ESC European Society of Cardiology

European Heart Journal (2023) **00**, 1–15
https://doi.org/10.1093/eurheartj/ehad119

STATE OF THE ART REVIEW
Thrombosis and antithrombotic treatment

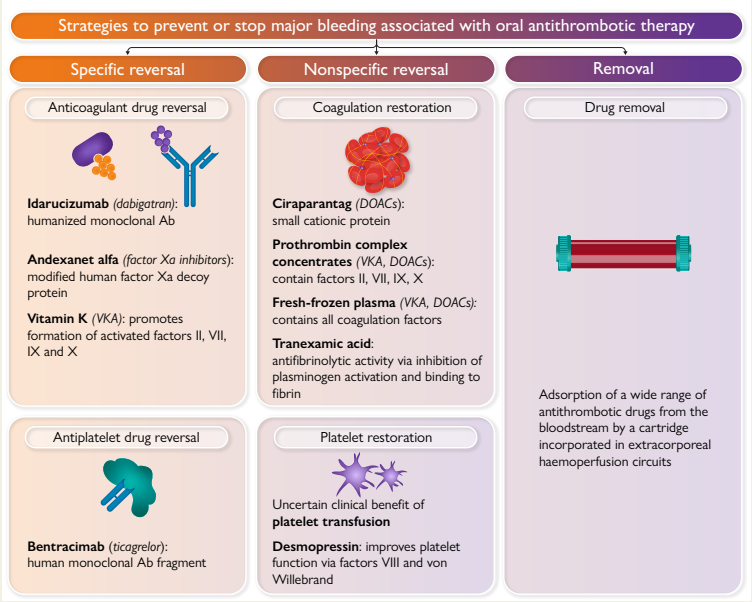
Reversal and removal of oral antithrombotic drugs in patients with active or perceived imminent bleeding

Davide Cao [1,2,3], Nicolas Amabile [4], Mauro Chiarito [2,5], Victoria T. Lee[6], Dominick J. Angiolillo[7], Davide Capodanno [8], Deepak L. Bhatt[9], Michael J. Mack[10], Robert F. Storey[11], Michael Schmoeckel[12], C. Michael Gibson[13], Efthymios N. Deliargyris[14], and Roxana Mehran [1]*

[1]Center for Interventional Cardiovascular Research and Clinical Trials, The Zena and Michael A. Wiener Cardiovascular Institute, Icahn School of Medicine at Mount Sinai, One Gustave L. Levy Place, Box 1030, New York, NY 10029-6574, USA; [2]Department of Biomedical Sciences, Humanitas University, Pieve Emanuele-Milan, Italy; [3]Department of Cardiology, Humanitas Gavazzeni, Bergamo, Italy; [4]Department of Cardiology, Institut Mutualiste Montsouris, Paris, France; [5]Department of Cardiology, IRCCS Humanitas Research Hospital, Rozzano-Milan, Italy; [6]PAVmed Inc., New York, NY, USA; [7]Division of Cardiology, University of Florida College of Medicine, Jacksonville, FL, USA; [8]Division of Cardiology, Azienda Ospedaliero Universitaria Policlinico 'G. Rodolico-San Marco', University of Catania, Catania, Italy; [9]Mount Sinai Heart, Icahn School of Medicine at Mount Sinai, New York, NY, USA; [10]Department of Cardiac Surgery, Baylor Scott and White Health, Plano, TX, USA; [11]Department of Infection, Immunity and Cardiovascular Disease, University of Sheffield, Sheffield, UK; [12]Department of Cardiac Surgery, Asklepios Klinik St. Georg, Hamburg, Germany; [13]Division of Cardiovascular Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA; and [14]CytoSorbents Corporation, Princeton, NJ, USA

Received 2 August 2022; revised 2 February 2023; accepted 17 February 2023

Graphical Abstract



In case of ongoing major bleeding, rapid and effective restoration of normal hemostatic functions with reversal agents on top of standard supportive measures may be required to successfully stop the bleeding. When major bleeding risk can be anticipated (e.g. due to the need for urgent invasive surgical procedures), antithrombotic drug removal and some reversal strategies may be considered before proceeding to surgery to mitigate perioperative bleeding risk. Bold text indicates reversal agents, parentheses indicate antithrombotic drugs that are reversed. Ab, antibody; DOACs, direct oral anticoagulants; VKA, vitamin K antagonists.

* Corresponding author. Tel: +1 212 659 9649, Fax: +1 (646) 537 8547, Email: roxana.mehran@mountsinai.org; Twitter: @Drroxmehran

Abstract

Remarkable progress has been made in the pharmacological management of patients with cardiovascular disease, including the frequent use of antithrombotic agents. Nonetheless, bleeding complications remain frequent and potentially life-threatening. Therapeutic interventions relying on prompt antithrombotic drug reversal or removal have been developed to assist clinicians in treating patients with active bleeding or an imminent threat of major bleeding due to urgent surgery or invasive procedures. Early phase studies on these novel strategies have shown promising results using surrogate pharmacodynamic endpoints. However, the benefit of reversing/removing antiplatelet or anticoagulant drugs should always be weighed against the possible prothrombotic effects associated with withdrawal of antithrombotic protection, bleeding, and surgical trauma. Understanding the ischemic-bleeding risk tradeoff of antithrombotic drug reversal and removal strategies in the context of urgent high-risk settings requires dedicated clinical investigations, but challenges in trial design remain, with relevant practical, financial, and ethical implications.

Keywords Reversal • Removal • Bleeding • Surgery • Antithrombotic drugs • Oral anticoagulants • Antiplatelet therapy

Introduction

Antithrombotic drugs are mainstay therapy for the secondary prevention of patients with established cardiovascular disease, including those with coronary, cerebrovascular, and peripheral artery disease, atrial fibrillation, and venous thromboembolism. These drugs have been shown to reduce recurrent ischemic events and to provide a consistent survival benefit.[1] Nonetheless, the use of antithrombotic therapies is encumbered by a well-recognized risk of bleeding complications,[2] which may have catastrophic consequences.[3]

About 40 000 tons of aspirin are produced each year worldwide.[4] In the USA alone, >50 million patients take aspirin while >4 million are treated with oral anticoagulant therapies.[4,5] The worldwide sales for direct-acting oral anticoagulants (DOACs) reached ~8 billion US dollars in 2015 and are continuing to grow at a rapid rate.[6] These numbers convey the idea of how many patients are potentially exposed to the bleeding side effects of antithrombotic drugs, with prognostic implications similar to the thrombotic events they are meant to prevent.[7]

Bleeding risk largely depends on the pharmacodynamic and pharmacokinetic attributes of each drug but persists even for those with the safest risk profiles. For instance, the widespread use of DOACs was thought to overcome the practical limitations of vitamin K antagonists (VKA) and to significantly reduce hemorrhagic complications. Nonetheless, a growing proportion of emergency department admissions are still linked to DOAC-related bleeding.[8,9] Notably, bleeding risk is further exacerbated in cases of combination therapy with two or more antithrombotic agents, as is often the case for patients on oral anticoagulants with acute coronary syndrome (ACS) or undergoing percutaneous coronary interventions (PCI).[10,11]

Raising awareness about the prognostic impact of bleeding prompted the search for management strategies aimed at preventing and, if necessary, treating hemorrhagic events related to antithrombotic therapies.[12,13] This review summarizes the evidence base for and practical approaches to antithrombotic drug reversal and removal strategies in patients facing active or an imminent threat of bleeding and critically appraises the challenges in clinical trial design and interpretation when studying reversal or removal of antithrombotic drugs in different clinical settings.

Reversal agents

Reversal of antithrombotic drugs may be used to prevent the detrimental consequences of bleeding. In addition to pooled platelet and coagulation factors supplementation, newer targeted strategies for antithrombotic drug reversal include monoclonal antibodies and recombinant factors that bind to the specific drug (*Table 1*). It must be noted that reversal agents are not themselves hemostatic agents and reversal is only part of a multimodal approach to antithrombotic drug-associated bleeding.

Reversal of antiplatelet drugs

Reversal of ticagrelor

Bentracimab is a neutralizing recombinant human immunoglobulin G1 monoclonal antibody fragment that binds to free ticagrelor and its active metabolite with high affinity, ~100-fold greater than the affinity of ticagrelor for the $P2Y_{12}$ receptor.[14] In a Phase 1 randomized, placebo-controlled trial in healthy volunteers, bentracimab reversed the ticagrelor-induced platelet inhibitory effect with excellent tolerability and no prothrombotic rebound effect in platelet reactivity.[15,16] Drug reversal occurred shortly (within 5 min) following treatment administration and was sustained for 16–24 h in patients who received the highest doses.[16] The clinical effects of bentracimab have been investigated in the REVERSE-IT trial, a Phase 3, single-arm study enrolling 200 patients with reported use of ticagrelor within the prior 3 days who presented with uncontrolled major or life-threatening bleeding or who required urgent surgery or invasive procedure. A prespecified interim analysis of the first 150 patients, of whom 142 required urgent surgery (mainly coronary artery bypass grafting) and 8 had major hemorrhage, demonstrated immediate and sustained reversal of ticagrelor's platelet inhibition within 5–10 min following infusion, with more than 90% of patients achieving protocol-defined good or excellent hemostasis within 24 h. There were eight non-fatal thrombotic events (5.3%), none considered to be related to bentracimab.[17]

Platelet transfusion

Platelet transfusion is theoretically a valid option for patients on oral antiplatelet agents with an urgent need to restore platelet function because of ongoing life-threatening bleeding. However, the effectiveness of platelet transfusion is contingent on the pharmacodynamic and pharmacokinetic characteristics of the specific antiplatelet drug, the time of last drug intake, and the bleeding site and mechanism (traumatic or spontaneous).[18] Moreover, when translated to clinical practice, the evidence in support of platelet transfusion in an urgent setting remains relatively scarce.

Platelet transfusion seems to adequately reverse the inhibitory effects of aspirin and, at higher doses, also clopidogrel and prasugrel.[19,20] Meanwhile, the efficacy of transfusion appears to be reduced in ticagrelor-treated patients, particularly within few hours of last drug

Table 1 New agents for antithrombotic drug reversal

Agent	Drug reversed	Structure	Mechanism of action	Mode of administration	Dosage(s)	Onset of action	Offset of action
Bentracimab	Ticagrelor	Human monoclonal antibody	Antigen-binding fragment	i.v. bolus (10 min) followed by loading (4 h) and maintenance (12 h) infusions	6 g bolus; 6 g loading infusion; 6 g maintenance infusion	5 min	24 h
Idarucizumab	Dabigatran	Humanized monoclonal antibody	Thrombin analogue	Two i.v. boluses or 5–10 min infusions (no longer than 15 min apart)	2 × 2.5 mg	<5 min	24–72 h
Andexanet alfa	Direct and indirect factor Xa inhibitors[a]	Recombinant truncated human factor Xa variant	Decoy receptor	i.v. bolus followed by 2-h infusion	400–800 mg bolus; 480–960 mg infusion	2 min	12 h
Ciraparantag	All DOACs, heparin and fondaparinux	Small cationic molecule	Hydrogen bonding and charge–charge interactions with DOACs and heparins	i.v. bolus	100–300 mg	5–10 min	24 h

i.v., intravenous; DOACs, direct oral anticoagulants.
[a]Limited efficacy for low-molecular-weight heparin.

intake.[21–26] To avoid inhibition of the newly transfused platelets, transfusions should be given only after the active forms of irreversibly acting antiplatelet drugs are no longer present at therapeutic plasma concentrations (i.e. at least 2 h from the last dose of aspirin or 4–5 h with enteric-coated preparations and 4 h from the last dose of the thienopyridine clopidogrel and prasugrel when absorption is not delayed by opiate). Ticagrelor, however, binds to the $P2Y_{12}$ receptor reversibly. Hence, in addition to unbound ticagrelor, dissociation of reversibly bound ticagrelor may redistribute to the transfused platelets.[27] As timing is critical in urgent scenario, these pharmacological properties limit the ability to address urgent reversal using platelet transfusions.

A single-center randomized study of patients undergoing emergency craniotomy for hypertensive basal ganglia hemorrhage found that, among those with an aspirin effect detectable by aggregometry, one or two units of previously frozen apheresis platelets were associated with lower postoperative hemorrhage and mortality.[28] By contrast, the multicenter Platelet Transfusion in Cerebral Hemorrhage (PATCH) trial failed to demonstrate a benefit of platelet transfusion among 190 patients with intracerebral hemorrhage and a Glasgow Coma Scale ≥8 while on antiplatelet therapy (nearly 80% on aspirin).[29] Platelet transfusions were associated with a higher risk of death or dependence at 3 months. In addition, serious adverse events were more common in the group of patients receiving platelet transfusion, while the enlargement of the intracranial hemorrhage was comparable between the two arms.[29] Similar findings have been reported from retrospective studies in patients with major gastrointestinal bleeding.[30] The reasons behind these unfavorable outcomes are poorly understood, but possible hypotheses include the increased risk of thrombotic events and the proinflammatory effects of any transfusions.[31,32]

Reversal of anticoagulant drugs

The enthusiasm for the emerging role of DOACs was initially dampened by concerns about the lack of targeted reversal strategies, such as for VKA. More recently, specific antidotes have been approved or are under development for patients treated with direct thrombin inhibitors (dabigatran) or factor Xa inhibitors (rivaroxaban, edoxaban, apixaban, betrixaban).

