than for correction of the aspirin effect (Vilahur *et al*, 2007; Li *et al*, 2012). The efficacy of platelet transfusion may be reduced in patients who have recently ingested clopidogrel. There are no specific reversal agents for the $P2Y_{12}$ antagonists.

Glycoprotein IIb/IIIa inhibitors

Glycoprotein (GP) IIb/IIIa inhibitors are parenteral drugs that prevent fibrinogen- mediated platelet aggregation and are usually administered with other anti-platelet drugs and parenteral anticoagulants to patients with acute coronary syndrome as an adjunct to percutaneous coronary intervention (PCI). In a meta-analysis of six pivotal randomized controlled clinical trials, the risk of major bleeding associated with GPIIb/IIIa antagonists (co-prescribed with other antithrombotics) was 2·4% compared to 1·4% in placebo or control groups (Boersma *et al*, 2002).

Abciximab

Abciximab is a monoclonal anti-GPIIb/IIIa antibody that has a rapid onset of action and a plasma half-life of *c.* 30 min. Abciximab is eliminated from plasma by rapid binding to platelets but platelets may remain inhibited for 12–24 h because of persistent binding to the GPIIb/IIIa fibrinogen receptor (Tcheng *et al*, 1994).

Moderate thrombocytopenia ($<50 \times 10^9$/l) was reported in 2·5–5·2% and severe thrombocytopenia ($<20 \times 10^9$/l) in 0·3–0·5% of patients receiving abciximab and may develop within 2–4 h of the start of infusion (Madan & Berkowitz, 1999); (Berkowitz *et al*, 1997). Thrombocytopenia typically resolves within 4–7 d of cessation of abciximab but carries high bleeding risk. Platelet transfusion is effective for thrombocytopenic bleeding after abciximab and has been proposed as a prophylactic measure for thrombocytopenia $<10 \times 10^9$/l (Madan & Berkowitz, 1999). Re-exposure to abciximab is associated with severe thrombocytopenia in 2·4% of recipients (Tcheng *et al*, 2001).

Tirofiban and eptifibatide

Tirofiban and eptifibatide are fully reversible blockers of the fibrinogen binding site on GPIIb/IIIa that have rapid onset of action and short plasma half-lives (tirofiban *c.* 1·5 h; eptifibatide *c.* 2·5 h). Both agents are eliminated by the kidneys (tirofiban *c.* 66% renal clearance; eptifibatide *c.* 50%) and confer increased bleeding risk in patients with renal impairment (Smith & Gandhi, 2001). However, in the absence of renal impairment, the bleeding risk diminishes rapidly after cessation of treatment (Peerlinck *et al*, 1993). Thombocytopenia is uncommon in patients receiving tirofiban and eptifibatide and a causal association has not been proven (Madan & Berkowitz, 1999).

Recommendations

- **Decisions to withhold anti-platelet drugs or to administer pro-haemostatic agents should be made after a careful multi-disciplinary assessment of the risks and benefits of intervention. (1C).**
- **Bleeding in patients during treatment with aspirin, $P2Y_{12}$ antagonists or GPIIa/IIIb inhibitors should be managed in the first instance with general haemostatic measures. If necessary, drug cessation and reversal of the effect of co-prescribed anticoagulants should also be considered (2C).**
- **Platelet transfusion (2–3 adult doses) should be considered as an additional measure for critical bleeding or prevention of bleeding before emergency surgery (2C).**
- **Platelet transfusion should be considered to prevent bleeding in severe thrombocytopenia ($<10 \times 10^9$/l) caused by abciximab (2C).**

Fibrinolytic drugs

The fibrinolytic agents currently licensed in the UK are: alteplase, tenecteplase, reteplase, urokinase and streptokinase. All five agents function indirectly by promoting generation of plasmin, which then mediates clot lysis.

Alteplase is recombinant native-type tissue plasminogen activator (tPA) with a plasma half-life of 4–8 min. It is cleared mainly by metabolism in the liver.

Tenecteplase is a recombinant modified form of tPA with six amino acid substitutions causing increased half-life of *c.* 20 min, increased resistance to PAI-1 inhibition and increased fibrin specificity (Melandri *et al*, 2009). It is cleared mainly by metabolism in the liver.

Reteplase is a recombinant truncated form of tPA (Simpson *et al*, 2006; Van de Werf, 1999). Reteplase is less specific to fibrin than tPA and thus, causes a greater systemic reduction in fibrinogen. The initial half-life is *c.* 15 min and it is cleared via kidney and liver.

Streptokinase binds plasminogen, forcing it into an active configuration to activate other free plasminogen molecules. It therefore lacks fibrin specificity and produces greater reduction in plasma fibrinogen. Peak fibrinolytic activity occurs about 20 min after administration and the plasma half-life of the drug is 23–39 min. However, the half-life of the antithrombotic effect of streptokinase is about 80 min.

Urokinase is a direct plasminogen activator and has partial fibrin specificity. It is eliminated rapidly from the circulation by metabolism in the liver with a half-life of 20 min. Elimination is delayed in patients with liver disease and impaired kidney function.

Bleeding after treatment with fibrinolytic drugs may arise through several mechanisms including plasmin-mediated lysis of fibrin clot and antiplatelet actions (Benedict *et al*, 1995; Moser *et al*, 1999; Serebruany *et al*, 2003; Gurbel *et al*, 2005). The fibrinolytics also reduce plasma concentrations of antiplasmin leading to plasminaemia and depletion of fibrinogen and other clotting factors, notably factor V (Tracy *et al*, 1997; Stangl *et al*, 1998). The magnitude of fibrinogen and factor V reduction does not correlate with the frequency of intracerebral haemorrhage (ICH) during treatment with fibrinolytic drugs (Tracy *et al*, 1997; Stewart *et al*, 2003).

Although the half-lives of the fibrinolytic drugs are themselves relatively short, their effect on coagulation parameters is much longer. After alteplase for stroke or myocardial infarction (MI), fibrinogen was lowest at 2–3 h, remained low at 24 h and returned to normal at 48 h (Stangl *et al*, 1998; Szabo *et al*, 2002; Tanne *et al*, 2006). A similar pattern was seen with reteplase (Hoffmeister *et al*, 2000). The factor V nadir occurs at approximately 1 h (Tracy *et al*, 1997).

Goldstein *et al* (2010) reported on 20/352 patients who developed ICH after thrombolytic therapy for stroke. None had fibrinogen < 1 *g*/l and only 11 received therapy, which included FFP, cryoprecipitate, vitamin K, platelets and aminocaproic acid. However, it is impossible to assess the benefit of these measures due to the very small numbers in each group. There are no clinical data regarding the efficacy of any measure to reverse fibrinolytic drugs *in vivo*. Recommendations are derived from expert opinion, and are consistent with previously published guidelines (Broderick *et al*, 2007; Uchino *et al*, 2011) and opinion (Wechsler, 2011).

Recommendations

For major bleeding (e.g. intracerebral) within 48 h of administration we recommend:

- **Stop infusion of fibrinolytic drugs and other antithrombotic drugs (1C).**
- **Administer FFP 12 ml/kg (2C).**
- **Administer intravenous tranexamic acid 1 g tds (2C).**
- **If there is depletion of fibrinogen, administer cryoprecipitate or fibrinogen concentrate (2C).**
- **Further therapy should be guided by results of coagulation tests (2C).**

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