Commentary

Reversal of oral anticoagulation in emergency conditions

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INTRODUCTION

Oral anticoagulation is strongly recommended by international guidelines for treatment and secondary prevention of venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), and for prevention of ischemic stroke and systemic embolism in patients with atrial fibrillation (AF) or patients with mechanical heart valves[1-3]. Altogether, these diseases represent very widespread conditions, which often require life-long anticoagulation.

According to the report of the Italian Medical Agency (AIFA)[4], in 2022 in Italy, only for the indication of AF, about 1.790.000 patients were on anticoagulant treatment. According to the global disease burden registry, by 2019 there were 59 million individuals living with AF worldwide, with 75% of them receiving anticoagulant treatment. Projections indicate that these numbers are predicted to increase[5].

Anticoagulation is the mainstay of prevention and treatment of thromboembolic phenomena and is a life-saving therapy. However, the mechanisms by which anticoagulants provide beneficial effects to the cure of patients also cause an increment of bleeding risks. Therefore, the availability of antidotes for the reversal of their anticoagulant effects is of utmost importance.

ORAL ANTICOAGULANT AGENTS

To date, two classes of oral anticoagulant drugs are available in clinics:

1. The vitamin K antagonists (VKAs), also named coumarins, i.e., warfarin, acenocoumarol, phenprocoumon. They inhibit blood coagulation by blocking the vitamin K-dependent carboxylation of factors VII (FVII), IX (FIX), X (FX), and II (FII), fundamental for generating fully active factors, overall named "vitamin K-dependent factors" or "prothrombin complex factors". Due to the variable anticoagulant effect of VKAs (for their numerous food and drug interactions and high protein affinity), periodic laboratory monitoring of their anticoagulant activity is required by testing the prolongation of the prothrombin time (PT), usually expressed as an international normalized ratio (INR). Dose adjustments may be necessary according to the PT INR values.
2. The Direct Oral Anticoagulants (DOACs), i.e., a) dabigatran, which directly and selectively binds to and inactivates thrombin (FIIa); b) rivaroxaban, apixaban, and edoxaban, which directly and selectively inhibit activated FX (FXa). DOACs are simple to dose, less exposed to food and drug interactions, and have a rapid onset and offset of anticoagulant effect. All DOACs are administered at fixed doses and do

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not require routine laboratory monitoring. However, specific laboratory tests are available and are useful for measuring (not monitoring) their plasma levels in particular conditions, as described in a dedicated chapter by Tripodi *et al.*[6] in this volume. In general, laboratory results should be available within less than 20 minutes of blood collection to be useful for clinical decisions in emergency[7].

Evidence-based clinical trials recognize DOACs as the first-line option for treating VTE and preventing stroke and systemic embolism in non-valvular AF. Differently, VKAs are the only option for patients with mechanical heart valves or AF with moderate to severe mitral valve stenosis. These recommendations are strongly supported by international guidelines[1-3,8]. In randomized clinical trials, DOACs show a reduced risk of intracranial hemorrhage (ICH), while the results for major bleeding (MB) and clinically relevant non-major bleeding (CRNMB) events vary among the agents when compared to VKAs. However, as their use has become more favored over the last decade, the reported incidence of DOAC-related bleeding adverse events has also increased, emphasizing the need for available reversal treatments.

ANTIDOTES OF ORAL ANTICOAGULANT DRUGS

For patients on anticoagulant drugs who experience MB or require urgent surgery, reestablishing effective hemostasis is crucial, using antidotes and standardized reversal strategies. Initially, the enthusiasm about the use of DOACs was tempered by the lack of specific antidotes, as compared to VKAs, for which the pharmacological reversal by vitamin K administration plus the replacement of coagulation factors was well experienced for many years. Nowadays, antidotes are available for all approved oral anticoagulant drugs (**Figure 1**). Specific agents are vitamin K, idarucizumab, and andexanet. Unspecific agents include prothrombin complex concentrates (PCCs), fresh frozen plasma (FFP), and ciraparantag,