Reversal of vitamin K antagonists

In patients with VKA-associated bleeding, prothrombin complex concentrates (PCC) and activated PCC (aPCC) can restore hemostasis and normalize the international normalized ratio (INR) within few minutes.[33] PCC come in both three- and four-factor complexes that include the vitamin K-dependent cofactors II, IX, and X. The four-factor complexes include a higher concentration of factor VII and are generally preferred over three-factor PCC.[34] Caution should be exercised with PCC as overuse in presence of normalized INR may elicit a prothrombotic state, with an increased risk of venous and arterial thrombosis.[35]

If PCC are not available, fresh frozen plasma (FFP) may be considered.[36] FFP contains plasma proteins plus all coagulation factors and is prepared by removing plasma from donated whole blood and freezing it at −18°C or lower. The risks commonly associated with plasma transfusion include acute lung injury, circulatory overload, and allergic reactions.[37]

Vitamin K (phytomenadione) reverses the anticoagulant effect of VKA (i.e. warfarin, acenocumarol, and phenprocoumon), is administered intravenously (to ensure a faster and more predictable effect) or orally, can be guided by INR, and can be repeated every 12 h in case of persistent INR elevation.[38] As vitamin K takes several hours to exert its reversal effect, it is generally administered in combination with PCC or FFP to counteract the long half-life of warfarin. The use of vitamin K as reversal agent is not intrinsically linked to an increased thrombotic risk,[39] but the risk of anaphylaxis should be carefully considered.[40]

Reversal of factor IIa (thrombin) inhibitors

The direct thrombin inhibitor dabigatran can be specifically inhibited by idarucizumab. This humanized monoclonal antibody irreversibly binds to free and thrombin-bound dabigatran with a 350-fold greater affinity

than thrombin.[41,42] Indications for treatment include reversal of dabigatran, when needed, for emergency surgery/urgent procedures or life-threatening or uncontrolled bleeding.[43] Idarucizumab infusion was found to immediately reduce circulating unbound-dabigatran, reverse dabigatran-induced anticoagulation, and restore normal hemostasis.[42,44,45] In the Phase 3 single-arm RE-VERSE AD study, which included patients with severe uncontrolled gastrointestinal or neurological bleeds or undergoing urgent surgery that could not be delayed for at least 8 h, idarucizimab rapidly and consistently reversed the anticoagulant effect of dabigatran.[44,46] In the bleeding cohort, time to cessation of bleeding was 2.5 h, while in the surgical cohort, time to initiation of the procedure was 1.6 h, with surgeon assessment of periprocedural hemostasis being 'normal' in 93.4% of cases.[44,46] At 90 days, thrombotic events had occurred in 6.3% of the bleeding cohort and 7.4% of the surgical cohort, which the investigators attributed to the high-risk profile of the patients included in the study.

Reversal of factor Xa inhibitors

Andexanet alfa is a specific reversal agent that neutralizes the anticoagulant effects of both direct and indirect factor Xa inhibitors. This recombinant modified human factor Xa decoy protein is enzymatically inactive but binds with high affinity to the active site of apixaban, rivaroxaban, edoxaban, unfractionated and low-molecular-weight heparin, and fondaparinux.[47] Andexanet alfa sequesters factor Xa inhibitors within the vascular space and rapidly normalizes hemostasis, as shown in a Phase 2 dose-ranging study involving healthy volunteers.[48] Andexanet alfa is also efficient in reducing anti-factor Xa activity and restoring hemostatic functions in patients with acute major bleeding associated with the use of either apixaban or rivaroxaban. In the Phase 3b/4 ANNEXA-4 study, 82% patients achieved excellent or good hemostasis assessed 12 h after the end of the infusion.[49] Nonetheless, concerns have been raised regarding the high rates of thrombotic events (10%), including ischemic stroke (4%) and deep-vein thrombosis (4%). Moreover, andexanet alfa causes reversal of and unresponsiveness to the anticoagulant effects of heparin and should not be used for patients requiring urgent heparinization such as cardiopulmonary bypass during surgery.[50,51]

Non-specific anticoagulant reversal

Ciraparantag is a small, synthetic, water-soluble cation that binds non-covalently to heparins and DOACs (both factor Xa and direct thrombin inhibitors).[52] *In vitro* and preliminary clinical data demonstrated that ciraparantag rapidly reversed factor Xa inhibitor–induced anticoagulation, was well tolerated, displayed a prolonged pharmacodynamic effect, and reduced blood loss in animal models.[52–54] Two recent dose-ranging trials showed sustained reversal of DOAC activity achieved with 60 mg ciraparantag for apixaban and 180 mg ciraparantag for rivaroxaban among healthy subjects aged 50–75 years.[55] Although seemingly promising, the potential use of ciraparantag as a therapeutic reversal agent in phase 3 clinical trials is yet to be studied. Moreover, when compared to other reversal molecule including andexanet alfa, ciraparantag was found to have weaker affinity and direct reversal activity for heparins, rivaroxaban, and edoxaban.[56]

PCC and aPCC have been proposed as second-line strategies when the specific DOAC reversal agent is not available, despite debated evidence.[57] PCC can induce a non-specific reversal of DOAC-related coagulopathy by overloading the coagulation cascade with upstream factors.[57] However, some of these factors could also be in turn inhibited by the circulating unbound DOAC metabolites, which limits their effectiveness and explains the wide variability in hemostasis restoration. In addition, the use of PCC is also limited by their potential prothrombotic effects, although the extent of this risk is unknown and likely varies in different settings.[58] Hence, while frequently used with this off-label indication, the clinical benefits of PCC in DOAC-treated patients with major bleeding are uncertain and remain poorly investigated in well-conducted clinical trials.[59,60]

Other hemostatic agents

Tranexamic acid is a synthetic lysine derivative that blocks the lysine binding sites on plasminogen resulting in inhibition of plasminogen activation and reduced affinity to bind to fibrin. Hence, tranexamic acid exerts its antifibrinolytic effects via stabilization of fibrin clots and is considered a universal hemostatic agent rather than a reversal agent.[61] It was first developed in the 1960s and can be administered either systemically or topically, and the evidence supporting its effectiveness in diminishing bleeding and the need for transfusion in different settings is compelling.[62] Recently, tranexamic acid has been investigated in large randomized controlled trials on surgical patients and demonstrated a significant reduction in bleeding complications without increasing thrombotic risk, though at the cost of more postoperative seizure especially with administration of high doses (>2 g/day) and during cardiac surgery.[63–65] By contrast, among healthy volunteers treated with supratherapeutic doses of rivaroxaban, tranexamic acid was found to have no effect on either thrombin generation or bleeding in a skin biopsy model.[66]

Desmopressin improves platelet function by increasing the release of factors VIII and von Willebrand[67] and is recommended in patients with inherited bleeding disorders such as hemophilia A and von Willebrand disease. Desmopressin has also been suggested for patients with platelet dysfunction or on antiplatelet agents with active bleeding (intracranial hemorrhage) or undergoing major surgery, despite conflicting results from relatively small and low-quality studies.[68–70]

Clinical implications

There are two key scenarios involving the use of reversal strategies in patients on oral antithrombotic drugs: (i) ongoing major bleeding and (ii) threat of major bleeding (e.g. non-deferrable surgery). Ongoing major bleeding is a clinical emergency, where rapid and effective restoration of normal hemostatic functions on top of standard supportive measures (e.g. mechanical compression or intervention at the bleeding site, red blood cell transfusion, vasopressors, fluid infusion) may be required to successfully halt bleeding. Oral antithrombotic drugs exert their effect—at least in part—for days after the last intake. In case of life-threatening bleeding, immediate drug discontinuation, although necessary, is generally not sufficient to promptly restore procoagulant pathways. Hence, antidotes allowing an immediate reversal of the inhibition of platelet or coagulation factors activity represent a key therapeutic option.

The second scenario involves situations where the bleeding risk can be anticipated due to the need for urgent invasive surgical procedures (in some situations as quickly as <24 h from the last antithrombotic dose). Antithrombotic drug removal, and some reversal strategies, may be considered before proceeding to surgery to mitigate perioperative bleeding complications. These approaches might also be useful in semi-elective but time-sensitive settings to minimize the period without antithrombotic protection and avoid the need for 'bridging' while awaiting surgery in patients at high risk of ischemic events.

Ongoing major bleeding

The benefit of reversing antiplatelet or anticoagulant effects should always be weighed against the potential harm related to prothrombotic effects.[60] Indeed, ischemic events may result from withdrawal of antithrombotic protection, prothrombotic states associated with bleeding and/or trauma, and procoagulant rebound mechanisms, although the latter have never been fully demonstrated. From this perspective, the use of reversal agents requires judicious review of indications and should only be considered in case of major, life-threatening bleeding not responsive to maximal supportive measures where there is concomitant evidence or reasonable suspicion of clinically relevant antiplatelet or anticoagulant drug levels.[18,71] A 2020 expert consensus suggested an updated and simplified definition of major bleeding for patients on antithrombotic drugs that includes bleeding associated with hemodynamic instability, occurring in a critical area or organ (i.e. intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome), or resulting in a hemoglobin drop of ≥2 g/dL or transfusion of ≥2 units of packed red cells.[72,73]

Until bentracimab will become available, there is currently no specific reversal agent that rapidly and effectively neutralizes antiplatelet drugs. The utility of platelet transfusion remains controversial, especially in the absence of low platelet count. Tranexamic acid is not systematically recommended to reverse antiplatelet medications; however, it is inexpensive and widely available and has a positive track record in various types of bleeding.[74] Desmopressin has shown to reduce bleeding, blood transfusions, and reoperations in patients taking antiplatelet therapy undergoing cardiac surgery and may thus be a viable option to improve platelet function.[68]

Figure 1 summarizes the approach to the use of OAC reversal agents relative to each specific drug. Four-factor PCC neutralize the effects of VKA and are administered following a stepwise approach based on INR, e.g. 25 U/kg if INR is 2–4.0, 35 U/kg if INR is 4–6.0, and 50 U/kg if INR is >6.0.[75] For DOAC-associated bleeding, targeted reversal is preferable to PCC. Idarucizumab is administered intravenously at a total dose of 5 g (two 2.5 g boluses no more than 15 min apart).[44] Because the half-life of idarucizumab (10 h) is shorter than dabigatran (12–17 h), repeated doses may be necessary.[76] Moreover, as dabigatran is mostly not protein-bound in the plasma (>85%), hemodialysis may be considered, especially in the presence of impaired renal function.[77] Andexanet alfa is administered as an intravenous bolus of 400–800 mg followed by a 2 h infusion of 480–960 mg depending on the dose and timing of the last DOAC intake.[49] More specific clinical scenarios with the relevant recommendations are discussed below.

The post-reversal management of antithrombotic drugs, including indication and timing of therapy resumption, depends on the individual thrombotic and bleeding risk balance. In general, restarting oral antithrombotic therapy at the lowest effective dose is warranted in all situations where there is a clear indication based on practice guidelines and if bleeding risk is not prohibitive.[78]

At present, there is paucity of real-world data on the safety and efficacy of these agents, and close collaboration between cardiologists, hematologists, and multidisciplinary specialists is warranted to make individualized recommendations and standardization of bleeding management protocols.

Intracranial bleed

Intracranial hemorrhage remains the most feared and devastating complication of antithrombotic drugs, affecting 0.2%–0.3% of patients on antiplatelet therapy, and up to 0.5% and 0.85% of those on DOAC and VKA, respectively, every year.[13,79] Reversal of aspirin with platelet transfusion might be considered in patients with intracranial hemorrhage only if emergency neurosurgery is scheduled; otherwise, it is contraindicated. Ticagrelor is not affected by platelet transfusion but may be reversed by its specific antidote bentracimab, when available. The effectiveness of desmopressin with or without platelet transfusions to reduce the expansion of the hematoma is uncertain.[80,81] Studies of antiplatelet-related intracranial hemorrhage have mostly been focused on aspirin and more data are needed on reversal of $P2Y_{12}$ inhibitors.

