






# ANMCO/SIMEU consensus document on the use of reversal agents for antithrombotic therapies in patients with ongoing bleeding or at high risk of haemorrhagic events

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## KEYWORDS

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In recent decades, an incredible evolution in antithrombotic therapies used for treating patients with atherosclerosis, atrial fibrillation, and venous thromboembolism has been observed, leading to the availability of increasingly safe drugs. Nonetheless, bleeding complications remain a significant concern, with considerable health, social, and economic implications. To improve the acute management of patients experiencing or at risk for major bleeding events, specific reversal agents for antithrombotic drugs have been recently developed. While these agents demonstrate effectiveness in small-scale pharmacodynamic studies and clinical trials, it is imperative to balance the benefits of reversing antiplatelet or anticoagulant therapy against the risk of prothrombotic effects. These risks include the potential loss of antithrombotic protection and the prothrombotic tendencies associated with bleeding, major surgery,

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or trauma. This joint document of the Italian Association of Hospital Cardiologists (*Associazione Nazionale Medici Cardiologi Ospedalieri*) and the Italian Society of Emergency Medicine (*Società Italiana di Medicina d'Emergenza-Urgenza*) delineates the key features and efficacy of available reversal agents. It also provides practical flowcharts to guide their use in patients with active bleeding or those at elevated risk of major bleeding events.

Antithrombotic medications are fundamental in managing atherosclerosis, atrial fibrillation, and venous thromboembolism, with extensive evidence supporting their role in reducing ischaemic events and improving survival.<sup>1</sup> Despite their benefits, these therapies carry an inherent risk of haemorrhagic complications,<sup>2,3</sup> which can have prognostic consequences comparable to the thrombotic events they aim to prevent.<sup>4</sup> The likelihood of bleeding is influenced by the specific pharmacodynamic and pharmacokinetic properties of each drug and is heightened when drugs are used in combination. Notably, this risk remains a concern even with agents that are considered to have safer bleeding profiles.<sup>2,3</sup>

The growing awareness of the prognostic impact of major bleeding has led to the pursuit of management strategies aimed at preventing and, if necessary, treating haemorrhagic events related to antithrombotic therapies. In this joint document of the Italian Association of Hospital Cardiologists (*Associazione Nazionale Medici Cardiologi Ospedalieri*, ANMCO) and the Italian Society of Emergency Medicine (*Società Italiana di Medicina d'Emergenza-Urgenza*, SIMEU), we will review the standard supportive measures and the supplementation of coagulation factors to stop the bleeding, as well as new strategies aimed at reversing the antithrombotic drug, such as monoclonal antibodies and recombinant factors binding to the specific drug, reducing or abolishing its anticoagulant activity.<sup>5,6</sup> The goal is to find a consensus on the management of the most complex cases.

## Antagonism of antiplatelet drugs

### Platelet transfusion

Platelet transfusion is theoretically a valid option for patients taking oral antiplatelet agents who have an urgent need to restore platelet function due to potentially lethal bleeding. However, the efficacy of platelet transfusion depends on the pharmacodynamic and pharmacokinetic characteristics of the specific antiplatelet drug, the time from the last drug intake, and the site and mechanism of bleeding (traumatic or spontaneous).<sup>7</sup> Platelet transfusion is potentially able to adequately reverse the effects of aspirin and, at higher doses, also of clopidogrel and prasugrel.<sup>8,9</sup>

The clinical effectiveness of platelet transfusion, which may be affected by variability in patient response and timing of administration, lacks robust support from clinical trials. The multicentre Platelet Transfusion in Cerebral Haemorrhage (PATCH) study failed to demonstrate the benefit of platelet transfusion among 190 patients with intracerebral haemorrhage during antiplatelet therapy (nearly 80% with aspirin).<sup>10</sup> Similar results have been reported from retrospective studies in patients with major

gastrointestinal bleeding,<sup>11</sup> possibly related to the hypothesized increase in the risk of thrombotic events and the pro-inflammatory effects of transfusions.<sup>12,13</sup>

Given ticagrelor's pharmacokinetic characteristics and reversible P2Y<sub>12</sub> receptor binding, the efficacy of platelet transfusion appears to be diminished, especially if administered shortly after the drug's last dose.<sup>14-18</sup>

