

Managing reversal of direct oral anticoagulants in emergency situations

Anticoagulation Education Task Force White Paper

Walter Ageno¹; Harry R. Büller²; Anna Falanga³; Werner Hacke⁴; Jeroen Hendriks^{5,6}; Trudie Lobban⁷; Jose Merino⁸; Ivan S. Milojevic⁹; Francisco Moya¹⁰; H. Bart van der Worp¹¹; Gary Randall¹²; Konstantinos Tsioufis¹³; Peter Verhamme¹⁴; A. John Camm^{15,16}

¹University of Insubria, Varese, Italy; ²Academic Medical Centre, Amsterdam, The Netherlands; ³Department of Immunohematology & Transfusion Medicine and the Hemostasis and Thrombosis Center, Hospital Papa Giovanni XXIII, Bergamo, Italy; ⁴Department of Neurology, Heidelberg University, Heidelberg, Germany; ⁵Centre for Heart Rhythm Disorders, University of Adelaide, Royal Adelaide Hospital, South Australian Health & Medical Research Institute, Adelaide, Australia; ⁶Department of Medical and Health Sciences, Linköping University, Linköping, Sweden; ⁷Arrhythmia Alliance and AF Association, Hampshire, UK; ⁸Arrhythmia Research Unit, Universitario La Paz, Madrid, Spain; ⁹General Hospital Cuprija, Cuprija, Serbia; ¹⁰International Medical Services and Emergency Medicine, Vithas-Xanit International Hospital, Benalmadena, Malaga, Spain; ¹¹Department of Neurology and Neurosurgery, Brain Center Rudolf Magnus, University Medical Center Utrecht, Utrecht, The Netherlands; ¹²Stroke Alliance For Europe (SAFE), London, UK; ¹³First Cardiology Clinic, Hippokraton Hospital, University of Athens, Greece; ¹⁴University of Leuven, Leuven, Belgium; ¹⁵Division of Cardiovascular Sciences, St George's University of London, London, UK; ¹⁶CMS, Imperial College, London, UK

Summary

Anticoagulation is the cornerstone of prevention and treatment of venous thromboembolism (VTE) and stroke prevention in patients with atrial fibrillation (AF). However, the mechanisms by which anticoagulants confer therapeutic benefit also increase the risk of bleeding. As such, reversal strategies are critical. Until recently, the direct oral anticoagulants (DOACs) dabigatran, rivaroxaban, apixaban, and edoxaban lacked a specific reversal agent. This report is based on findings from the Anticoagulation Education Task Force, which brought together patient groups and professionals representing different medical specialties with an interest in patient safety and expertise in AF, VTE, stroke, anticoagulation, and reversal agents, to discuss the current status of anticoagulation reversal and fundamental changes in management of bleeding associated with DOACs occasioned by the approval of idarucizumab, a specific reversal agent for dabigatran, as well as recent clinical data on specific reversal agents for factor Xa in-

hibitors. Recommendations are given for when there is a definite need for a reversal agent (e.g. in cases of life-threatening bleeding, bleeding into a closed space or organ, persistent bleeding despite local haemostatic measures, and need for urgent interventions and/or interventions that carry a high risk for bleeding), when reversal agents may be helpful, and when a reversal agent is generally not needed. Key stakeholders who require 24–7/around-the-clock access to these agents vary among hospitals; however, from a practical perspective the emergency department is recommended as an appropriate location for these agents. Clearly, the advent of new agents requires standardised protocols for treating bleeding on an institutional level.

Keywords

Anticoagulation, venous thromboembolism, stroke prevention, atrial fibrillation, reversal agents

Correspondence to:

Walter Ageno, MD
University of Insubria
Varese, Italy
E-mail: agewal@yahoo.com

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Introduction

Venous thromboembolism (VTE) and atrial fibrillation (AF) represent an important public health burden. VTE, which comprises both deep-vein thrombosis (DVT) and pulmonary embolism (PE), is an important source of morbidity and mortality in a broad range of patients. Similarly, AF is a global healthcare issue, with evidence indicating an increase in prevalence and incidence worldwide (1–3). Given the aging of the global population and the increasing prevalence of conditions such as diabetes and hypertension, the problems posed by stroke in patients with AF are likely to grow (4).