Among VKA-treated patients with intracranial hemorrhage, PCC in addition to vitamin K are recommended to normalize and prevent reincrease of INR.[80,81] These measures have been shown to reduce hematoma expansion and mortality.[36] PCC are preferred over FFP, while tranexamic acid and recombinant factor VIIa are not recommended in this setting.[80,81] For intracranial hemorrhage associated with DOAC use, specific reversal agents such as idarucizumab for dabigatran and andexanet alfa for factor Xa inhibitors remain the treatment of choice. If these are not available, PCC should be considered (*Figure 2*).[80,81] Ciraparantag is currently not recommended outside of clinical trials.

Gastrointestinal bleed

In patients with atherosclerotic disease, the gastrointestinal tract is a common source of bleeding, often arising from peptic ulcers associated with aspirin use.[83] The risk of gastrointestinal bleeding is also enhanced with DOAC, and in particular with dabigatran and rivaroxaban.[84] However, the gastrointestinal tract is not considered a critical bleeding site, and there is no evidence supporting the routine use of platelet transfusion and antifibrinolytic or reversal agents in patients who have acute gastrointestinal hemorrhage,[30,85] for whom hemodynamic resuscitation and early endoscopic hemostasis (≤24 h) remain the treatment of choice.[86] Nonetheless, if bleeding is severe and associated with hemodynamic instability, DOAC reversal agents or PCC should be considered.[86]

Traumatic bleed

Post-traumatic bleeding is the leading cause of death among injured patients, one-third of whom have signs of coagulopathy at hospital admission.[82] Trauma-related coagulopathy is a multifactorial process resulting from the activation of anticoagulant and fibrinolytic pathways as well as coagulation factors loss and consumption.[87] Patient-related factors such as age, comorbidities, and concomitant medications further exacerbate this risk. Therefore, besides antifibrinolytic agents (i.e. tranexamic acid) to be administered as soon as possible, targeted reversal of antithrombotic drugs may be indicated for major traumatic bleeding.

Platelet concentrates and desmopressin should be considered in patients on antiplatelet medications, despite conflicting evidence in support of this practice. Emergency reversal of VKA with early use of both four-factor PCC and vitamin K is recommended. In the presence of life-threatening bleeding and anti-factor Xa or anti-factor IIa activity, specific antidotes (i.e. andexanet alfa and idarucizumab, respectively) should be administered. If these are not available, PCC should be considered (*Figure 3*).[82]

Imminent bleeding risk

In case of non-deferrable major surgery, timely discontinuation of antiplatelet therapy (5–7 days prior), VKA (6 days prior, depending on INR), or DOAC (24–72 h prior) may not be feasible. When evaluating the need for reversal of antithrombotic drugs, one must carefully weigh the bleeding and thrombotic risks of both the procedure and the patient.[88,89] In subjects at high thrombotic risk (e.g. ACS or PCI within 1 month, CHA_2DS_2-VASc score ≥6, stroke or venous

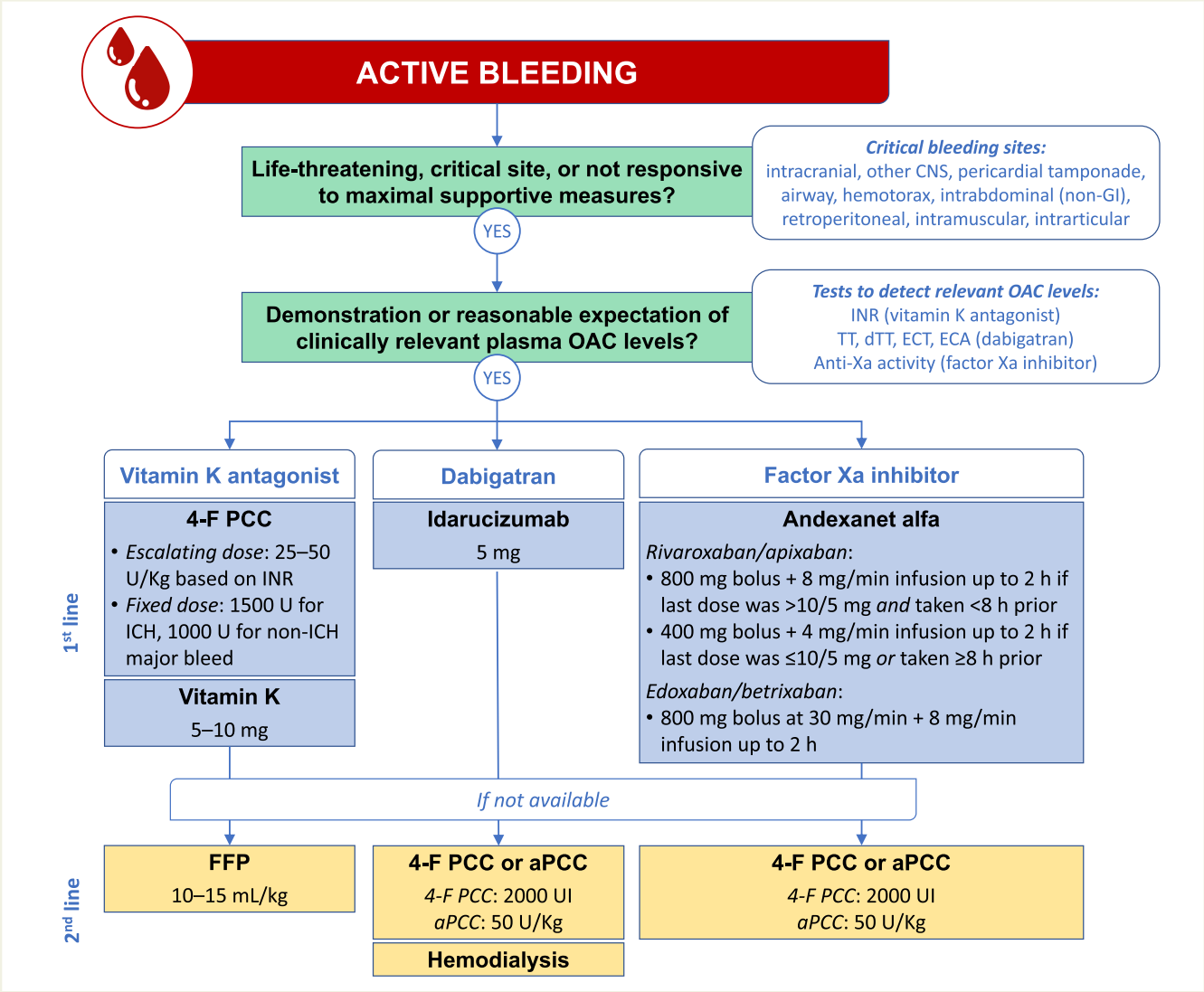


Figure 1 Practical approach to OAC reversal agents. Treatment algorithm adapted from the 2020 American College of Cardiology expert consensus decision pathway on management of bleeding in patients on oral anticoagulants[72] and guidance document from the Anticoagulation Forum on reversal of direct oral anticoagulants.[71] INR, International Normalized Ratio; 4-F, four-factor; PCC, prothrombin complex concentrates; aPCC, activated prothrombin complex concentrates; CNS, central nervous system; FFP, fresh frozen plasma; ICH, intracranial hemorrhage; OAC, oral anticoagulants; TT, thrombin time; dTT, diluted thrombin time; ECT, ecarin clotting time; ECA, ecarin chromogenic assay.

thromboembolism within 3 months, or mechanical heart valves), full drug reversal is justified only in the presence of life-threatening bleeding. Characterization of bleeding risk depends on the anticipated risk of perioperative hemorrhagic complications of a specific surgery and the presence of baseline clinical conditions that increase the risk of bleeding.[90] Several documents have been issued to guide physicians in assessing the balance between perioperative thrombotic and bleeding risk relative to the need for antithrombotic medications in different clinical settings, including the perioperative phase.[89,91–93] However, there is lack of high-quality evidence on drug reversal before non-elective surgery, and recommendations are mostly based on expert opinions and the clinical experience of the individual physician.

Platelet transfusion is often used to restore hemostasis during surgical operations, even though current guidelines do not provide specific recommendations either in favor of or against this practice.[94] Idarucizumab is the only agent with a label indication for drug reversal (i.e. dabigatran) in case of emergency surgery. Meanwhile, for patients with evidence of factor Xa inhibition, PCC may be considered.[89]

The role of platelet function assays or measuring DOAC levels on top of standard coagulation tests to inform decisions on perioperative drug reversal is uncertain. Unlike patients presenting with life-threatening bleeding where immediate reversal should be pursued without unnecessary delay, in nonbleeding patients requiring emergency or urgent invasive procedures, laboratory confirmation of antithrombotic drug levels should be considered.[89]

Monitoring of reversal

Pharmacodynamic parameters can be useful for evaluating normalization of the patient's hemostatic functions once antithrombotic drugs have been discontinued or reversed. Platelet function tests have been

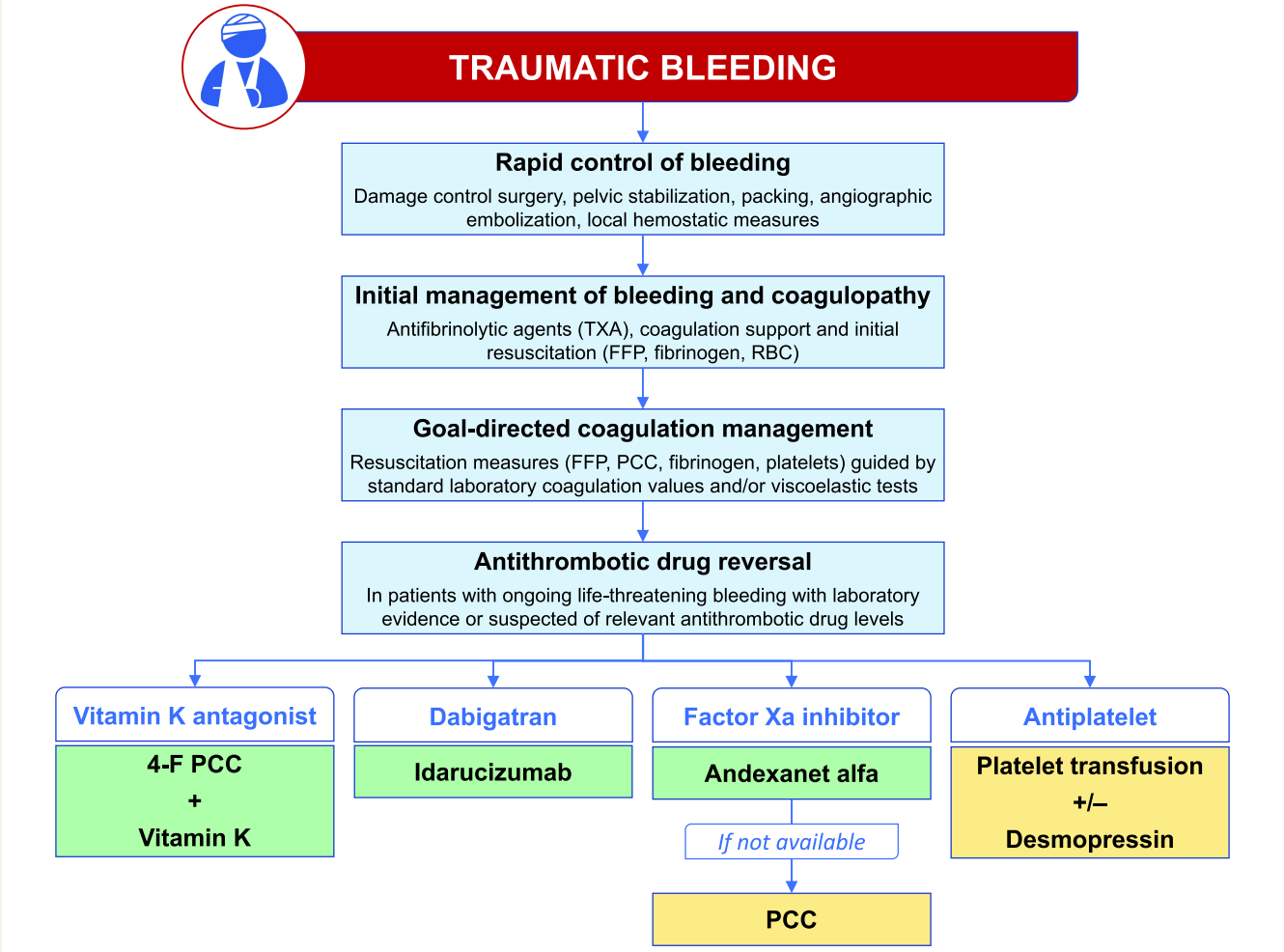


Figure 2 Recommendations on reversal agents in patients major bleeding and coagulopathy following trauma. Treatment algorithm adapted from the European guideline on management of major bleeding and coagulopathy following trauma: fifth edition.[82] Treatments colored in green are recommended, and treatments colored in orange are suggested or may be considered. TXA, tranexamic acid; PCC, prothrombin complex concentrates; FFP, fresh frozen plasma.

utilized for evaluating antiplatelet treatment effect either in the clinical and/or research settings (see Supplementary data online, *Table S1*).[95] Major limitations of platelet function tests include variable thresholds to define therapeutic ranges and bleeding risk, lack of definitive evidence to demonstrate improvement in clinical outcomes when these assays are used for guidance of therapy, and poor agreement between tests.[96,97]

Efficacy of VKA reversal is evaluated with INR. After use of vitamin K, INR should be checked regularly during the next week to monitor warfarin clearance from the blood and prevent overcorrection.