### Reversal of ticagrelor (bentracimab)

Bentracimab is a recombinant neutralizing fragment of human immunoglobulin G1 monoclonal antibody that binds to free ticagrelor and its active metabolite with high affinity<sup>19</sup> (*Table 1*). In a Phase 1 randomized, placebo-controlled study involving healthy volunteers, bentracimab effectively reversed ticagrelor-induced platelet inhibition, demonstrating excellent tolerability and no prothrombotic effects.<sup>20,21</sup> The reversal of the drug occurred within 5 min of treatment administration and was sustained for 16-24 h in patients who received the highest doses.<sup>21</sup> The clinical effects of bentracimab were studied in the Rapid and Sustained Reversal of Ticagrelor-Intervention Trial (REVERSE-IT), a single-arm Phase 3 study that enrolled 200 patients who had taken ticagrelor within the previous 3 days and who presented with uncontrolled major or potentially lethal bleeding or required urgent surgery or an invasive procedure<sup>22</sup> (*Table 2*). The prespecified interim analysis of the first 150 patients showed immediate and prolonged reversal of ticagrelor platelet inhibition within 5-10 min after infusion, with >90% of patients achieving good or excellent haemostasis within 24 h.<sup>22</sup> Bentracimab is not currently available in several countries including Italy.

## Antagonism of anticoagulant drugs

Despite the advantages of direct oral anticoagulants (DOACs) over vitamin K antagonists (VKAs), including fewer haemorrhagic complications, DOAC-related bleeding still accounts for a significant number of emergency room admissions.<sup>23</sup> Moreover, mortality within 2 months related to major DOAC bleeding is between 10 and 20%.<sup>24,25</sup> Recently, specific antidotes have been approved for patients treated with direct thrombin inhibitors, such as dabigatran, or factor Xa (FXa) inhibitors such as rivaroxaban, edoxaban, and apixaban.

### Reversal of the effects of vitamin K antagonists

In patients with bleeding associated with VKAs, prothrombin complex concentrates (PCCs) and activated PCC (aPCC) can restore haemostasis and normalize the international normalized ratio (INR) in a few minutes.

**Table 1** Main characteristics of the new reversal agents for antithrombotic therapies

| Reversal agent | Inhibited drug                           | Dosage and timing   | Start/end of action |
|----------------|--|---|---------------------|
| Andexanet alfa | Direct and indirect factor Xa inhibitors | Low dose: 400 mg bolus (15 min) + 480 mg infusion (2 h)<br>High dose: 800 mg bolus (15 min) + 960 mg infusion (2 h) | 2 min/12 h          |
| Bentracimab    | Ticagrelor                               | Bolus 6 g (10 min)<br>Loading infusion 6 g (4 h)<br>Maintenance 6 g (12 h)  | 5 min/24 h          |
| Ciraparantag   | DOACs, heparins, fondaparinux            | Bolus of 100-300 mg   | 5-10 min/24 h       |
| Idarucizumab   | Dabigatran                               | Two boluses (not more than 15 min apart) of 2.5 mg each (5-10 min)  | 5 min/24-72 h       |

DOAC, direct oral anticoagulant.

Prothrombin complex concentrates are plasma products containing variable amounts of vitamin K-dependent coagulation factors. Four-factor complexes (4F-PCC) that include a higher concentration of factor VII are generally preferred over three-factor PCCs and are the only PCCs approved for urgent reversal of VKAs in adults with acute major bleeding.<sup>26</sup> Excessive use of PCCs in the presence of INR in range can provoke a prothrombotic state, with an increased risk of venous and arterial thrombosis.<sup>26</sup>

PCCs and aPCCs are used for VKA inhibition, but they have also been proposed as second-line strategies when the specific DOAC reversal agent is not available, despite their use still being debated.<sup>27</sup> PCCs can indeed induce a non-specific reversal of DOAC-related coagulopathy by overloading the coagulation cascade with upstream factors.<sup>27</sup> The effectiveness of these factors may be compromised by circulating unbound DOAC metabolites, which could account for the observed variability in restoring haemostasis. The effect of 4F-PCC in the presence of DOACs like apixaban or rivaroxaban has been variable and dependent on the concentration of FXa inhibitors.<sup>28</sup> In a randomized crossover study in healthy subjects, 4F-PCC did not significantly reduce FXa inhibitor concentrations or anti-FXa activity.<sup>29</sup>

In cases of VKA bleeding, if PCCs are not available, fresh frozen plasma (FFP) can be considered.<sup>30</sup> Fresh frozen plasma contains plasma proteins, in addition to all coagulation factors, and is prepared by removing the plasma from donated whole blood and freezing it at a temperature of at least  $-18^{\circ}\text{C}$ . Commonly associated risks with FFP transfusion include acute lung injury, circulatory overload, and allergic reactions.<sup>31</sup>

Vitamin K inhibits the anticoagulant effect of VKAs and is administered intravenously (with a more predictable effect) or orally, can be guided by INR, and can be repeated every 12 h in case of persistent increase in INR.<sup>32</sup> Due to the delayed action of vitamin K, it is typically co-administered with PCCs or FFP to mitigate warfarin's prolonged half-life.