Fundamentally, both VTE and stroke in patients with AF are diseases of disordered coagulation. As such, these patients may

require anticoagulation, which until the past six years has primarily consisted of parenterally administered heparin and low-molecular-weight heparin (LMWH), and orally administered vitamin K antagonists (VKAs). These agents have revolutionised the management of these disease states, but—particularly in the case of VKAs—are associated with considerable clinical liabilities.

The use of the direct oral anticoagulants (DOACs), also referred to as new or non-vitamin K oral anticoagulants (NOACs), which include the direct thrombin inhibitor dabigatran and the factor Xa inhibitors rivaroxaban, apixaban, and edoxaban, has—in many parts of the world and for several indications—largely supplanted the use of conventional agents, particularly the VKAs. The underlying reasons for this shift in practice pattern are clear: these agents are generally simple to dose, are not subject to a broad spec-

trum of drug and food interactions, do not require routine monitoring, and have a rapid onset and offset of effect. Further, these benefits do not appear to come at a major cost in terms of either efficacy or safety; the pivotal studies for each of these agents show at least equivalent, and in some respects, superior performance to alternative strategies for managing both VTE and AF (5–9).

The primary limitation of the DOACs, to date, has been the lack of readily available and clinically proven reversal agents. This is in contrast to VKAs, for which bleeding has been managed for decades with the administration of vitamin K and repletion of coagulation factors. As such, there is a perceived need for reversal agents for the DOACs.

This publication is based, in part, on findings from the Anticoagulation Education Task Force, a meeting held in Mainz, Germany. This meeting was chaired by an internist with interest in thrombosis and bleeding disorders, Walter Ageno, and a cardiologist, A. John Camm. The two chairmen invited a broad range of medical professional societies, patient groups, healthcare providers, to nominate physicians and lay members with interest and expertise in anticoagulation and reversal agents. The aim of the meeting was to discuss the current status of anticoagulation reversal and the fundamental changes in the management of bleeding associated with DOACs occasioned by the approval of idarucizumab, a novel, specific reversal agent for dabigatran, as well as recent clinical data on specific reversal agents for factor Xa inhibitors. This meeting was funded by Boehringer Ingelheim. This paper describes the main results of the discussion and the recommendations for the correct use of the reversal agents proposed by the members of the task force. No formal consensus strategies were applied. After the meeting, a white paper was drafted by the two chairmen together with one of the invited experts, Peter Verhamme. The content of the paper was shared with all members of the Task Force who agreed on the final content after thorough discussion of the text and of the recommendations. No formal endorsement was sought from national or international scientific societies, so the content of this white paper solely reflects the opinion of the members of the Task Force.

Safety of the DOACs

The efficacy and safety of DOACs for stroke prophylaxis in non-valvular AF and for the treatment and secondary prevention of

Table 1: Approximate half-lives of current oral anticoagulants in healthy subjects. Information from respective package inserts.

Agent	Half-life, hours
Warfarin	Mean ~40
Dabigatran	12–17
Rivaroxaban	5–13
Apixaban	12
Edoxaban	10–14

VTE has been established in several phase 3 clinical trials and confirmed by a number of meta-analyses.