For the reversal of anticoagulation by VKA, the antidote is vitamin K, which facilitates the resumption of active gamma-carboxylated prothrombin complex factors[9]. Due to its delayed effect, vitamin K alone is insufficient in case of major or life-threatening bleeding. For a rapid reversal, global treatment guidelines advocate for the use of PCCs along with vitamin K (**Figure 2**). PCCs are blood-derived products containing non-activated vitamin K-dependent factors. Those containing FII, FX,

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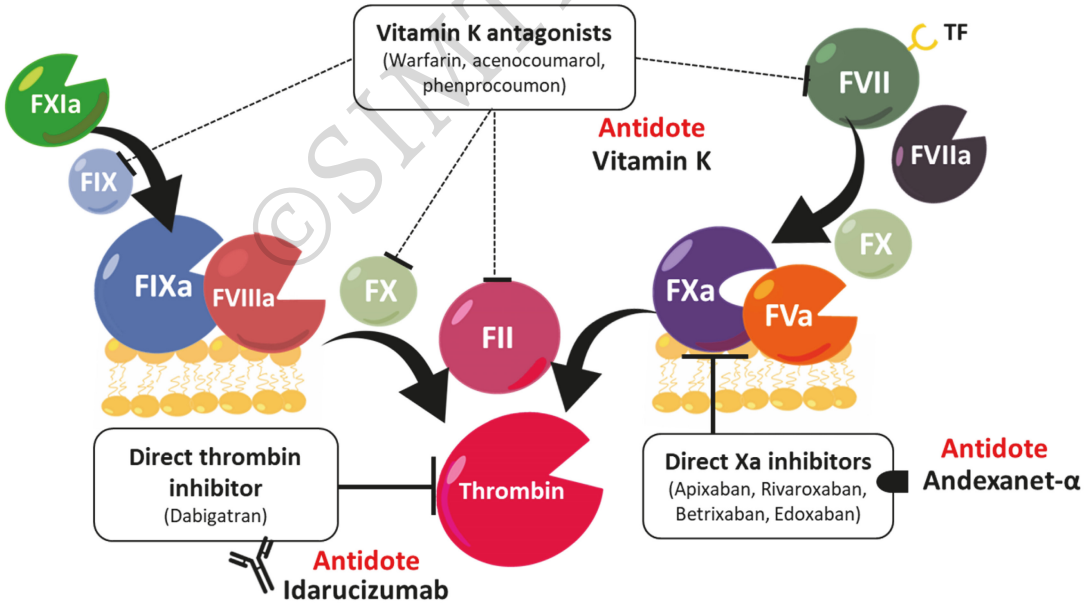


Figure 1 - Oral anticoagulant drugs and their specific antidotes
Vitamin K antagonists (VKAs), such as warfarin, acenocoumarol, and phenprocoumon, deplete the active form of vitamin K by inhibiting the enzyme vitamin K epoxide reductase, impairing the synthesis of fully active vitamin K-dependent coagulation factors II, VII, IX, and X. The specific antidote for VKAs is Vitamin K. The direct oral anticoagulants (DOACs) factor Xa inhibitors (rivaroxaban, apixaban, edoxaban, betrixaban) inhibit both free and clot-bound factor Xa, as well as prothrombinase activity, while dabigatran is a potent, synthetic, reversible, non-peptide inhibitor of thrombin (FIIa). Specific antidotes for DOACs include idarucizumab for dabigatran, and andexanet alfa for factor Xa inhibitors. *TF: tissue factor.*