### Specific reversal of dabigatran: idarucizumab

The direct thrombin inhibitor dabigatran can be specifically inhibited by idarucizumab, a humanized monoclonal antibody that irreversibly binds to free dabigatran and dabigatran bound to thrombin with an affinity 350 times

greater than that of thrombin<sup>33,34</sup> (Table 1). Preclinical studies have found that the infusion of idarucizumab immediately reduces the circulation of unbound dabigatran, reverses dabigatran-induced anticoagulation, and restores normal haemostasis.<sup>33,34</sup> In the REVERSal Effects of Idarucizumab in Patients on Active Dabigatran (RE-VERSE AD) study, which included patients with severe uncontrolled gastrointestinal or neurological bleeding or undergoing urgent surgery that could not be delayed for at least 8 h, idarucizumab rapidly and consistently reversed the anticoagulant effect of dabigatran<sup>35,36</sup> (Table 2). In the cohort of patients with ongoing bleeding, the time to the cessation of bleeding was 2.5 h, while in the surgical cohort, the time to the start of the procedure was 1.6 h.<sup>35,36</sup> At 90 days, thrombotic events occurred in 6.3% of the bleeding cohort and 7.4% of the surgical cohort. Idarucizumab is the only reversal agent with a specific indication in patients undergoing urgent surgery. The safety data of idarucizumab have also been confirmed in various real-world clinical settings.<sup>37-40</sup>

### Specific reversal of factor Xa inhibitors: andexanet alfa

Andexanet alfa is a specific reversal agent that neutralizes the anticoagulant effects of direct and indirect FXa inhibitors and is the only antidote approved for FXa inhibitors (specifically by the European Medicines Agency only for apixaban and rivaroxaban) in patients with potentially fatal or uncontrolled bleeding. Andexanet alfa is a modified human recombinant FXa protein with a 'decoy' function, catalytically inactive, that retains the ability to bind FXa inhibitors (apixaban, rivaroxaban, edoxaban, unfractionated heparin, low molecular weight heparin, and fondaparinux) at the active site with high affinity.<sup>41</sup> Andexanet alfa causes reversal and lack of response to the anticoagulant effects of heparin and should not be used for patients requiring urgent heparinization during surgery.<sup>42</sup> Two dosing regimens for andexanet alfa exist. The dosage should be chosen based on the molecule, the dose of the FXa inhibitor, and the time elapsed since the last dose of the FXa inhibitor was taken (Table 1).

In the ANNEXA (Andexanet Alfa, a Novel Antidote to the Anticoagulation Effects of Factor Xa Inhibitors)-A and ANNEXA-R studies, andexanet alfa demonstrated rapid

**Table 2** Main Phase 3 studies conducted with the new reversal agents for antithrombotic therapies

| Reversal agent | Trial       | Patients   | Main endpoints   | Main results   |
|----------------|-------------|--|--|--|
| Andexanet alfa | ANNEXA-4    | 479 patients with major bleeding $\geq 18$ h after taking a factor Xa inhibitor                          | (1) Percentage change in anti-Xa activity<br>(2) Percentage of patients with good/excellent haemostatic efficacy at 12 h after the end of andexanet alfa infusion              | (1) Patients on apixaban: 93% reduction in anti-Xa activity (95% CI 91-93); patients on rivaroxaban: 94% reduction in anti-Xa activity (95% CI 88-94)<br>(2) Good/excellent haemostatic efficacy in 80% of assessable cases            |
| Bentracimab    | REVERSE-IT  | 150 patients with major bleeding or requiring urgent procedure while on ticagrelor                       | (1) Percentage inhibition of PRU $< 4$ h after administration of bentracimab, measured by VerifyNow P2Y12<br>(2) Restoration of haemostasis                                    | (1) 135% reduction in PRU from baseline<br>(2) Normal haemostasis achieved in 98.4% of cases   |
| Idarucizumab   | RE-VERSE AD | 503 patients with major bleeding (cohort A) or requiring urgent procedure (cohort B) while on dabigatran | (1) Maximum percentage of reversal of dabigatran's anticoagulant effect $< 4$ h after administration of idarucizumab, measured by dTT or ECT<br>(2) Restoration of haemostasis | (1) Maximum of 100% reversal (95% CI 100-100)<br>(2) Cohort A: median time to cessation of bleeding: 2.5 h. Cohort B: median time to the procedure: 1.6 h, with the restoration of normal periprocedural haemostasis in 93.4% of cases |

dTT, diluted thrombin time; ECT, ecarin clotting time; CI, confidence interval; PRU, platelet reactivity units.