Several post-marketing studies have then shown that the risks for major bleeding do not appear higher outside of the clinical trial setting, as illustrated in several studies. In the first, conducted in patients receiving thromboprophylaxis for stroke prevention in AF, the risk of major bleeding was similar in patients who received dabigatran 110 mg (hazard ratio [HR], 0.82; 95% confidence interval [CI], 0.59–1.12) or 150 mg (HR, 0.77; 95% CI, 0.67–1.83) compared with warfarin (10). Consistent with the results seen in pivotal phase 3 clinical trials of the DOACs, there was a profound reduction in the risk for intracranial haemorrhage among patients who received dabigatran 110 mg (HR, 0.24; 95% CI, 0.08–0.56) or 150 mg (HR, 0.08; 95% CI, 0.01–0.40) compared with those who received warfarin. In a retrospective cohort study leveraging US Medicare data in elderly patients who received dabigatran or warfarin for stroke prevention in AF, the HRs for dabigatran versus warfarin were 0.80 (95% CI, 0.67–0.96) for ischaemic stroke; 0.34 (95% CI, 0.26–0.46) for intracranial haemorrhage; 1.28 (95% CI, 1.14–1.44) for major gastrointestinal bleeding; 0.92 (95% CI, 0.78–1.08) for acute myocardial infarction, and 0.86 (95% CI, 0.77–0.96) for death (11). In addition, in a real-world, prospective, observational study of patients treated with rivaroxaban for stroke prevention in AF (N=6784), the rate of major bleeding was low (2.1/100 patient-years) and fatal bleeding was rare (0.2/100 patient-years) (12). Finally, the results of a recent post-marketing, prospective, observational study confirmed the safety of rivaroxaban in the treatment of patients with DVT (13).

Although the DOACs have several advantages when compared with the subcutaneous heparins and oral VKAs, concern about the lack of readily available and easily implemented antidotes has tempered enthusiasm for these agents among both physicians and patients.

The current situation: Reversibility of conventional agents and DOACs

While the conventional agents have numerous limitations, some have the benefit of reversibility with either vitamin K and coagulation factor concentrates (in the case of VKAs), or protamine in the case of unfractionated heparin (and to a lesser extent, the LMWHs) (14). However, the administration of vitamin K only provides partial and slow reversal of VKAs. Warfarin acts by inhibiting the synthesis of vitamin K-dependent clotting factors, which include factors II, VII, IX, and X, through the inhibition of the regeneration of vitamin K1 epoxide (15). Warfarin inhibition of vitamin K epoxide is essentially irreversible (16); thus, full recovery of anticoagulant function depends on synthesis of vitamin K1 epoxide and, subsequently, production of vitamin K-dependent clotting factors. For this reason, immediate reversal of warfarin requires repletion of coagulation factors, often accomplished with fresh frozen plasma or prothrombin complex concentrates (17).

The LMWHs and parenteral factor Xa inhibitors, in general, have poor reversibility, but benefit in this regard from a short half-

life, in particular for LMWH (3-5 hours [h] for LMWHs, 17-21 h for fondaparinux) (14). Likewise, the DOACs have a relatively short half-life in healthy patients (► Table 1) that, in non-urgent situations, permit the relatively rapid reversal simply through the discontinuation of treatment.

The lack of tested reversal agents, and the consequent fear of uncontrolled bleeding, have represented a matter of concern with the use of DOACs in the clinical setting. Indeed, in a number of clinical situations the urgency is such that simple discontinuation of a DOAC is insufficient to address the clinical need, such as life-threatening bleeding, urgent interventions, trauma, or accidental or deliberate overdose. Because all of the currently available DOACs are cleared in part by the kidney, the need for a rapid reversal agent is particularly strong among patients with renal impairment.

In the absence of a specific reversal agent, a number of strategies have been proposed (18). Activated charcoal, which acts by reducing drug absorption from the gastrointestinal tract, has been evaluated as a potential method for inactivating these agents if ingested within 2 h. In a porcine model, dabigatran was successfully removed from the circulation after activated charcoal perfusion, with 75% to 80% clearance after 1 h and undetectable levels after 2 h (19). Haemodialysis may also reverse the effects of dabigatran (19); however, because of high protein binding none of the factor Xa inhibitors are expected to be dialysable.

Reversal of the anticoagulant effects may also, at least theoretically, be accomplished through the use of nonspecific agents, such as prothrombin complex concentrate (PCC), activated PCC (APCC), and recombinant factor VIIa (rVIIa). Again, none of these agents has been studied prospectively in bleeding patients, and current evidence for their efficacy is based on a range of animal models and studies in healthy volunteers (18). A comprehensive review of the efficacy of these agents in patients receiving DOACs can be found in Siegal 2015 (18).