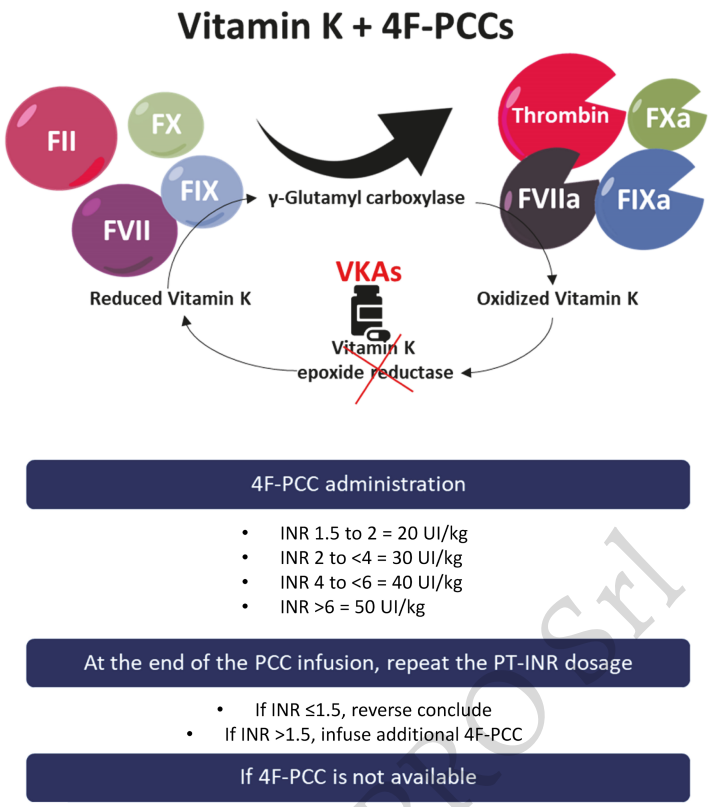


Figure 2 - Reversal of vitamin K antagonist
A dose of 10 mg of vitamin K, diluted in 100 mL saline solution, is administered intravenously (IV) over 30 minutes. This treatment facilitates the synthesis of active prothrombin complex factors, reducing prothrombin time-international normalized ratio (PT-INR) within 4 to 6 hours, with complete normalization achieved within 24 hours. Due to the latency of vitamin K action, in cases of major bleeding, it is necessary to start the restitution of factors by administering prothrombin complex concentrates (PCC). The baseline INR determines the recommended dose of four-factor-PCC (4F-PCC) for patients needing urgent reversal of VKAs. The dosing guidelines are as follows: administer 50 IU/kg for an INR of 6, 35 IU/kg for an INR between 4 and 6, and 25 IU/kg for an INR between 2 and 4.

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and FIX are known as "3-factor PCCs" (3F-PCC), while those containing also FVII are known as "4-factor PCCs" (4F-PCC)[10]. They are available as freeze-dried products to be infused intravenously in a small volume, thus not conferring a risk of fluid overload to the patient. They have immediate effect and currently represent, together with vitamin K, the treatment of choice for rapid reversal of therapy with VKAs. Recommended doses according to PT-INR values are depicted in **Figure 2**. When PPCs are not available, FFP may be considered.

Idarucizumab is the antidote of the anti-FIIa DOAC dabigatran. It was the first antidote approved to reverse a DOAC's effect. Registrative studies and real-life data show its good efficacy and safety profile. It is a humanized monoclonal antibody that competitively binds dabigatran with an affinity 350-fold higher than thrombin and an onset of action of less than 10 minutes[11]. The recommended dose and administration modality are shown in **Figure 3A**.

Andexanet alfa is the specific antidote of the anti-FXa DOACs. It is a recombinant protein with a similar structure to endogenous FXa but lacks enzymatic activity. It competes with FXa for binding to FXa inhibitors[12]. Doses and administration approaches are shown in **Figure 3B**.