efficacy (2-5 min from bolus) in terms of anti-FXa activity from baseline to nadir and thrombin generation from baseline to peak after treatment, as well as safety in terms of adverse and/or thrombotic events in healthy volunteers aged 50-75 years who had received apixaban for 3.5 days or rivaroxaban for 4 days.<sup>43</sup> In the Phase 3b/4 ANNEXA-4 study, a  $\geq 93\%$  decrease in anti-FXa activity was recorded in patients with bleeding taking apixaban and rivaroxaban from baseline to nadir (71% in patients treated with edoxaban and 75% in patients treated with enoxaparin), and 82% of patients achieved excellent or good haemostasis assessed at 12 h from the end of the infusion<sup>44,45</sup> (Table 2). In all patients, a correlation was observed between haemostatic efficacy and lower mortality; moreover, in patients aged  $< 75$  years and in those with intracranial haemorrhage, the median reduction in anti-FXa activity levels at nadir was correlated with haemostatic efficacy and lower mortality.<sup>45</sup> About 10% of thrombotic events, including ischaemic stroke (4.6%) and deep vein thrombosis (3.1%), were recorded in the first few weeks after the andexanet alfa bolus, while no thrombotic events were recorded after the resumption of oral anticoagulant therapy. At the 30-day follow-up, total mortality was 15.7%.

Recent real-world studies have confirmed the safety and efficacy of andexanet alfa with a reduction in in-hospital and 30-day mortality ranging between 46 and 64% compared with 4F-PCC or other standard therapies.<sup>46-48</sup> These results are now complemented by those of the preliminary analysis of the ANNEXA-I trial, a controlled and randomized study that aimed to compare the haemostatic efficacy of andexanet alfa with standard therapy in cerebral bleeding through a multiple endpoint that combined a haematoma expansion  $\leq 35\%$  associated

with a change in National Institutes of Health Stroke Scale score  $< 7$ , without the use of haemostatic products. This study, prematurely terminated for reaching the predetermined superiority criteria and presented at the World Stroke Congress, showed an absolute difference of 11% ( $P=0.008$ ) in favour of andexanet alfa in a population of 530 patients compared with the 900 initially planned by the study protocol. About 87% of the 267 patients in the control arm were treated with PCC. The study also confirmed the efficacy of andexanet alfa on anti-FXa activity, with a reduction from baseline to nadir of 94.4% for the specific antidote and 23.5% for conventional therapy. The risk of thrombotic events was in line with what was already observed in ANNEXA-4 (about 10%), although higher than that of the control arm (5.6%).

### Non-specific reversal of anticoagulants: ciraparantag

Ciraparantag is a small synthetic water-soluble cation that non-covalently binds to heparins (including fondaparinux) and DOACs<sup>49</sup> (Table 1). Preliminary clinical and *in vitro* data have shown that ciraparantag rapidly reversed FXa inhibition induced by anticoagulation and reduced blood loss in animal models.<sup>49-51</sup> Two recent dose-ranging studies showed sustained reversal of DOAC activity achieved with 60 mg of ciraparantag for apixaban and 180 mg of ciraparantag for rivaroxaban in healthy subjects aged between 50 and 75 years.<sup>52</sup> Compared with other reversal molecules, including andexanet alfa, ciraparantag has shown weaker affinity and direct reversal activity for rivaroxaban and edoxaban.<sup>53</sup> The efficacy of ciraparantag as a therapeutic reversal agent still needs to be evaluated in Phase 3 clinical studies; therefore, its use is not



proposed in the flowcharts of this document also because it is not yet commercially available.

### Non-specific haemostatic agents

Tranexamic acid is a synthetic derivative of lysine used as an antifibrinolytic agent in the treatment and prevention of severe bleeding, particularly, in post-traumatic situations and hyperfibrinolytic disorders. It has a similar mechanism of action to aminocaproic acid but is approximately 10 times more potent.<sup>54</sup> Tranexamic acid can be administered systemically or topically, and evidence has demonstrated its antihemorrhagic efficacy in various clinical emergency contexts.<sup>54</sup> Recently, tranexamic acid has been studied in large randomized controlled trials on surgical patients and has shown a significant reduction in hemorrhagic complications without increasing the risk of thrombosis.<sup>55,56</sup>

Desmopressin, a synthetic analogue of the posterior pituitary hormone arginine vasopressin, enhances platelet function by increasing the release of factor VIII and von Willebrand factor and is recommended for patients with hereditary bleeding disorders such as haemophilia A and von Willebrand's disease.<sup>57</sup> Desmopressin has also been suggested for patients with platelet dysfunction or undergoing treatment with antiplatelet agents and bleeding or undergoing major surgery, although the results of relatively small studies are conflicting.<sup>58,59</sup>

### Mechanical removal of the drug

Haemoabsorption involves passing the patient's blood directly through an absorbent material for the selective removal of specific molecules. Absorption devices can be useful in patients treated with antithrombotic drugs who require urgent or non-deferrable surgery with a significant risk of hemorrhagic complications. The removal of the drug can be achieved by incorporating the absorption device into any extracorporeal blood perfusion circuit.