Together, these data do not provide a strong foundation on which to base reversal strategies in actively bleeding patients taking DOACs. To address the clinical need for specific reversal agents, a number of compounds have been recently developed, one, idarucizumab, has been approved for clinical use and a second, andexanet alfa, is under evaluation by regulatory agencies.

Specific reversal agents for the DOACs

The recent approval of idarucizumab, the first specific reversal agent for a DOAC, has led to questions regarding how it should be implemented in daily practice. Idarucizumab is a monoclonal antibody fragment that binds to dabigatran with an affinity that is 350-fold higher than that observed with thrombin. As a result, idarucizumab binds both free and thrombin-bound dabigatran and rapidly neutralises its activity. Idarucizumab was recently approved in the United States, Canada, and European Union under an accelerated approval based on a reduction in unbound dabigatran and normalization of coagulation parameters in healthy volunteers for reversal of the anticoagulant effects of dabigatran

for emergency surgery/urgent procedures and in cases of life-threatening or uncontrolled bleeding as well as data from a phase III real-world study (20–22). It is administered in a total dose of 5 g intravenously, either as two consecutive intravenous infusions of 2.5 g or as a single intravenous bolus injection (20).

The efficacy of idarucizumab was initially evaluated in healthy young volunteers with normal renal function, volunteers aged 64-80 years, and volunteers aged 45-80 years with mild or moderate renal impairment (21, 23, 24). In these studies, administration of idarucizumab resulted in immediate and complete reversal of the anticoagulant effects of dabigatran, without procoagulant effects. More recently, the efficacy and safety of idarucizumab was evaluated in a prospective cohort study conducted in patients with serious bleeding or who required an urgent procedure (22, 25). This ongoing, multicentre, prospective study will recruit up to 450 to 500 patients at multiple centres worldwide; a recently reported interim analysis included 90 patients, including 51 who received idarucizumab for serious bleeding and 39 who required an urgent intervention. Patients received 5 g intravenous idarucizumab, administered as two 50-ml bolus infusions, each containing 2.5 g idarucizumab, no more than 15 minutes (min) apart. This dose was chosen to reverse the total body load of dabigatran associated with the 99th percentile of dabigatran levels measured in the Randomized Evaluation of Long-Term Anticoagulation (RE-LY) study, which was conducted in patients with AF at risk for stroke (5).

The primary outcome of the study was the maximum percentage reversal of the anticoagulant effect of dabigatran, as determined at any point from the end of the first idarucizumab infusion to 4 h after the second infusion. The percentage reversal was assessed on the basis of measurement of the dilute thrombin time or ecarin clotting time at a central laboratory at different times up to 24 h and again at three months. Clinical events were secondary outcomes. Among patients who required reversal for urgent bleeding, the extent of bleeding and haemodynamic stability was assessed at 10 and 30 min and at regular intervals after the second infusion. Among those who required reversal because of the need for an urgent intervention, haemostasis was classified by the physician as normal or as mildly, moderately, or severely abnormal.

Among patients with bleeding, 18 had intracranial haemorrhage, 20 had gastrointestinal bleeding, nine had bleeding from trauma, and 11 had other causes of bleeding; the median time from the last dose of dabigatran was approximately 15 h. Across both groups of patients, the median maximum percentage reversal of anticoagulant activity was 100%, as assessed by both dilute thrombin time and ecarin clotting time. After the target dose was administered, complete reversal was evident at 4 h. At 12 and 24 h, the dilute thrombin time was below the upper limit of the normal in 90% of patients with bleeding who could be evaluated and 81% of those who underwent urgent procedures. The median reported time to cessation of bleeding among patients who required reversal because of major bleeding was 11.4 h. Among 36 patients in group B who underwent a procedure, normal intraoperative haemostasis was reported in 33 (92%), and mildly or moderately abnormal haemostasis was reported in two patients and one patient, respectively. Thrombotic events occurred in five patients. None was re-

ceiving antithrombotic therapy when these events occurred. No serious adverse reactions were seen in these studies, nor were anti-drug antibodies detected.