Routine therapeutic drug monitoring in DOAC-treated patients is not standard of care; however, a number of laboratory tests have been proposed to quantify the degree of anticoagulation (see Supplementary data online, *Table S2*). Non-specific coagulation tests that are widely available include the activated partial thromboplastin time (aPTT) and the prothrombin time (PT). aPTT may serve as a screening test for dabigatran, and PT as a screening test for rivaroxaban and edoxaban while it is less sensitive for apixaban.[98,99] A notable limitation of these tests is that, while prolonged aPTT and PT suggest on-therapy or above on-therapy DOAC levels, normal aPTT and PT may not exclude on-therapy levels.[100] More specific coagulation tests to measure DOAC activity include direct thrombin inhibitor assays [i.e. thrombin time (TT) and diluted thrombin time (dTT)] and ecarin clotting time for dabigatran and chromogenic anti-factor Xa assays for rivaroxaban, apixaban, and edoxaban.[98,99] These chromogenic anti-factor Xa assays are calibrated to the specific drug and can be used to quantify drug levels, although accuracy may be somewhat reduced at very low drug concentrations (<30 ng/mL).[101,102] Once a DOAC reversal agent has been administered, it is important to repeat all coagulation tests within minutes to monitor efficacy of reversal. DOACs levels <30 ng/mL (the lower limit of detection for some assays) or <50 ng/mL have been suggested as thresholds to evaluate efficacy of reversal.[103]

Viscoelastic coagulation tests, such as thromboelastography (TEG) and rotational thromboelastometry (ROTEM), may also be helpful for monitoring DOAC plasma concentration. However, these are insufficiently sensitive and specific to inform decisions about use of reversal agents.[72] More studies are needed to define the role of point-of-care laboratory tests in guiding reversal strategies.

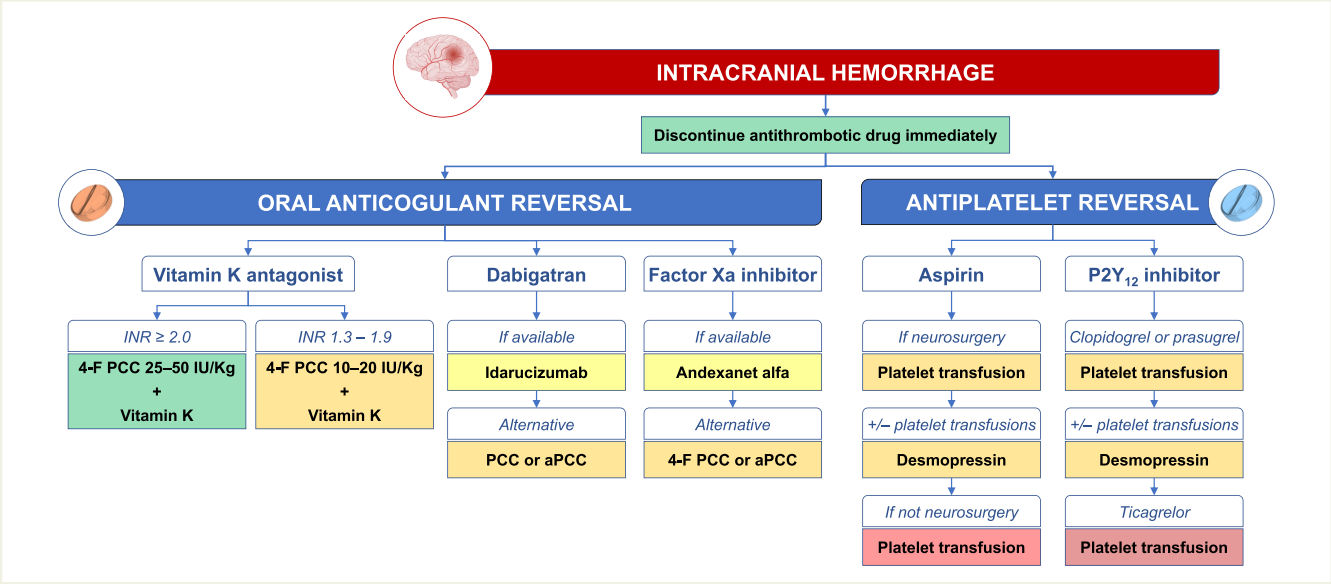


Figure 3 Recommendations on reversal agents in patients with intracranial hemorrhage. Treatment algorithm adapted from the 2022 American Heart Association and American Stroke Association guidelines for the management of spontaneous intracerebral hemorrhage.[80] Green color indicates class of recommendation 1a, yellow indicates class 2a, orange indicates class 2b, red indicates class 3. INR, international normalized ratio; 4-F, four-factor; PCC, prothrombin complex concentrates; aPCC, activated prothrombin complex concentrates.

Drug removal

Hemoadsorption involves passing the patient's blood directly through a sorbent material for selective removal of specific molecules. Adsorption devices may be useful in patients on antithrombotic drugs requiring urgent/non-deferrable surgery with a significant risk of bleeding complications. Drug removal can be achieved by incorporating the adsorber device into any extracorporeal hemoperfusion circuit such as cardiopulmonary bypass, extracorporeal membrane oxygenation, continuous renal replacement therapy/continuous veno-venous hemofiltration, or simple hemoperfusion (*Figure 4*).

One such device is a biocompatible sorbent bead-filled hemoperfusion cartridge that is approved in Europe under CE mark to remove ticagrelor and rivaroxaban intraoperatively during cardiopulmonary bypass surgery. This hemoadsorption technology relies in part on size-selectivity to remove small hydrophobic molecules from the blood and efficiency of removal is concentration-dependent. An *in vitro* recirculation model (300 mL/min), utilizing bovine whole blood spiked at clinically relevant concentrations of ticagrelor, apixaban, or rivaroxaban, demonstrated efficient drug adsorption with a removal rate at 30, 60, 120, and 360 min of 81.5%, 96.3%, 99.3% > 99.8% for apixaban; 80.7%, 95.1%, 98.9%, > 99.5% for rivaroxaban; and 62.5%, 75%, 86.6%, > 95% for ticagrelor, respectively.[105] Importantly, blood pH and other hematological parameters were not significantly affected by the hemoadsorption device when compared with the control circuit. Consistent results were observed in models using dabigatran and edoxaban.[106,107]

A retrospective case–control series evaluated the use of hemoadsorption in patients on ticagrelor ($n = 43$) or rivaroxaban ($n = 12$) undergoing emergency cardiothoracic surgery with cardiopulmonary bypass and showed significant improvements in multiple measures of post-operative bleeding compared with a historical cohort, with a mean operative time reduced by >60 min and median 24 h chest tube drainage volume reduced by 50%. Intensive care unit and total hospital length of stay were also reduced.[108] Successful use of the same device for apixaban removal during emergency cardiac surgery was published in a case report showing ~50% reduction in anti-factor Xa activity.[109] The device is currently being studied in two randomized trials of ticagrelor and rivaroxaban or apixaban in patients undergoing urgent/emergency cardiac surgery.[104] No clinical experience has yet been published for intraoperative drug removal of dabigatran or edoxaban.

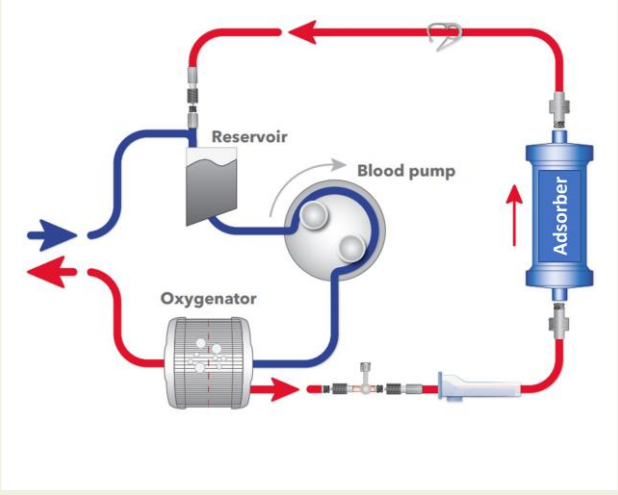


Figure 4 Hemoadsorption device for antithrombotic drug removal. The device is integrated as a parallel shunt circuit to the main cardiopulmonary bypass circuit. Blood flow intake to the parallel circuit is after the pump in the main circuit, and blood flow return from the parallel circuit is to the blood reservoir in the main circuit. Adapted from Gibson et al.[104].

Trial design considerations

Patient population

There are several inherent challenges facing clinical trial design when studying reversal or removal of antithrombotic drugs. As discussed above, antithrombotic drug reversal/removal is indicated to address either of two scenarios: (i) ongoing major bleeding or (ii) threat of major bleeding (e.g. non-deferrable surgery). In the first scenario, a single-arm design may be viewed as particularly desirable due to the potential risk of placebo assignment in this high-risk and vulnerable population. For example, the RE-VERSE AD and ANNEXA-4 trials were designed to evaluate efficacy and safety of pharmacologic reversal agents in patients with intracranial or gastrointestinal hemorrhage associated with DOAC use. To test this indication, the study population was by necessity those already in crisis (i.e. experiencing major bleeding), and for which lack of clinical equipoise would have raised ethical concerns surrounding subject randomization. Thus, all enrolled patients in both trials received the intervention.[44,49] However, the absence of a control cohort does not allow for a direct comparator in the evaluation of safety outcomes. In ANNEXA-4, thrombotic events occurred in 34 subjects (10%) and death in 49 subjects (14%).[49] Although thrombosis is a known risk associated with DOAC interruption, and despite data from the literature demonstrating similar rates of adverse events when PCC was used for the treatment of DOAC-related bleeding, in the absence of a control arm, a correlation of the outcomes with the study treatment could not be ruled out.[110,111] The lack of a control arm was identified as a key limitation of the ANNEXA-4 trial and resulted in plans for a randomized study (NCT03661528).

For the second scenario, the goal is prevention of major (perioperative) bleeding. As the patient conditions are not critical, a randomized design might be viewed as ethically acceptable. Blinding to treatment allocation provides the highest quality data; however, logistical concerns include development of an appropriate placebo (for pharmacologic therapies) or sham procedure (for medical devices) to reduce bias. Additionally, there remains a need to address clinical equipoise, which limits the population of patients that physicians might feel comfortable randomizing to only those undergoing urgent or emergency operations (i.e. situations in which no safer standard of care options exist). Dependence on such high-risk settings for trial execution has the potential to dramatically reduce both the speed and predictability of enrollment, with important financial implications. As such, most randomized trials in this clinical space have been limited to enrollment of healthy individuals in Phase 1 and 2 pharmacological studies, and no such experience has yet been published for the removal of antithrombotic drugs via medical device.[16,42,112,113] *Table 2* provides an overview of ongoing trials for antithrombotic drug reversal and removal strategies in patients with major bleeding or undergoing non-deferrable surgery.

Surrogate endpoints of efficacy

Pharmacodynamic tests can be valuable when assessing efficacy of antithrombotic reversal agents, as these reversal agents are intended to restore platelet function or normalize the coagulation pathway in the setting of high circulating drug concentrations. This is in contrast to antithrombotic drug removal strategies, where reduction in circulating drug concentrations is the primary intent and is therefore best assessed by direct measurement of drug levels. Reliable means for obtaining drug levels and pharmacodynamic measures are relatively accessible, and these endpoints can serve as a bridge between the treatment mechanism of action and subsequent clinical outcomes (i.e. reduced time to hemostasis and reduced bleeding complications). In the most generalized sense, these endpoints can serve as surrogate markers of bleeding risk; nevertheless, the desired certainty for clinical benefit with these strategies would ultimately be via the demonstration of reduced bleeding (*Table 3*).

Platelet function tests have been used to predict bleeding risk before cardiac surgery and to guide perioperative transfusion protocols. However, the ability of pharmacodynamic measures, especially of simple dichotomous cutoffs, to reliably predict multifactorial events such as postoperative bleeding remains uncertain.[114–117] Another major clinical problem is the ability to measure platelet function in bleeding patients, as whole blood point-of-care tests, such as VerifyNow, are also dependent on hematocrit, and determining the role of platelet dysfunction is always challenging to the clinician. In addition, specifically in the setting of cardiac surgery on cardiopulmonary bypass, platelet function can be severely impacted by the procedure itself, a phenomenon termed by some as 'platelet exhaustion,' further complicating the interpretation of platelet function tests.[118,119] Therefore, caution should be exercised when interpreting surrogate platelet function measures, particularly in the postoperative setting, as direct correlates of bleeding reduction.