One such device is a haemoabsorption cartridge filled with biocompatible absorbent microspheres, approved in Europe for the intraoperative removal of ticagrelor and rivaroxaban during coronary artery bypass surgery. A retrospective case-control series evaluating the use of haemoabsorption in patients treated with ticagrelor or rivaroxaban has shown significant improvements in postoperative bleeding compared with a historical cohort.<sup>60</sup> The device is currently being studied in two randomized trials in patients undergoing urgent cardiac surgery.

### Laboratory monitoring after the use of reversal agents

Unlike patients with life-threatening bleeding where immediate resolution should be pursued without unnecessary delays, laboratory confirmation of antithrombotic drug levels and evaluation of the normalization of haemostatic functions should be considered in non-bleeding patients requiring emergency or urgent invasive procedures.<sup>61</sup>

Platelet function tests have been used to assess the effect of antiplatelet treatment in clinical and/or research settings.<sup>62</sup> The main limitations of platelet function tests include variable thresholds to define therapeutic ranges and the risk of bleeding, the lack of certain data on the improvement of clinical outcomes when these tests are

used to guide therapy, and the poor agreement between tests.<sup>63</sup>

The efficacy of reducing the effect of VKAs is assessed with the INR. After the use of vitamin K, INR should be regularly checked during the following week to monitor the clearance of warfarin from the blood and prevent overcorrection.

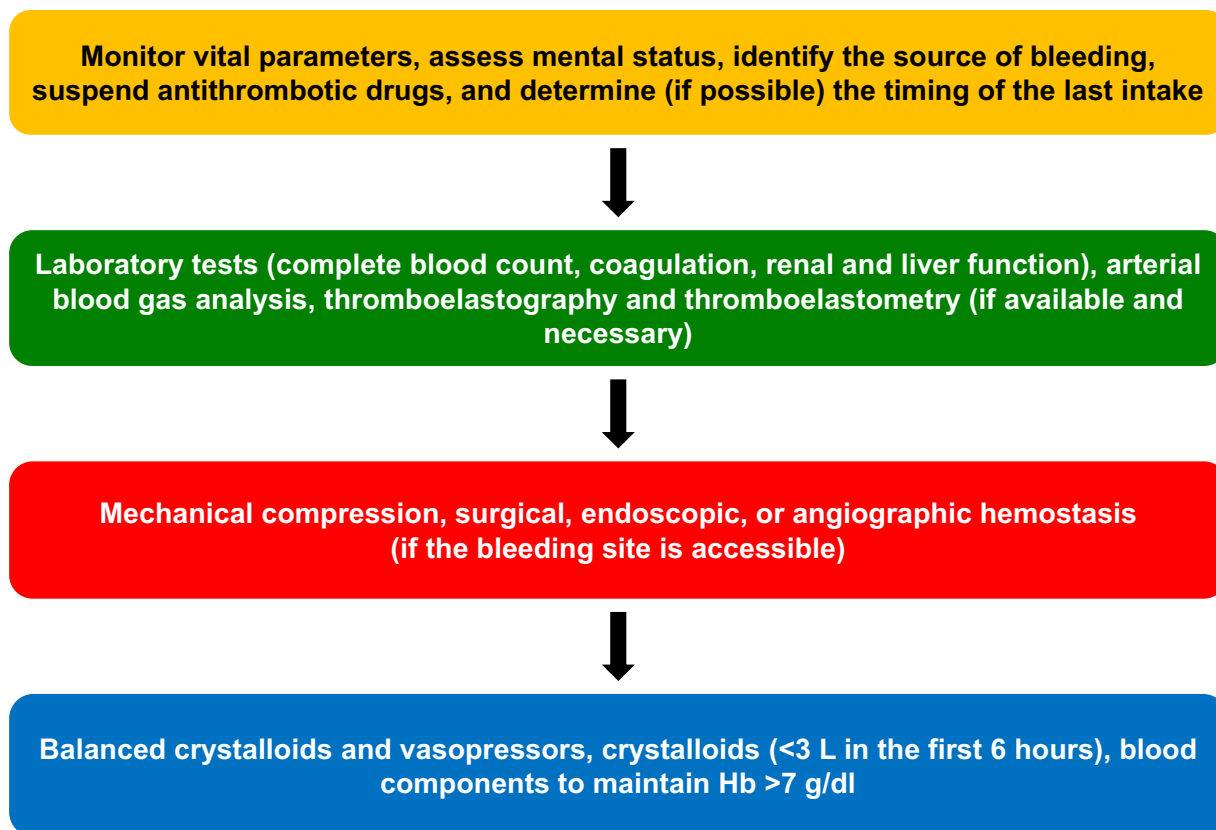
Routine therapeutic monitoring of drugs in patients treated with DOACs is not a standard of care; however, several more or less specific laboratory tests have been proposed to quantify the degree of anticoagulation. Non-specific widely available coagulation tests include activated partial thromboplastin time (aPTT) and prothrombin time (PT). The aPTT can serve as a qualitative test for dabigatran, and the PT for rivaroxaban and edoxaban, while it is less sensitive for apixaban.<sup>64,65</sup> More specific coagulation tests to measure DOAC activity include direct thrombin inhibitor tests (thrombin time and diluted thrombin time), ecarin clotting time for dabigatran, and chromogenic anti-FXa assays for rivaroxaban, apixaban, and edoxaban.<sup>64,65</sup> These chromogenic anti-FXa assays are calibrated for 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).<sup>66</sup> Importantly, the values obtained through these assays are unreliable after the administration of andexanet alfa, as they detect erroneously elevated levels of anti-FXa activity, thus substantially underestimating the reversal activity of andexanet alfa.<sup>67</sup> Viscoelastic coagulation tests, such as thromboelastography and rotational thromboelastometry, may also be useful for monitoring plasma concentrations of DOACs, as well as qualitative bedside evaluation in urine.<sup>68</sup>