One agent is under investigation for the specific reversal of factor Xa-directed agents and its approval will soon be discussed by the Food and Drug Administration in the United States. Andexanet alfa (andexanet) is a recombinant modified human factor Xa decoy protein (26). It is catalytically inactive; however, it retains the ability to bind factor Xa inhibitors at the active site with high affinity. Andexanet also maintains high affinity for the antithrombin-heparin complex and reverses antithrombin-dependent anticoagulant effects of indirect factor Xa inhibitors (enoxaparin, fondaparinux). It therefore acts by sequestering factor Xa inhibitors, restoring endogenous factor Xa activity, as measured by thrombin generation and anti-factor Xa activity (27).

The efficacy of andexanet in reversing the anticoagulant activity of factor Xa inhibitors was examined in several proof-of-concept and dose-ranging studies. These studies demonstrated that andexanet provides dose-dependent, rapid reversal of the anticoagulant effects of available factor Xa inhibitors, including the oral agents rivaroxaban, apixaban, and edoxaban and the parenteral agent enoxaparin (27–31). No serious adverse reactions were seen in these studies, nor were anti-factor Xa antibodies detected.

The efficacy and safety of andexanet was further examined in paired studies (ANNEXA-A and -R) conducted in older healthy volunteers taking apixaban and rivaroxaban, respectively (26). In these studies, healthy older volunteers received either twice-daily

apixaban 5 mg for 3.5 days or once-daily rivaroxaban 20 mg for four days; andexanet was administered either as a bolus (400 or 800 mg for apixaban or rivaroxaban, respectively) or as a bolus plus a 2-h infusion (4 or 8 mg/min, respectively). Among apixaban patients who received a bolus dose of andexanet, there was a 94% decrease in anti-factor Xa activity, compared with a 21% decrease among those who received placebo ($p < 0.001$). Thrombin generation was restored within 2–5 min in all andexanet patients versus 11% of placebo patients ($p < 0.001$). Similar results were observed in patients who received rivaroxaban, with a 92% vs 18% reduction in factor Xa activity and restoration of thrombin generation in 96% vs 7% of andexanet and placebo patients, respectively. The effects were sustained when andexanet was administered as a bolus followed by a 2-h infusion. Notably, transient increases in D-dimer and prothrombin fragments 1 and 2 were seen in a subset of patients, all of which resolved within 24–72 h. No serious adverse events or thrombotic events were observed. An ongoing study is evaluating the use of andexanet in patients with major bleeding.

A third agent, ciraparantag, is in earlier clinical development. It is a small, synthetic, water-soluble, positively charged molecule that may act as a universal reversal agent (32, 33). It has been shown to bind heparin, rivaroxaban, apixaban, edoxaban, and dabigatran in preclinical models, and has been tested with edoxaban and LMWH in healthy volunteers. After a single 60-mg oral dose of edoxaban, an intravenous bolus of ciraparantag shortened the whole blood clotting time to within 10% of baseline in a dose-dependent manner.

Table 2: Situations in which to consider use of a reversal agent.

Clinical situation	Definite need for a reversal agent	Reversal agent possibly helpful (patient-dependent)	Reversal agent generally not needed
Life-threatening bleeding (e.g., intracranial haemorrhage, symptomatic or expanding extradural haemorrhage, or uncontrollable haemorrhage)	X		
Bleeding in a closed space or critical organ (e.g., intracranial, intraspinal, intraocular, pericardial, pulmonary, retroperitoneal, or intramuscular with compartment syndrome)	X		
Persistent major bleeding despite local haemostatic measures, or risk of recurrent bleeding because of delayed DOAC clearance or DOAC overdose	X		
Need for urgent intervention that is associated with a high risk of bleeding and that cannot be delayed to allow for drug clearance	X		
Emergency surgery or intervention in patients at high risk for procedural bleeding: neurosurgery (intracranial, extradural, or spinal), lumbar puncture, cardiac, or vascular surgery (aortic dissection/aneurysm repair), hepatic, or other major organ surgery	X		
Need for urgent surgery or intervention in patients with acute renal failure		X	
Elective surgery			X
Gastrointestinal bleeds that respond to supportive measures			X
High drug levels or excessive anticoagulation without associated bleeding			X
Need for surgery or intervention that can be delayed long enough to permit drug clearance			X

DOACs, non-Vitamin K oral anticoagulants. Adapted from Levy et al. 2015 (31).