Non-specific coagulation tests (i.e. aPTT and PT) poorly correlate with DOAC levels or bleeding risks and are therefore rarely used for research purposes. The dTT and ecarin clotting time were included as effectiveness endpoints in the RE-VERSE AD study evaluating idarucizumab reversal of dabigatran, and chromogenic anti-factor Xa levels were an effectiveness endpoint in the ANNEXA-4 study evaluating rivaroxaban and apixaban reversal by andexanet alfa.[41,49] Notably, in ANEXXA-4, anti-factor Xa activity failed to predict adjudicated hemostatic efficacy as evaluated by receiver operating characteristic curves, thus challenging its use for prediction of clinical response.

Safety endpoints

DOACs have all been assigned warnings advising increased risk of thrombotic events when prematurely discontinued. As such, the risk of thrombotic and ischemic events associated with reversal of antithrombotic medications must be addressed in any trial evaluating this type of intervention. Coronary ischemic events are of particular concern in patients on antiplatelet therapy, whereas venous and cardiac thromboembolic events are most relevant in patients on anticoagulation.

The clinical trials evaluating the two DOAC reversal agents closely monitored thrombotic events occurring through 30 days of follow-up after treatment. As previously mentioned, their incidence was 10% in the ANEXXA-4 study and 4.8% in the RE-VERSE AD study.[44,49] Importantly, while in RE-VERSE AD most thrombotic events occurred within 5 days of treatment, in ANEXXA-4, two-thirds of events occurred more than 5 days after andexanet bolus and 24% after resumption of some form of anticoagulation. As neither study included a control cohort, it is difficult to discern whether these thrombotic events occurred as a direct result of the reversal treatment or rather due to early termination of the prescribed antithrombotic therapy (*Table 3*). In the case of active drug removal with hemoadsorption, the gradual reduction in circulating drug levels may not necessarily carry the same risk for rebound thrombosis as that seen with reversal agents. Nonetheless, assessment of this risk is necessary for all safety evaluations. Ultimately, randomized controlled trials remain the best approach to determine whether drug reversal or removal strategies may contribute excess thrombotic risk on top of the inherently high adverse event rates of these vulnerable patients.

Conclusions

Remarkable progress has been made in the pharmacological management of patients with cardiovascular disease. Contemporary

Table 2 Ongoing trials on antithrombotic reversal/removal strategies in patients with major bleeding or undergoing non-deferrable surgery

Study name	Design	*n*	Aim(s)	Population	Intervention(s)	Primary outcome(s)
Reversal strategy						
REVERSE-IT (NCT04286438)	Prospective single-arm study	200	To evaluate the efficacy of ticagrelor reversal with bentracimab	Patients with uncontrolled major or life-threatening bleeding or who require urgent surgery or invasive procedure within 3 days of last ticagrelor intake	Bentracimab 18 g (up to 36 g) IV infusion over 16 (up to 24) h	1. Minimum % inhibition of platelet reactivity units within 4 h of infusion initiation 2. Achievement of effective hemostasis within 4 h of infusion initiation
ANNEXA-I (NCT03661528)	Randomized placebo-controlled trial	1200	To determine the efficacy and safety of andexanet compared to usual care in patients presenting with acute intracranial hemorrhage	Patients presenting with acute intracranial hemorrhage within 6 h of symptom onset and within 15 h of taking an oral factor Xa inhibitor	Andexanet alfa IV bolus and infusion	Achievement of effective hemostasis within 12 h of infusion initiation
Removal strategy						
START-T (NCT04976530)	Randomized sham-controlled trial	120	To evaluate the efficacy of intraoperative ticagrelor removal during cardiopulmonary bypass	Patients undergoing on-pump cardiothoracic surgery within 48 h of last ticagrelor intake	Sorbent hemoperfusion system (DrugSorb-ATR) integrated into the cardiopulmonary bypass circuit	Perioperative bleeding up to 48 h post-operation
STAR-D (NCT05093504)	Randomized sham-controlled trial	120	To evaluate the efficacy of intraoperative apixaban or rivaroxaban removal during cardiopulmonary bypass	Patients undergoing on-pump cardiothoracic surgery within 30 h of last apixaban or rivaroxaban intake	Sorbent hemoperfusion system (DrugSorb-ATR) integrated into the cardiopulmonary bypass circuit	Perioperative bleeding up to 48 h post-operation

IV, intravenous; BARC, Bleeding Academic Research Consortium.

Table 3 **Challenges to efficacy and safety endpoints of trials on reversal/removal strategies**

Surrogate efficacy endpoints (bleeding)			Safety endpoints (thrombosis)	
Laboratory measurements	Imaging	Clinical parameters	Hard clinical endpoints	Surrogate endpoints
• Lack of evidence showing correlation between pharmacodynamic parameters and improvement in clinical outcomes	• Standardized protocols for multiple imaging assessments in urgent/ emergency settings	• Dissociation between the clinical course and the extent of bleeding	• Difficulty in establishing association between thrombotic events and reversal/removal treatment effects in the absence of a control arm	• Limited ability of prothrombotic markers levels to predict thrombotic events or document hypercoagulability and thrombotic rebound
• Limited ability of dichotomous laboratory cut-offs to predict multifactorial clinical events	• Dissociation between hematoma expansion and clinical or functional outcomes	• Lack of validated criteria to define achievement of effective hemostasis	• Confounding effect of early termination of antithrombotic therapy, ongoing bleeding, major invasive procedures, and non-specific hemostatic management	• Thresholds to define increased thrombotic risk not validated for most prothrombotic markers
• Thresholds to define increased bleeding risk and therapeutic window not validated for most laboratory tests	• Identifying accurate predictors of hematoma expansion	• Confounding effects of concomitant bleeding management treatments, major invasive procedures, and patient comorbidities	• Practical challenges in conducting large, adequately powered studies for hard safety endpoints in an urgent/emergency setting	• Confounding effect of ongoing bleeding, trauma, major invasive procedures, non-specific hemostatic management, and patient comorbidities
• Non-universal access to specialized coagulation and platelet function assays	• Potential need for repeated contrast media administration	• Use of blood products and volume expanders subject to interindividual variability		
• Specialized assays highly dependent on technical expertise		• Definition of the time window to assess reversal/removal effects on bleeding		
• Wide variability of the reagent sensitivity of non-specialized assays				
• Poor agreement between different tests				
• Pharmacodynamic outcomes generally not sufficient for regulatory approval				

antithrombotic drugs have increased our ability to navigate the delicate balance between ischemic event prevention and bleeding-related harm. Nonetheless, bleeding complications remain frequent and potentially life-threatening. A number of therapeutic interventions relying on prompt antithrombotic drug reversal or removal have been developed to assist clinicians in treating patients with an active or imminent threat of major bleeding (*Graphical Abstract*). Early phase studies have shown promising results, but, in most cases, evidence of a real clinical benefit is yet to be proven. Moreover, safety concerns related to the possible prothrombotic side effects of these interventions have been raised warranting judicious indications for use and the need for further clinical evaluations. This uncertainty reflects the challenges of conducting clinical trials in the context of urgent/emergency high-risk settings, with relevant practical, financial, and ethical implications. While awaiting further data from larger clinical studies, the demand for these removal/reversal options is expected to increase in the future, and therefore their timely availability is crucial to improve patient outcomes worldwide.

Author contributions

Davide Cao, Nicolas Amabile, Mauro Chiarito, Victoria T. Lee, Dominick J. Angiolillo, Davide Capodanno, Deepak L. Bhatt, Michael J. Mack, Robert F. Storey, Michael Schmoeckel, C. Michael Gibson, Efthymios N. Deliargyris, and Roxana Mehran.

Supplementary data

Supplementary data is available at *European Heart Journal* online.

Data availability

No data were generated or analysed for this manuscript.

Conflict of interest

Dr. Amabile reports proctoring fees Abbott, Boston Scientific; consulting fees from Shockwave Medical, Abbott, Boston Scientific; institutional research grants from Abbott Vascular, and Boston Scientific.

Dr. Lee is a former employee of CytoSorbents Inc.

Dr. Angiolillo has received payment as an individual for: a) Consulting fee or honorarium from Abbott, Amgen, AstraZeneca, Bayer, Biosensors, Boehringer Ingelheim, Bristol-Myers Squibb, Chiesi, Daiichi-Sankyo, Eli Lilly, Haemonetics, Janssen, Merck, PhaseBio, PLx Pharma, Pfizer, Sanofi, and The Medicines Company; b) Participation in review activities from CeloNova and St. Jude Medical. Institutional payments for grants from Amgen, AstraZeneca, Bayer, Biosensors, CeloNova, CSL Behring, Daiichi-Sankyo, Eisai, Eli-Lilly, Gilead, Idorsia, Janssen, Matsutani Chemical Industry Co., Merck, Novartis, Osprey Medical, Renal Guard Solutions and the Scott R. MacKenzie Foundation.

Dr. Capodanno reports personal fees from Amgen, Arena, Biotronik, Daiichi Sankyo, Sanofi, Terumo; consulting fees paid to the institution from Medtronic.

Dr. Bhatt discloses the following relationships - Advisory Board: AngioWave, Bayer, Boehringer Ingelheim, Cardax, CellProthera, Cereno Scientific, Elsevier Practice Update Cardiology, High Enroll, Janssen, Level Ex, McKinsey, Medscape Cardiology, Merck, MyoKardia, NirvaMed, Novo Nordisk, PhaseBio, PLx Pharma, Regado Biosciences, Stasys; Board of Directors: AngioWave (stock options), Boston VA Research Institute, Bristol Myers Squibb (stock), DRS.LINQ (stock options), High Enroll (stock), Society of Cardiovascular Patient Care, TobeSoft; Chair: Inaugural Chair, American Heart Association Quality Oversight Committee; Consultant: Broadview Ventures; Data Monitoring Committees: Acesion Pharma, Assistance Publique-Hôpitaux de Paris, Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute, for the PORTICO trial, funded by St. Jude Medical, now Abbott), Boston Scientific (Chair, PEITHO trial), Cleveland Clinic (including for the ExCEED trial, funded by Edwards), Contego Medical (Chair, PERFORMANCE 2), Duke Clinical Research Institute, Mayo Clinic, Mount Sinai School of Medicine (for the ENVISAGE trial, funded by Daiichi Sankyo; for the ABILITY-DM trial, funded by Concept Medical), Novartis, Population Health Research Institute; Rutgers University (for the NIH-funded MINT Trial); Honoraria: American College of Cardiology (Senior Associate Editor, Clinical Trials and News, ACC.org; Chair, ACC Accreditation Oversight Committee), Arnold and Porter law firm (work related to Sanofi/Bristol-Myers Squibb clopidogrel litigation), Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute; RE-DUAL PCI clinical trial steering committee funded by Boehringer Ingelheim; AEGIS-II executive committee funded by CSL Behring), Belvoir Publications (Editor in Chief, Harvard Heart Letter), Canadian Medical and Surgical Knowledge Translation Research Group (clinical trial steering committees), Cowen and Company, Duke Clinical Research Institute (clinical trial steering committees, including for the PRONOUNCE trial, funded by Ferring Pharmaceuticals), HMP Global (Editor in Chief, Journal of Invasive Cardiology), Journal of the American College of Cardiology (Guest Editor; Associate Editor), K2P (Co-Chair, interdisciplinary curriculum), Level Ex, Medtelligence/ReachMD (CME steering committees), MJH Life Sciences, Oakstone CME (Course Director, Comprehensive Review of Interventional Cardiology), Piper Sandler, Population Health Research Institute (for the COMPASS operations committee, publications committee, steering committee, and USA national co-leader, funded by Bayer), Slack Publications (Chief Medical Editor, Cardiology Today's Intervention), Society of Cardiovascular Patient Care (Secretary/Treasurer), WebMD (CME steering committees), Wiley (steering committee); Other: Clinical Cardiology (Deputy Editor), NCDR-ACTION Registry Steering Committee (Chair), VA CART Research and Publications Committee (Chair); Patent: Sotagliflozin (named on a patent for sotagliflozin assigned to Brigham and Women's Hospital who assigned to Lexicon; neither I nor Brigham and Women's Hospital receive any income from this patent); Research Funding: Abbott, Acesion Pharma, Afimmune, Aker Biomarine, Amarin, Amgen, AstraZeneca, Bayer, Beren, Boehringer Ingelheim, Boston Scientific, Bristol-Myers Squibb, Cardax, CellProthera, Cereno Scientific, Chiesi, CinCor, CSL Behring, Eisai, Ethicon, Faraday Pharmaceuticals, Ferring Pharmaceuticals, Forest Laboratories, Fractyl, Garmin, HLS Therapeutics, Idorsia, Ironwood, Ischemix, Janssen, Javelin, Lexicon, Lilly, Medtronic, Merck, Moderna, MyoKardia, NirvaMed, Novartis, Novo Nordisk, Owkin, Pfizer, PhaseBio, PLx Pharma, Recardio, Regeneron, Reid Hoffman Foundation, Roche, Sanofi, Stasys, Synaptic, The Medicines Company, Youngene, 89Bio; Royalties: Elsevier (Editor, Braunwald's Heart Disease); Site Co-Investigator: Abbott, Biotronik, Boston Scientific, CSI, Endotronix, St. Jude Medical (now Abbott), Philips, SpectraWAVE, Svelte, Vascular Solutions; Trustee: American College of Cardiology; Unfunded Research: FlowCo, Takeda.