### Consensus on different clinical scenarios

The main clinical scenarios where the use of reversal strategies in patients taking antithrombotic drugs should be considered are ongoing major bleeding and a high risk of major hemorrhagic events (e.g. due to non-deferrable surgery). In general, the benefit of reversing antiplatelet or anticoagulant effects should always be weighed against the potential harm related to prothrombotic effects, potentially arising from the same suspension of antithrombotic protection or from prothrombotic states associated with rebound procoagulant mechanisms in the case of bleeding, trauma, or major surgery.<sup>69</sup>

Ongoing major bleeding is a clinical emergency where rapid and effective restoration of normal haemostatic functions with specific agents in addition to standard supportive measures (e.g. mechanical compression or intervention at the bleeding site, red blood cell transfusion, vasopressors, and fluid infusion) may be necessary (*Figure 1*). In the case of life-threatening bleeding, the immediate discontinuation of the drug, although necessary, is generally not sufficient to promptly restore procoagulant pathways, as oral antithrombotic drugs can exert their effect for days after the last intake. Therefore, antidotes that allow immediate reversal of platelet inhibition or coagulation factors represent an important therapeutic option.

The second scenario involves situations where the risk of bleeding is related to the need for urgent surgical procedures where timely discontinuation of antiplatelet therapy (5-7 days before), VKAs (6 days before, depending



**Figure 1** Generic measures for initial management of patients with ongoing major bleeding. Hb, haemoglobin.

on the INR) or DOACs (24-72 h before) might not be feasible. In such cases, the removal of the antithrombotic drug and some reversal strategies can be considered before proceeding with surgery to mitigate perioperative haemorrhagic complications. In the case of urgent cardiac surgery, haemoabsorption can be considered, especially if the patient has taken rivaroxaban or ticagrelor.

When assessing the need for antagonism of antithrombotic drugs before surgery, it is necessary to carefully weigh the haemorrhagic and thrombotic risks of both the procedure and the patient.<sup>61</sup> The pragmatic characterization of the risk of bleeding depends on the expected risk of perioperative haemorrhagic complications of a specific surgical procedure and the presence of baseline clinical conditions that increase the risk of bleeding.<sup>70</sup>

### Treatment flowchart for patients with ongoing major bleeding or the need for non-deferrable surgery

Major bleeding is defined as bleeding associated with haemodynamic instability, occurring in a critical organ (e.g. intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome), or associated with a drop in haemoglobin  $\geq 2$  g/dL or transfusion of two or more units of concentrated red blood cells.<sup>68</sup>

As previously suggested, all emergency measures for the management of major bleeding should be implemented before considering the use of reversal agents (*Figure 1*).