Recommendations: Operationalising anticoagulant reversal in clinical practice

Patient safety is a priority when introducing new anticoagulant products to the healthcare environment.

Candidates: Who should receive reversal agents?

Given the short half-lives of the DOACs and the lower risk of bleeding compared with warfarin, the need for reversal agents is relatively limited. In fact, data before the advent of reversal agents suggest that major bleeds can be treated in up to one-third of patients without blood products or haemostatic agents (34). Nevertheless, there are circumstances in which very rapid reversal of anticoagulant therapy is desirable, such as serious bleeding, urgent interventions, or trauma. The reversal of warfarin has long been operationalised at most centres; new protocols are needed for patients taking the DOACs. The members of the Task Force unanimously decided to endorse the protocol proposed by the International Society on Thrombosis and Haemostasis (35) and reported in ► Table 2 to provide some guidance for when a specific reversal agent may be necessary in patients receiving DOACs.

There is an important issue of when and how to use reversal agents in urgent situations, particularly given that, like any therapeutic agent, their use may not be entirely benign, although there is currently little evidence for serious adverse effects associated with these agents. At present, there is no labelled requirement to conduct testing in advance of an urgent intervention. If such a requirement is added, however, manufacturers of these agents and device companies should collaborate to create point-of-care devices to permit rapid determination of DOAC exposure at the bedside.

Among known users of dabigatran, activated partial thromboplastin time (aPTT) and diluted thrombin time (dTT) may provide useful information both on the presence of active dabigatran and to confirm normal haemostasis before surgical intervention; among patients who receive a factor Xa inhibitor, a calibrated quantitative factor Xa assay or prothrombin time (PT) may be useful in situations in which knowledge of exposure may help inform clinical decisions. Until rapid determination of DOAC activity becomes available, however, laboratory testing should not drive the decision to administer reversal agents in the presence of life-threatening bleeding or in the need for emergency surgery for life-threatening conditions.

Protocol development

Who should control access to reversal agents?

Key stakeholders involved in anticoagulant reversal will vary from hospital to hospital, so there is a need for local anticoagulant reversal protocols to be developed involving all relevant disciplines. In general, reversal agents require round-the-clock access and should be rapidly available in the emergency department because they are most likely to be required on an urgent basis (► Table 3). Regard-

Table 3: Who should control access to reversal agents?

<ul style="list-style-type: none"> Investigate whether there is a hospital bleeding management protocol – if not contact relevant departments: haematology, cardiology, neurology, etc.
<ul style="list-style-type: none"> Check that the reversal agent has been incorporated into the hospital formulary – if not take steps for the reversal agent to be considered by the appropriate committee.
<ul style="list-style-type: none"> Redraft the policy and flow chart(s) regarding the management of bleeding related to DOACs.
<ul style="list-style-type: none"> Discuss with relevant staff where the reversal agent should be stored ([accident and] emergency department, pharmacy, etc).
<ul style="list-style-type: none"> Arrange a supply of the reversal agent via the pharmacy or contact with the pharmaceutical company.
<ul style="list-style-type: none"> All appropriate hospital staff members should be made aware of the availability of specific reversal agent therapy.
<ul style="list-style-type: none"> Where applicable, a patient prescribed DOAC therapy should be informed of the availability of a specific reversal agent.
<ul style="list-style-type: none"> After use of the reversal agent inform the pharmacy (and the pharmaceutical company) that a new supply is needed.
<ul style="list-style-type: none"> Maintain a log on the use of the reversal agent and consider joining a local, national or international registry of post-marketing experience with the reversal agent.
DOAC, direct oral anticoagulant.

less of who the key stakeholders are considered to be at an individual institution, it is critical to develop site-specific protocols to ensure appropriate use of these agents in a timely manner and without the need to convene a team of experts in what is likely to be a time-critical situation. Such protocols should be developed by a multidisciplinary team, including experts in emergency care and bleeding management as well as cardiologists and neurologists, and also relevant pharmacists, administrators, and allied healthcare professionals. These protocols must also include the assessment of a patient who presents with an emergency and general measures in case of bleeding. These aspects are covered in other published documents specifically aiming at the management of the bleeding patient (36).