Dr. Mack has served as the co-principal investigator or study chair for clinical trials sponsored by Abbott, Edwards Lifesciences, Medtronic and CytoSorbent.

Dr. Storey reports institutional research grants/support from AstraZeneca, Cytosorbents, GlyCardial Diagnostics and Thromboserin; and personal fees from Alnylam, AstraZeneca, Bayer, Bristol Myers Squibb/Pfizer, CSL Behring, Cytosorbents, GlyCardial Diagnostics, Hengrui, Idorsia, Intas Pharmaceuticals, Medscape, Novartis, PhaseBio, Portola, Sanofi Aventis and Thromboserin.

Dr. Schmoeckel reports institutional research grants (CyTation study, STAR registry) and personal fees from Cytosorbents.

Dr. Gibson discloses the following relationships as relevant to this work: research grant support from Cytosorbent, Portola (for past studies of Andexanet), and PhaseBio (spouse).

Dr. Deliargyris is an employee of CytoSorbents Inc.

Dr. Mehran reports institutional research grants from Abbott, Abiomed, Applied Therapeutics, Arena, AstraZeneca, Bayer, Biosensors, Boston Scientific, Bristol-Myers Squibb, CardiaWave, CellAegis, CERC, Chiesi, Concept Medical, CSL Behring, DSI, Insel Gruppe AG, Medtronic, Novartis Pharmaceuticals, OrbusNeich, Philips, Transverse Medical, Zoll; personal fees from ACC, Boston Scientific, California Institute for Regenerative Medicine (CIRM), Cine-Med Research, Janssen, WebMD, SCAI; consulting fees paid to the institution from Abbott, Abiomed, AM-Pharma, Alleviant Medical, Bayer, Beth Israel Deaconess, CardiaWave, CeloNova, Chiesi, Concept Medical, DSI, Duke University, Idorsia Pharmaceuticals, Medtronic, Novartis, Philips; Equity <1% in Applied Therapeutics, Elixir Medical, STEL, CONTROLRAD (spouse); Scientific Advisory Board for AMA, Biosensors (spouse).

The other authors have nothing to disclose.

Funding

All authors declare no funding for this contribution.

References

1. Chan NC, Weitz JI. Antithrombotic agents. *Circ Res* 2019;**124**:426–436. https://doi.org/10.1161/CIRCRESAHA.118.313155
2. Cao D, Chandiramani R, Chiarito M, Claessen BE, Mehran R. Evolution of antithrombotic therapy in patients undergoing percutaneous coronary intervention: a 40-year journey. *Eur Heart J* 2021;**42**:339–351. https://doi.org/10.1093/eurheartj/ehaa824
3. Piccolo R, Oliva A, Avvedimento M, Franzone A, Windecker S, Valgimigli M, *et al.* Mortality after bleeding versus myocardial infarction in coronary artery disease: a systematic review and meta-analysis. *EuroIntervention* 2021;**17**:550–560. https://doi.org/10.4244/EIJ-D-20-01197
4. Fuster V, Sweeny JM. Aspirin: a historical and contemporary therapeutic overview. *Circulation* 2011;**123**:768–778. https://doi.org/10.1161/CIRCULATIONAHA.110.963843
5. Colacci M, Tseng EK, Sacks CA, Fralick M. Oral anticoagulant utilization in the United States and United Kingdom. *J Gen Intern Med* 2020;**35**:2505–2507. https://doi.org/10.1007/s11606-020-05904-0
6. Lippi G, Mattiuzzi C, Cervellin G, Favaloro EJ. Direct oral anticoagulants: analysis of worldwide use and popularity using Google trends. *Ann Transl Med* 2017;**5**:322. https://doi.org/10.21037/atm.2017.06.65
7. Valgimigli M, Costa F, Lokhnygina Y, Clare RM, Wallentin L, Moliterno DJ, *et al.* Trade-off of myocardial infarction vs. Bleeding types on mortality after acute coronary syndrome: lessons from the thrombin receptor antagonist for clinical event reduction in acute coronary syndrome (TRACER) randomized trial. *Eur Heart J* 2017;**38**:804–810.
8. Geller AI, Shehab N, Lovegrove MC, Rose KO, Weidle NJ, Goring SK, *et al.* Emergency visits for oral anticoagulant bleeding. *J Gen Intern Med* 2020;**35**:371–373. https://doi.org/10.1007/s11606-019-05391-y
9. Lamberts M, Staerk L, Olesen JB, Fosbøl EL, Hansen ML, Harboe L, *et al.* Major bleeding complications and persistence with oral anticoagulation in non-valvular atrial fibrillation: contemporary findings in real-life danish patients. *J Am Heart Assoc* 2017;**6**:e004517. https://doi.org/10.1161/JAHA.116.004517
10. Hansen ML, Sorensen R, Clausen MT, Fog-Petersen ML, Raunso J, Gadsboll N, *et al.* Risk of bleeding with single, dual, or triple therapy with warfarin, aspirin, and clopidogrel in patients with atrial fibrillation. *Arch Intern Med* 2010;**170**:1433–1441. https://doi.org/10.1001/archinternmed.2010.271
11. van Rein N, Heide-Jørgensen U, Lijfering WM, Dekkers OM, Sørensen HT, Cannegieter SC. Major bleeding rates in atrial fibrillation patients on single, dual, or triple antithrombotic therapy. *Circulation* 2019;**139**:775–786. https://doi.org/10.1161/CIRCULATIONAHA.118.036248
12. Capodanno D, Bhatt DL, Gibson CM, James S, Kimura T, Mehran R, *et al.* Bleeding avoidance strategies in percutaneous coronary intervention. *Nat Rev Cardiol* 2022;**19**:117–132. https://doi.org/10.1038/s41569-021-00598-1
13. Ha ACT, Bhatt DL, Rutka JT, Johnston SC, Mazer CD, Verma S. Intracranial hemorrhage during dual antiplatelet therapy: jACC review topic of the week. *J Am Coll Cardiol* 2021;**78**:1372–1384. https://doi.org/10.1016/j.jacc.2021.07.048
14. Buchanan A, Newton P, Pehrsson S, Inghardt T, Antonsson T, Svensson P, *et al.* Structural and functional characterization of a specific antidote for ticagrelor. *Blood* 2015;**125**:3484–3490. https://doi.org/10.1182/blood-2015-01-622928
15. Pehrsson S, Johansson KJ, Janefeldt A, Sandinge AS, Maqbool S, Goodman J, *et al.* Hemostatic effects of the ticagrelor antidote MEDI2452 in pigs treated with ticagrelor on a background of aspirin. *J Thromb Haemost* 2017;**15**:1213–1222. https://doi.org/10.1111/jth.13680
16. Bhatt DL, Pollack CV, Weitz JI, Jennings LK, Xu S, Arnold SE, *et al.* Antibody-based ticagrelor reversal agent in healthy volunteers. *N Engl J Med* 2019;**380**:1825–1833. https://doi.org/10.1056/NEJMoa1901778
17. Bhatt DL, Pollack CV, Mazer CD, Angiolillo DJ, Steg PG, James SK, *et al.* Bentracimab for ticagrelor reversal in patients undergoing urgent surgery. *NEJM Evid* 2021;**1**:oa2100047.
18. Godier A, Albaladejo P. French Working Group on Perioperative Haemostasis. Management of bleeding events associated with antiplatelet therapy: evidence, uncertainties and pitfalls. *J Clin Med* 2020;**9**:2318. https://doi.org/10.3390/jcm9072318
19. Vilahur G, Choi BG, Zafar MU, Viles-Gonzalez JF, Vorchheimer DA, Fuster V, *et al.* Normalization of platelet reactivity in clopidogrel-treated subjects. *J Thromb Haemost* 2007;**5**:82–90. https://doi.org/10.1111/j.1538-7836.2006.02245.x
20. Zafar MU, Santos-Gallego C, Vorchheimer DA, Viles-Gonzalez JF, Elmariah S, Giannarelli C, *et al.* Platelet function normalization after a prasugrel loading-dose: time-dependent effect of platelet supplementation. *J Thromb Haemost* 2013;**11**:100–106. https://doi.org/10.1111/jth.12058
21. Hansson EC, Shams Hakimi C, Åström-Olsson K, Hesse C, Wallén H, Dellborg M, *et al.* Effects of ex vivo platelet supplementation on platelet aggregability in blood samples from patients treated with acetylsalicylic acid, clopidogrel, or ticagrelor. *Br J Anaesth* 2014;**112**:570–575. https://doi.org/10.1093/bja/aet339
22. Godier A, Taylor G, Gaussem P. Inefficacy of platelet transfusion to reverse ticagrelor. *N Engl J Med* 2015;**372**:196–197. https://doi.org/10.1056/NEJMc1409373
23. Teng R, Carlson GF, Nylander S, Andersson TL. Effects of autologous platelet transfusion on platelet inhibition in ticagrelor-treated and clopidogrel-treated subjects. *J Thromb Haemost* 2016;**14**:2342–2352. https://doi.org/10.1111/jth.13511
24. Bonhomme F, Bonvini R, Reny JL, Poncet A, Fontana P. Impact of non-inhibited platelet supplementation on platelet reactivity in patients treated with prasugrel or ticagrelor for an acute coronary syndrome: an *ex vivo* study. *Platelets* 2015;**26**:324–330. https://doi.org/10.3109/09537104.2015.1035247
25. Martin AC, Berndt C, Calmette L, Philip I, Decouture B, Gaussem P, *et al.* The effectiveness of platelet supplementation for the reversal of ticagrelor-induced inhibition of platelet aggregation: an in-vitro study. *Eur J Anaesthesiol* 2016;**33**:361–367. https://doi.org/10.1097/EJA.0000000000000348
26. Zafar MU, Smith DA, Baber U, Sartori S, Chen K, Lam DW, *et al.* Impact of timing on the functional recovery achieved with platelet supplementation after treatment with ticagrelor. *Circ Cardiovasc Interv* 2017;**10**:e005120. https://doi.org/10.1161/CIRCINTERVENTIONS.117.005120
27. Bertling A, Fender AC, Schüngel L, Rumpf M, Mergemeier K, Geißler G, *et al.* Reversibility of platelet P2Y12 inhibition by platelet supplementation: ex vivo and in vitro comparisons of prasugrel, clopidogrel and ticagrelor. *J Thromb Haemost* 2018;**16**:1089–1098. https://doi.org/10.1111/jth.14014
28. Li X, Sun Z, Zhao W, Zhang J, Chen J, Li Y, *et al.* Effect of acetylsalicylic acid usage and platelet transfusion on postoperative hemorrhage and activities of daily living in patients with acute intracerebral hemorrhage. *J Neurosurg* 2013;**118**:94–103. https://doi.org/10.3171/2012.9.JNS112286
29. Baharoglu MI, Cordonnier C, Al-Shahi Salman R, de Gans K, Koopman MM, Brand A, *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. *Lancet* 2016;**387**:2605–2613. https://doi.org/10.1016/S0140-6736(16)30392-0
30. Zakko L, Rustagi T, Douglas M, Laine L. No benefit from platelet transfusion for gastrointestinal bleeding in patients taking antiplatelet agents. *Clin Gastroenterol Hepatol* 2017;**15**:46–52. https://doi.org/10.1016/j.cgh.2016.07.017
31. Goel R, Ness PM, Takemoto CM, Krishnamurti L, King KE, Tobian AA. Platelet transfusions in platelet consumptive disorders are associated with arterial thrombosis and in-hospital mortality. *Blood* 2015;**125**:1470–1476. https://doi.org/10.1182/blood-2014-10-605493
32. Ducrocq G, Gonzalez-Juanatey JR, Puymirat E, Lemesle G, Cachanado M, Durand-Zaleski I, *et al.* Effect of a restrictive vs liberal blood transfusion strategy on Major cardiovascular events among patients with acute myocardial infarction and anemia: the REALITY randomized clinical trial. *JAMA* 2021;**325**:552–560. https://doi.org/10.1001/jama.2021.0135
33. Dentali F, Ageno W, Crowther M. Treatment of coumarin-associated coagulopathy: a systematic review and proposed treatment algorithms. *J Thromb Haemost* 2006;**4**:1853–1863. https://doi.org/10.1111/j.1538-7836.2006.01986.x
34. Hellstern P. Production and composition of prothrombin complex concentrates: correlation between composition and therapeutic efficiency. *Thromb Res* 1999;**95**:S7–S12. https://doi.org/10.1016/S0049-3848(99)00078-X
35. Hunt BJ, Levi M. Urgent reversal of vitamin K antagonists. *BMJ* 2018;**360**:j5424. https://doi.org/10.1136/bmj.j5424
36. Steiner T, Poli S, Griebe M, Hüsing J, Hajda J, Freiberger A, *et al.* Fresh frozen plasma versus prothrombin complex concentrate in patients with intracranial haemorrhage related to vitamin K antagonists (INCH): a randomised trial. *Lancet Neurol* 2016;**15**:566–573. https://doi.org/10.1016/S1474-4422(16)00110-1
37. Pandey S, Vyas GN. Adverse effects of plasma transfusion. *Transfusion* 2012;**52**:65S–79S. https://doi.org/10.1111/j.1537-2995.2012.03663.x