In the case of post-traumatic bleeding, the possibility of administering antifibrinolytic agents (e.g. tranexamic acid) as soon as possible should be considered, except for intracranial haemorrhage where tranexamic acid is not recommended.

Four-factor prothrombin complex concentrate neutralizes the effects of VKAs and is administered following a graded approach based on the INR (e.g. 25 U/kg if the INR is 2-4, 35 U/kg if the INR is 4-6, and 50 U/kg if the INR is  $>6$ ).<sup>26</sup>

For bleeding associated with DOACs, specific reversal agents are preferred over PCC, which can be used as a second line if specific agents are not available. Idarucizumab is administered intravenously at a total dose of 5 g (two boluses of 2.5 g no more than 15 min apart). Since the half-life of idarucizumab (10 h) is shorter than that of dabigatran (12-17 h), repeated doses of idarucizumab may be required.<sup>33-36</sup> Given that dabigatran is mostly not bound to plasma proteins ( $>85\%$ ), haemodialysis can be considered a second-line treatment for major bleeding, especially in the presence of compromised renal function.

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 dose of DOAC.<sup>42-45</sup> Both idarucizumab and andexanet alfa do not require dose adjustments in patients with renal or liver dysfunction.

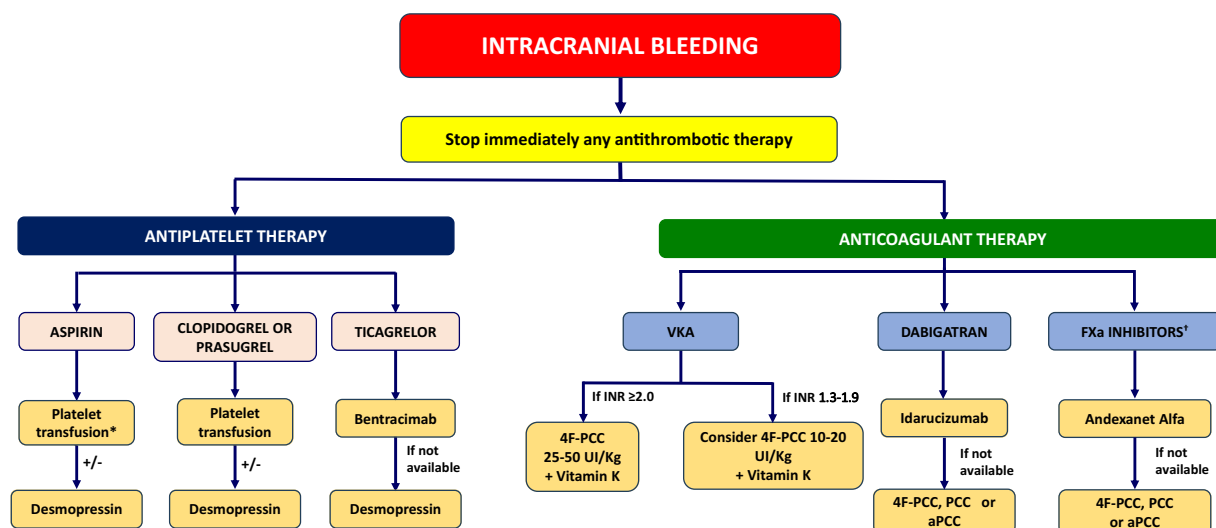
With the only exception of bentracimab for ticagrelor, there is no other specific reversal agent that rapidly and

Provide emergency treatment / supportive care (see Figure 1)

| Class     | Direct thrombin inhibitor | Direct FXa inhibitor   |   | AT-mediated inhibition of Xa | Thrombin inhibitor; inactivates FXa indirectly |                        | Vitamin K antagonist                                    | ASA/P2Y <sub>12</sub> inhibitor | P2Y <sub>12</sub> inhibitor                                |
|-----------|---------------------------|--|---|------------------------------|--|------------------------|---|---------------------------------|--|
| Agent     | Dabigatran                | Rivaroxaban/ Apixaban  | Edoxaban  | Fondaparinux                 | Unfractionated heparin                         | Enoxaparin/ Dalteparin | Warfarin  | Aspirin Clopidogrel/Prasugrel   | Ticagrelor   |
| Last dose | (<8-12 h)                 | (<18 h)  | (10-14 h)   | (17-21 h)                    | (based on PTT) (1-2 h)                         | (3-5 h)                | (Based on INR) (20-60 h)                                | (<24 h)                         | (<12 h)  |
| Level 1   | Idarucizumab 5 mg         | Andexanet Alfa<br>Last DOAC dose >10/5 mg or taken < 8 h: high dose (see Table 1)<br>Last DOAC dose ≤10/5 mg or taken ≥8 h: low dose (see Table 1) | 4F-PCC/aPCC*  | 4F-PCC/aPCC*                 | Protamine                                      |                        | Vitamin K (5-10 mg) & 4F-PCC (25-50 UI/Kg based on INR) | Platelet transfusion            | Bentricimab  |
| Level 2   | 4F-PCC/aPCC*   Dialysis   | 4F-PCC/aPCC*<br>Consider blood absorption in case of surgical intervention   | Andexanet Alfa†<br>Bolus 800 mg at 30 mg/min + infusion of 8 mg/min until 2 h | 4F-PCC/aPCC*                 |  |                        | FFP 10-15 ml/Kg   | Desmopressin                    | Consider blood absorption in case of surgical intervention |