From a strictly practical perspective, logistical matters, such as storage, must be considered. Idarucizumab requires refrigeration, andexanet is likely to require refrigeration, and ciraparantag may not. Given the cost of these agents and the need to carefully select appropriate patients (see below), reversal agents are likely to be stored in the pharmacy with carefully controlled access; however, storage in a locked refrigerator in the emergency department may provide more rapid access for management of patients with urgent bleeding (35).

How should reversal agents be used in clinical practice?

Bleeding is highly heterogeneous, and as such, bleeding management needs to be individualised in any patient receiving an anticoagulant based on the location and severity of haemorrhage. Institutional protocols for the management of bleeding will need to be

updated to include idarucizumab and other reversal agents as they become available to clinicians. In addition, idarucizumab was also tested in non-bleeding patients requiring urgent surgery or procedures; the use of a reversal agent in these clinical settings needs to be considered in triage protocols, based on the results demonstrated in REVERSE-AD.

As with bleeding management, the decision whether and when to resume anticoagulation following severe bleeding or intervention is highly individual to the patient. Idarucizumab has a short half-life, allowing for resumption of dabigatran and normal anticoagulation efficacy within 24 h of administration. If the risk for thrombosis clearly outweighs the risk for bleeding, resumption of anticoagulation is warranted, potentially at a lower dose initially, with an increase to therapeutic levels when the risk-to-benefit ratio is deemed appropriate. Such a strategy has not yet been fully evaluated with other reversal agent–anticoagulant pairings.

The protocol shown in ►Figure 1 provides but one way to manage reversal in the era of specific DOAC reversal agents. Addi-

tional real-world data will assist in improving the efficient use of reversal agents in clinical practice and situations and patient types for which they can improve outcomes. Further studies are needed to clarify the residual role of concentrated clotting factors in patients with life-threatening bleeding treated with reversal agents and the circumstances when redosing of idarucizumab may become necessary.

Patient education: How should patients be educated about reversal agents?

Education of patients about DOACs by healthcare professionals should focus on the index conditions and the serious consequences of non-adherence. The patient should be clearly informed about treatment indication, dosing schemes, dosing instructions in case one or more doses are missed, risks associated with non-adherence and risks associated with drug intake. Most of all, the patient should receive adequate instructions for detecting and proper