38. Garcia DA, Crowther MA. Reversal of warfarin: case-based practice recommendations. *Circulation* 2012;**125**:2944–2947. https://doi.org/10.1161/CIRCULATIONAHA.111.081489
39. Dezee KJ, Shimeall WT, Douglas KM, Shumway NM, O'Malley PG. Treatment of excessive anticoagulation with phytonadione (vitamin K): a meta-analysis. *Arch Intern Med* 2006;**166**:391–397.
40. Fiore LD, Scola MA, Cantillon CE, Brophy MT. Anaphylactoid reactions to vitamin K. *J Thromb Thrombolysis* 2001;**11**:175–183. https://doi.org/10.1023/A:1011237019082
41. Pollack CV Jr, Reilly PA, Eikelboom J, Glund S, Verhamme P, Bernstein RA, *et al.* Idarucizumab for dabigatran reversal. *N Engl J Med* 2015;**373**:511–520. https://doi.org/10.1056/NEJMoa1502000
42. Glund S, Stangier J, Schmohl M, Gansser D, Norris S, van Ryn J, *et al.* Safety, tolerability, and efficacy of idarucizumab for the reversal of the anticoagulant effect of dabigatran in healthy male volunteers: a randomised, placebo-controlled, double-blind phase 1 trial. *Lancet* 2015;**386**:680–690. https://doi.org/10.1016/S0140-6736(15)60732-2
43. Praxbind® (idarucizumab) Boehringer Ingelheim Pharmaceuticals. https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/761025lbl.pdf.
44. Pollack CV, Reilly PA, van Ryn J, Eikelboom JW, Glund S, Bernstein RA, *et al.* Idarucizumab for dabigatran reversal—full cohort analysis. *N Engl J Med* 2017;**377**:431–441. https://doi.org/10.1056/NEJMoa1707278
45. Hutcherson TC, Cieri-Hutcherson NE, Bhatt R. Evidence for idarucizumab (praxbind) in the reversal of the direct thrombin inhibitor dabigatran: review following the RE-VERSE AD full cohort analysis. *P T* 2017;**42**:692–698.
46. Van der Wall SJ, Lopes RD, Aisenberg J, Reilly P, van Ryn J, Glund S, *et al.* Idarucizumab for dabigatran reversal in the management of patients with gastrointestinal bleeding. *Circulation* 2019;**139**:748–756. https://doi.org/10.1161/CIRCULATIONAHA.118.036710
47. Lu G, DeGuzman FR, Hollenbach SJ, Karbarz MJ, Abe K, Lee G, *et al.* A specific antidote for reversal of anticoagulation by direct and indirect inhibitors of coagulation factor Xa. *Nat Med* 2013;**19**:446–451. https://doi.org/10.1038/nm.3102
48. Siegal DM, Curnutte JT, Connolly SJ, Lu G, Conley PB, Wiens BL, *et al.* Andexanet alfa for the reversal of factor Xa inhibitor activity. *N Engl J Med* 2015;**373**:2413–2424. https://doi.org/10.1056/NEJMoa1510991
49. Connolly SJ, Crowther M, Eikelboom JW, Gibson CM, Curnutte JT, Lawrence JH, *et al.* Full study report of andexanet alfa for bleeding associated with factor Xa inhibitors. *N Engl J Med* 2019;**380**:1326–1335. https://doi.org/10.1056/NEJMoa1814051
50. Maneno JN, Ness GL. Andexanet alfa, the possible alternative to protamine for reversal of unfractionated heparin. *Ann Pharmacother* 2021;**55**:261–264. https://doi.org/10.1177/1060028020943160
51. *Ondexxya (andexanet alfa): Avoid use of andexanet prior to heparinization*. https://www.ema.europa.eu/en/medicines/dhpc/ondexxya-andexanet-alfa-avoid-use-andexanet-prior-heparinization.
52. Ansell J, Laulicht BE, Bakhru SH, Burnett A, Jiang X, Chen L, *et al.* Ciraparantag, an anticoagulant reversal drug: mechanism of action, pharmacokinetics, and reversal of anticoagulants. *Blood* 2021;**137**:115–125. https://doi.org/10.1182/blood.2020007116
53. Ansell JE, Bakhru SH, Laulicht BE, Steiner SS, Grosso M, Brown K, *et al.* Use of PER977 to reverse the anticoagulant effect of edoxaban. *N Engl J Med* 2014;**371**:2141–2142. https://doi.org/10.1056/NEJMc1411800
54. Ansell JE, Bakhru SH, Laulicht BE, Steiner SS, Grosso MA, Brown K, *et al.* Single-dose ciraparantag safely and completely reverses anticoagulant effects of edoxaban. *Thromb Haemost* 2017;**117**:238–245. https://doi.org/10.1160/TH16-03-0224
55. Ansell J, Bakhru S, Laulicht BE, Tracey G, Villano S, Freedman D. Ciraparantag reverses the anticoagulant activity of apixaban and rivaroxaban in healthy elderly subjects. *Eur Heart J* 2022;**43**:985–992. https://doi.org/10.1093/eurheartj/ehab637
56. Kalathottukaren MT, Creagh AL, Abbina S, Lu G, Karbarz MJ, Pandey A, *et al.* Comparison of reversal activity and mechanism of action of UHRA, andexanet, and PER977 on heparin and oral FXa inhibitors. *Blood Adv* 2018;**2**:2104–2114. https://doi.org/10.1182/bloodadvances.2016003616
57. Kaide CG, Gulseth MP. Current strategies for the management of bleeding associated with direct oral anticoagulants and a review of investigational reversal agents. *J Emerg Med* 2020;**58**:217–233. https://doi.org/10.1016/j.jemermed.2019.10.011
58. Rawal A, Ardeshna D, Minhas S, Cave B, Ibeguogu U, Khouzam R. Current status of oral anticoagulant reversal strategies: a review. *Ann Transl Med* 2019;**7**:411. https://doi.org/10.21037/atm.2019.07.101
59. Piran S, Khatib R, Schulman S, Majeed A, Holbrook A, Witt DM, *et al.* Management of direct factor Xa inhibitor-related major bleeding with prothrombin complex concentrate: a meta-analysis. *Blood Adv* 2019;**3**:158–167. https://doi.org/10.1182/bloodadvances.2018024133
60. Gómez-Outes A, Alcubilla P, Calvo-Rojas G, Terleira-Fernández AI, Suárez-Gea ML, Lecumberri R, *et al.* Meta-analysis of reversal agents for severe bleeding associated with direct oral anticoagulants. *J Am Coll Cardiol* 2021;**77**:2987–3001. https://doi.org/10.1016/j.jacc.2021.04.061
61. Hunt BJ. The current place of tranexamic acid in the management of bleeding. *Anaesthesia* 2015;**70**:50–e18. https://doi.org/10.1111/anae.12910
62. Tengborn L, Blombäck M, Berntorp E. Tranexamic acid–an old drug still going strong and making a revival. *Thromb Res* 2015;**135**:231–242. https://doi.org/10.1016/j.thromres.2014.11.012
63. Myles PS, Smith JA, Forbes A, Silbert B, Jayarajah M, Painter T, *et al.* Tranexamic acid in patients undergoing coronary-artery surgery. *N Engl J Med* 2017;**376**:136–148. https://doi.org/10.1056/NEJMoa1606424
64. Devereaux PJ, Marcucci M, Painter TW, Conen D, Lomivorotov V, Sessler DI, *et al.* Tranexamic acid in patients undergoing noncardiac surgery. *N Engl J Med* 2022;**386**:1986–1997. https://doi.org/10.1056/NEJMoa2201171
65. Murao S, Nakata H, Roberts I, Yamakawa K. Effect of tranexamic acid on thrombotic events and seizures in bleeding patients: a systematic review and meta-analysis. *Crit Care* 2021;**25**:380. https://doi.org/10.1186/s13054-021-03799-9
66. Levy JH, Moore KT, Neal MD, Schneider D, Marcsisin VS, Ariyawansa J, *et al.* Rivaroxaban reversal with prothrombin complex concentrate or tranexamic acid in healthy volunteers. *J Thromb Haemost* 2018;**16**:54–64. https://doi.org/10.1111/jth.13894
67. Kaufmann JE, Vischer UM. Cellular mechanisms of the hemostatic effects of desmopressin (DDAVP). *J Thromb Haemost* 2003;**1**:682–689. https://doi.org/10.1046/j.1538-7836.2003.00190.x
68. Desborough MJ, Oakland KA, Landoni G, Crivellari M, Doree C, Estcourt LJ, *et al.* Desmopressin for treatment of platelet dysfunction and reversal of antiplatelet agents: a systematic review and meta-analysis of randomized controlled trials. *J Thromb Haemost* 2017;**15**:263–272. https://doi.org/10.1111/jth.13576
69. Frontera JA, Lewin JJ III, Rabinstein AA, Aisiku IP, Alexandrov AW, Cook AM, *et al.* Guideline for reversal of antithrombotics in intracranial hemorrhage: executive summary. A statement for healthcare professionals from the neurocritical care society and the society of critical care medicine. *Crit Care Med* 2016;**44**:2251–2257. https://doi.org/10.1097/CCM.0000000000002057
70. Andersen LK, Hvas AM, Hvas CL. Effect of desmopressin on platelet dysfunction during antiplatelet therapy: a systematic review. *Neurocrit Care* 2021;**34**:1026–1046. https://doi.org/10.1007/s12028-020-01055-6
71. Cuker A, Burnett A, Triller D, Crowther M, Ansell J, Van Cott EM, *et al.* Reversal of direct oral anticoagulants: guidance from the anticoagulation forum. *Am J Hematol* 2019;**94**:697–709. https://doi.org/10.1002/ajh.25475
72. Tomaselli GF, Mahaffey KW, Cuker A, Dobesh PP, Doherty JU, Eikelboom JW, *et al.* 2020 ACC expert consensus decision pathway on management of bleeding in patients on oral anticoagulants: a report of the American college of cardiology solution set oversight committee. *J Am Coll Cardiol* 2020;**76**:594–622. https://doi.org/10.1016/j.jacc.2020.04.053
73. Schulman S, Angerås U, Bergqvist D, Eriksson B, Lassen MR, Fisher W. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in surgical patients. *J Thromb Haemost* 2010;**8**:202–204. https://doi.org/10.1111/j.1538-7836.2009.03678.x
74. Fischer K, Bodalbhai F, Awudi E, Surani S. Reversing bleeding associated with antiplatelet use: the role of tranexamic acid. *Cureus* 2020;**12**:e10290.
75. Sarode R, Milling TJ Jr, Refaai MA, Mangione A, Schneider A, Durn BL, *et al.* Efficacy and safety of a 4-factor prothrombin complex concentrate in patients on vitamin K antagonists presenting with major bleeding: a randomized, plasma-controlled, phase IIIb study. *Circulation* 2013;**128**:1234–1243. https://doi.org/10.1161/CIRCULATIONAHA.113.002283
76. Hegemann I, Ganter C, Widmer CC, Becker M, Müller D, Spahn DR. Ongoing redistribution of dabigatran necessitates repetitive application of idarucizumab. *Br J Anaesth* 2018;**121**:505–508. https://doi.org/10.1016/j.bja.2018.04.025
77. Chai-Adisaksopha C, Hillis C, Lim W, Boonyawat K, Moffat K, Crowther M. Hemodialysis for the treatment of dabigatran-associated bleeding: a case report and systematic review. *J Thromb Haemost* 2015;**13**:1790–1798. https://doi.org/10.1111/jth.13117
78. Halvorsen S, Storey RF, Rocca B, Sibbing D, Ten Berg J, Grove EL, *et al.* Management of antithrombotic therapy after bleeding in patients with coronary artery disease and/or atrial fibrillation: expert consensus paper of the European society of cardiology working group on thrombosis. *Eur Heart J* 2017;**38**:1455–1462.
79. Eikelboom J, Merli G. Bleeding with direct oral anticoagulants vs warfarin: clinical experience. *Am J Med* 2016;**129**:S33–S40. https://doi.org/10.1016/j.amjmed.2016.06.003
80. Greenberg SM, Ziai WC, Cordonnier C, Dowlatshahi D, Francis B, Goldstein JN, *et al.* 2022 guideline for the management of patients with spontaneous intracerebral hemorrhage: a guideline from the American heart association/American stroke association. *Stroke* 2022;**53**:e282–e361. https://doi.org/10.1161/STR.0000000000000407
81. Christensen H, Cordonnier C, Kõrv J, Lal A, Ovesen C, Purrucker JC, *et al.* European Stroke Organisation guideline on reversal of oral anticoagulants in acute intracerebral haemorrhage. *Eur Stroke J* 2019;**4**:294–306. https://doi.org/10.1177/2396987319849763
82. Spahn DR, Bouillon B, Cerny V, Duranteau J, Filipescu D, Hunt BJ, *et al.* The European guideline on management of major bleeding and coagulopathy following trauma: fifth edition. *Crit Care* 2019;**23**:98. https://doi.org/10.1186/s13054-019-2347-3