Re-evaluate: | clinical status, laboratory and imaging findings

**Figure 2** Use and dosage of reversal agents in cases of major ongoing bleeding or in patients requiring urgent procedures. 4F-PCC, four-factor prothrombin complex concentrate; aPCC, activated prothrombin complex concentrate; aPTT, activated partial thromboplastin time; ASA, acetylsalicylic acid; AT, antithrombin; DOAC, direct oral anticoagulant; FFP, fresh frozen plasma; INR, international normalized ratio. \*4F-PCC: 2000 IU; aPCC: 50 IU/kg. †Currently not recommended by the European Medicines Agency; however, 55 patients on edoxaban were studied in ANNEXa-4. The dosing regimen for these patients is shown in the figure.



**Figure 3** Flowchart for the use and dosage of reversal agents in the case of intracranial haemorrhage. 4F-PCC, four-factor prothrombin complex concentrate; aPCC, activated prothrombin complex concentrate; VKA, vitamin K antagonist; FXa, factor Xa; INR, international normalized ratio; PCC, prothrombin complex concentrate. \*Only in the case of neurosurgical intervention. †Rivaroxaban and apixaban according to the indications of the European Medicines Agency.

effectively neutralizes antiplatelet drugs. Tranexamic acid is not systematically recommended for reversing antiplatelet drugs, while platelet transfusion and desmopressin have been shown to reduce bleeding, blood transfusions, and reoperations in patients taking antiplatelet therapy undergoing cardiac surgery,<sup>7,57,58</sup> and can therefore be a valid option for improving platelet function in these circumstances. To avoid the

inhibition of newly transfused platelets, transfusions should be performed only after the active forms of antiplatelet drugs are no longer present at therapeutic plasma concentrations (i.e. at least 2 h after the last intravenous dose of aspirin or 4-5 h if administered orally and 4 h after the last dose of clopidogrel and prasugrel when absorption is not delayed by opioids).

**Figure 2** illustrates the panel recommendations on first- and second-level treatment strategies in case of ongoing major bleeding or in patients at risk of major haemorrhagic events.

Post-reversal management of antithrombotic drugs, including the indication and timing of resuming therapy, depends on the individual balance of thrombotic and bleeding risk, operating in close multidisciplinary collaboration. Specific laboratory tests for coagulation monitoring after the administration of reversal agents are generally recommended.

### Intracranial bleeding

Intracranial haemorrhage remains the most feared and devastating complication of antithrombotic drugs and deserves specific consideration.

The reversal of aspirin by platelet transfusion can be considered in this context only in the case of emergency neurosurgery. Platelet transfusion can instead be used in the case of clopidogrel or prasugrel (it is ineffective with ticagrelor). To antagonize ticagrelor, the use of bencicabimab can be considered, if available. The use of desmopressin, with or without concomitant platelet transfusion, to antagonize antiplatelet therapy in this setting can be considered, although controversial.

In patients with intracranial haemorrhage treated with VKAs, PCCs in addition to vitamin K are recommended to normalize the INR and have been shown to reduce haematoma expansion and mortality.<sup>71</sup> In patients on dabigatran therapy, idarucizumab represents the treatment of choice, while andexanet alfa is suggested in some categories of patients taking apixaban or rivaroxaban (**Figure 3**). If these DOAC reversal agents are not available, the use of PCCs can be considered.

### Conclusions

Recent advances in antithrombotic strategies have improved our ability to balance ischaemic event prevention with the risks of bleeding-related harm. Despite these advancements, haemorrhagic complications are still common and can be life-threatening. To address this, new interventions aimed at rapidly reversing or neutralizing antithrombotic drugs have emerged, focusing on managing major bleeding or imminent risk of severe haemorrhagic events. Early research on these agents is encouraging, yet conclusive evidence of their clinical efficacy remains forthcoming. Moreover, concerns about potential prothrombotic side effects call for careful use of these interventions in specific emergency settings.

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