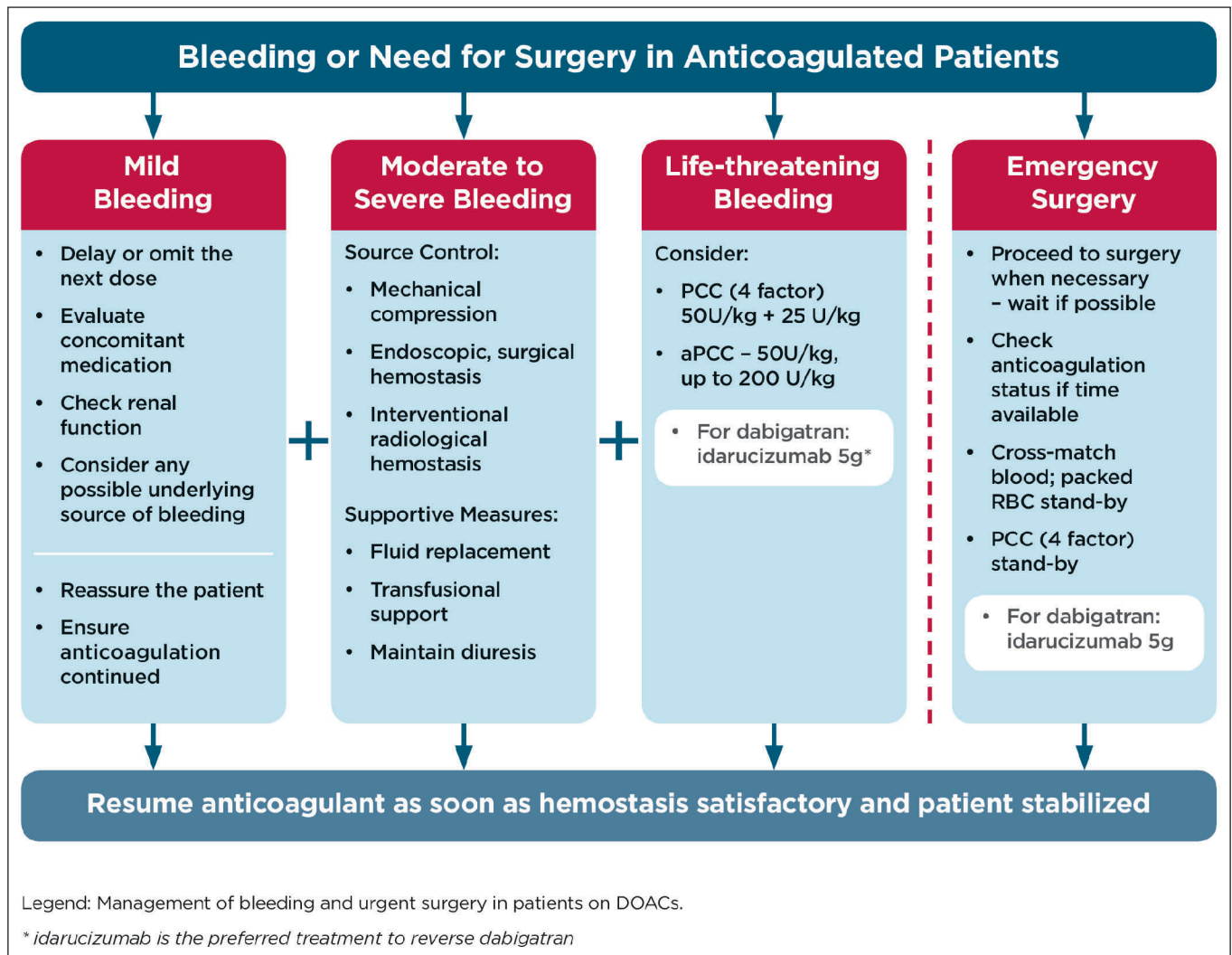


Figure 1: An algorithm for management of patients treated with a DOAC who present with mild, moderate to severe, or life-threatening bleeding or who require emergency surgery. DOAC, direct oral anticoagulant.

reporting of adverse reactions and should therefore receive contact information of the prescribing clinic. The availability of handout booklets summarizing all this information is strongly recommended. Nevertheless, in the interest of transparency, other aspects such as the question of reversal when initiating a DOAC should also be addressed with patients.

Conclusions

The advent of reversal agents for the DOACs may reduce concerns regarding the use of DOACs by facilitating ready control of bleeding in emergency situations. However, the appropriate use of reversal agents requires further delineation in order to avoid unnecessary risks and costs. Certain situations (e.g. life-threatening or persistent bleeding, bleeding into a closed space, and urgent interventions) warrant prompt use of reversal agents; other situations should be decided on a case-by-case basis. Use of these agents in patients in whom bleeds respond to supportive measures, or to accelerate time to elective surgery or reduce high drug levels, is probably not warranted in most cases. In addition, rapid reversal of anticoagulation per se will never solve bleeding until the source of bleeding has been appropriately managed and treated.

Here, we have provided recommendations regarding the use of reversal agents. However, entry of these agents into clinical practice requires consideration of access and operationalization that must be clearly elucidated on an institutional level to prevent over- and misuse of reversal agents.

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Conflicts of interest

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