83. García Rodríguez LA, Hernández-Díaz S, de Abajo FJ. Association between aspirin and upper gastrointestinal complications: systematic review of epidemiologic studies. *Br J Clin Pharmacol* 2001;**52**:563–571. https://doi.org/10.1046/j.0306-5251.2001.01476.x
84. Holster IL, Valkhoff VE, Kuipers EJ, Tjwa E. New oral anticoagulants increase risk for gastrointestinal bleeding: a systematic review and meta-analysis. *Gastroenterology* 2013;**145**:105–112.e15. https://doi.org/10.1053/j.gastro.2013.02.041
85. HALT-IT Trial Collaborators. Effects of a high-dose 24-h infusion of tranexamic acid on death and thromboembolic events in patients with acute gastrointestinal bleeding (HALT-IT): an international randomised, double-blind, placebo-controlled trial. *Lancet* 2020;**395**:1927–1936. https://doi.org/10.1016/S0140-6736(20)30848-5
86. Gralnek IM, Stanley AJ, Morris AJ, Camus M, Lau J, Lanas A, *et al.* Endoscopic diagnosis and management of nonvariceal upper gastrointestinal hemorrhage (NVUGIH): european society of gastrointestinal endoscopy (ESGE) guideline - update 2021. *Endoscopy* 2021;**53**:300–332. https://doi.org/10.1055/a-1369-5274
87. Hess JR, Brohi K, Dutton RP, Hauser CJ, Holcomb JB, Kluger Y, *et al.* The coagulopathy of trauma: a review of mechanisms. *J Trauma* 2008;**65**:748–754.
88. Hornor MA, Duane TM, Ehlers AP, Jensen EH, Brown PS Jr, Pohl D, *et al.* American College of surgeons' guidelines for the perioperative management of antithrombotic medication. *J Am Coll Surg* 2018;**227**:521–536e1. https://doi.org/10.1016/j.jamcollsurg.2018.08.183
89. Douketis JD, Spyropoulos AC, Murad MH, Arcelus JI, Dager WE, Dunn AS, *et al.* Perioperative management of antithrombotic therapy: an American college of chest physicians clinical practice guideline. *Chest* 2022;**162**:e207–e243. https://doi.org/10.1016/j.chest.2022.07.025
90. Cao D, Chandiramani R, Capodanno D, Berger JS, Levin MA, Hawn MT, *et al.* Non-cardiac surgery in patients with coronary artery disease: risk evaluation and periprocedural management. *Nat Rev Cardiol* 2021;**18**:37–57. https://doi.org/10.1038/s41569-020-0410-z
91. Rossini R, Tarantini G, Musumeci G, Masiero G, Barbato E, Calabrò P, *et al.* A multidisciplinary approach on the perioperative antithrombotic management of patients with coronary stents undergoing surgery: surgery after stenting 2. *JACC Cardiovasc Interv* 2018;**11**:417–434. https://doi.org/10.1016/j.jcin.2017.10.051
92. Urban P, Mehran R, Colleran R, Angiolillo DJ, Byrne RA, Capodanno D, *et al.* Defining high bleeding risk in patients undergoing percutaneous coronary intervention: a consensus document from the academic research consortium for high bleeding risk. *Eur Heart J* 2019;**40**:2632–2653. https://doi.org/10.1093/eurheartj/ehz372
93. Spyropoulos AC, Brohi K, Caprini J, Samama CM, Siegal D, Tafur A, *et al.* Scientific and standardization committee communication: guidance document on the periprocedural management of patients on chronic oral anticoagulant therapy: recommendations for standardized reporting of procedural/surgical bleed risk and patient-specific thromboembolic risk. *J Thromb Haemost* 2019;**17**:1966–1972.
94. Kaufman RM, Djulbegovic B, Gernsheimer T, Kleinman S, Tinmouth AT, Capocelli KE, *et al.* Platelet transfusion: a clinical practice guideline from the AABB. *Ann Intern Med* 2015;**162**:205–213. https://doi.org/10.7326/M14-1589
95. Paniccia R, Priora R, Liotta AA, Abbate R. Platelet function tests: a comparative review. *Vasc Health Risk Manag* 2015;**11**:133–148. https://doi.org/10.2147/VHRM.S44469
96. Dias JD, Pottgiesser T, Hartmann J, Duerschmied D, Bode C, Achneck HE. Comparison of three common whole blood platelet function tests for in vitro P2Y12 induced platelet inhibition. *J Thromb Thrombolysis* 2020;**50**:135–143. https://doi.org/10.1007/s11239-019-01971-1
97. Can MM, Tanboğa IH, Türkyilmaz E, Karabay CY, Akgun T, Koca F, *et al.* The risk of false results in the assessment of platelet function in the absence of antiplatelet medication: comparison of the PFA-100, multiplate electrical impedance aggregometry and verify now assays. *Thromb Res* 2010;**125**:e132–e137. https://doi.org/10.1016/j.thromres.2009.11.005
98. Samuelson BT, Cuker A, Siegal DM, Crowther M, Garcia DA. Laboratory assessment of the anticoagulant activity of direct oral anticoagulants: a systematic review. *Chest* 2017;**151**:127–138. https://doi.org/10.1016/j.chest.2016.08.1462
99. Douxfils J, Ageno W, Samama CM, Lessire S, Ten Cate H, Verhamme P, *et al.* Laboratory testing in patients treated with direct oral anticoagulants: a practical guide for clinicians. *J Thromb Haemost* 2018;**16**:209–219. https://doi.org/10.1111/jth.13912
100. Cuker A. Laboratory measurement of the non-vitamin K antagonist oral anticoagulants: selecting the optimal assay based on drug, assay availability, and clinical indication. *J Thromb Thrombolysis* 2016;**41**:241–247. https://doi.org/10.1007/s11239-015-1282-7
101. Gosselin RC, Adcock DM, Bates SM, Douxfils J, Favaloro EJ, Gouin-Thibault I, *et al.* International council for standardization in haematology (ICSH) recommendations for laboratory measurement of direct oral anticoagulants. *Thromb Haemost* 2018;**118**:437–450. https://doi.org/10.1055/s-0038-1627480
102. Hollestelle MJ, Meijer P. International external quality assessment for measurements of direct oral anticoagulants: results and recommendations. *Br J Haematol* 2020;**188**:460–464. https://doi.org/10.1111/bjh.16179
103. Dunois C. Laboratory monitoring of direct oral anticoagulants (DOACs). *Biomedicines* 2021;**9**:445. https://doi.org/10.3390/biomedicines9050445
104. Gibson CM, Mack MJ, Lee VT, Schneider DJ, Sellke FW, Ohman EM, *et al.* Rationale and design of the safe and timely antithrombotic removal - ticagrelor (STAR-T) trial: a prospective, multi-center, double-blind, randomized controlled trial evaluating reductions in postoperative bleeding with intraoperative removal of ticagrelor by the drugsorb™-ATR device in patients undergoing cardiothoracic surgery within 48 h from last ticagrelor dose. *Am Heart J* 2021;**245**:19–28.
105. Tripathi R, Morales J, Lee V, Gibson CM, Mack MJ, Schneider DJ, *et al.* Antithrombotic drug removal from whole blood using haemoadsorption with a porous polymer bead sorbent. *Eur Heart J Cardiovasc Pharmacother* 2022;**8**:847–856. https://doi.org/10.1093/ehjcvp/pvac036
106. Angheloiu AA, Angheloiu GO. Removal of dabigatran using sorbent hemadsorption. *Int J Cardiol* 2019;**293**:73–75. https://doi.org/10.1016/j.ijcard.2019.06.078
107. Angheloiu AA, Tan Y, Ruse C, Shaffer SA, Angheloiu GO. In-vitro sorbent-mediated removal of edoxaban from human plasma and albumin solution. *Drugs R D* 2020;**20**:217–223. https://doi.org/10.1007/s40268-020-00308-1
108. Hassan K, Kannmacher J, Wohlmuth P, Budde U, Schmoeckel M, Geidel S. Cytosorb adsorption during emergency cardiac operations in patients at high risk of bleeding. *Ann Thorac Surg* 2019;**108**:45–51. https://doi.org/10.1016/j.athoracsur.2018.12.032
109. Mendes V, Colombier S, Verdy F, Bechtold X, Schlaepfer P, Scala E, *et al.* Cytosorb® hemoadsorption of apixaban during emergent cardio-pulmonary bypass: a case report. *Perfusion* 2021;**36**:873–875. https://doi.org/10.1177/0267659120967827
110. Majeed A, Ågren A, Holmström M, Bruzelius M, Chaireti R, Odeberg J, *et al.* Management of rivaroxaban- or apixaban-associated major bleeding with prothrombin complex concentrates: a cohort study. *Blood* 2017;**130**:1706–1712. https://doi.org/10.1182/blood-2017-05-782060
111. Schulman S, Gross PL, Ritchie B, Nahirniak S, Lin Y, Lieberman L, *et al.* Prothrombin complex concentrate for Major bleeding on factor Xa inhibitors: a prospective cohort study. *Thromb Haemost* 2018;**118**:842–851. https://doi.org/10.1055/s-0038-1636541
112. Yasaka M, Ikushima I, Harada A, Imazu S, Taniguchi A, Norris S, *et al.* Safety, pharmacokinetics and pharmacodynamics of idarucizumab, a specific dabigatran reversal agent in healthy Japanese volunteers: a randomized study. *Res Pract Thromb Haemost* 2017;**1**:202–215. https://doi.org/10.1002/rth2.12029
113. Lu G, Conley PB, Leeds JM, Karbarz MJ, Levy GG, Mathur VS, *et al.* A phase 2 PK/PD study of andexanet alfa for reversal of rivaroxaban and edoxaban anticoagulation in healthy volunteers. *Blood Adv* 2020;**4**:728–739. https://doi.org/10.1182/bloodadvances.2019000885
114. Bolliger D, Tanaka KA. Point-of-care coagulation testing in cardiac surgery. *Semin Thromb Hemost* 2017;**43**:386–396. https://doi.org/10.1055/s-0037-1599153
115. Kuliczkowski W, Sliwka J, Kaczmarski J, Zysko D, Zembala M, Steter D, *et al.* Predicting bleeding risk by platelet function testing in patients undergoing heart surgery. *Clin Cardiol* 2015;**38**:679–683. https://doi.org/10.1002/clc.22472
116. Kim MH, Choi SY, An SY, Serebruany V. Validation of three platelet function tests for bleeding risk stratification during dual antiplatelet therapy following coronary interventions. *Clin Cardiol* 2016;**39**:385–390. https://doi.org/10.1002/clc.22540
117. Ranucci M, Pistuddi V, Di Dedda U, Menicanti L, De Vincentiis C, Baryshnikova E. Platelet function after cardiac surgery and its association with severe postoperative bleeding: the PLATFORM study. *Platelets* 2019;**30**:908–914. https://doi.org/10.1080/09537104.2018.1535706
118. Van Poucke S, Stevens K, Wetzels R, Kicken C, Verhezen P, Theunissen M, *et al.* Early platelet recovery following cardiac surgery with cardiopulmonary bypass. *Platelets* 2016;**27**:751–757. https://doi.org/10.3109/09537104.2016.1173665
119. Velik-Salchner C, Maier S, Innerhofer P, Kolbitsch C, Streif W, Mittermayr M, *et al.* An assessment of cardiopulmonary bypass-induced changes in platelet function using whole blood and classical light transmission aggregometry: the results of a pilot study. *Anesth Analg* 2009;**108**:1747–1754. https://doi.org/10.1213/ane.0b013e3181a198ac