Andexanet alpha is approved for the reversal of anticoagulant effect of apixaban and rivaroxaban, not edoxaban. Different doses of andexanet alfa are to be utilized depending on the type of FXa inhibitor taken and time from the last dose, which makes its use challenging in a busy emergency scenario. Also, due to the lack of data, uncertainty remains on its use for patients needing urgent surgery in the subsequent 12 hours. Despite these limitations, andexanet alpha represents an additional

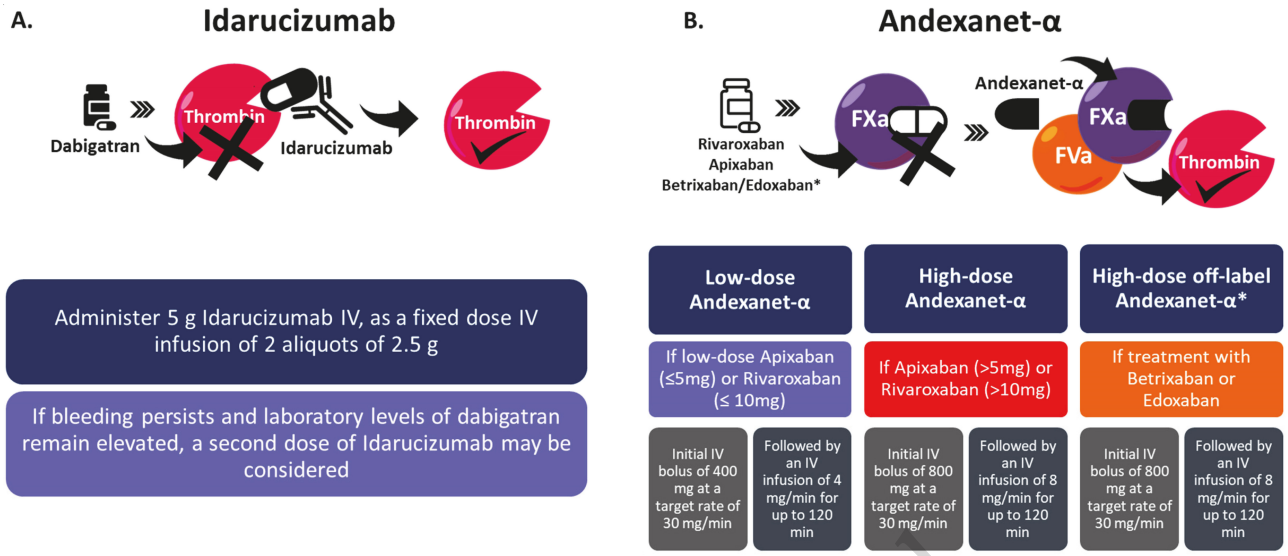


Figure 3 - Antidotes for anti-IIa (Idarucizumab) and anti-Xa (Andexanet-α)
A) Idarucizumab is a humanized monoclonal antibody that binds dabigatran with an affinity 350-fold higher than thrombin. The recommended dose of Idarucizumab is 5 g as a fixed IV infusion of two aliquots of 2.5 g.
B) Andexanet-alfa is a recombinant protein with a similar structure to endogenous FXa that binds FXa inhibitors but lacks enzymatic activity. For patients taking low doses of apixaban or rivaroxaban, andexanet should be administered as an initial intravenous (IV) bolus of 400 mg at a target rate of 30 mg/min. This should be followed by an IV infusion of 4 mg/min for up to 120 minutes. For patients taking standard doses, a higher dose of andexanet is recommended. This should consist of an initial IV bolus of 800 mg at a target rate of 30 mg/min, followed by an IV infusion of 8 mg/min for up to 120 minutes.

step forward in controlling the most adverse event of anticoagulant therapy[13].

As andexanet alfa is not yet available in all institutions, PCCs are often used for reversal of FXa inhibitors, based on limited evidence coming from observational studies[14].

Another antidote, not yet available but already investigated in phase 2 trials is Ciraparantag, a small water-soluble synthetic molecule. Ciraparantag binds to all, anti-IIa and anti-Xa DOACs, and heparins via non-covalent hydrogen bonds and charge-charge interactions and reverts the anticoagulant drug effects by displacing them from FXa and FIIa[15].

WHO SHOULD RECEIVE REVERSAL AGENTS?

According to the International Society of Thrombosis and Hemostasis criteria, bleeding episodes can be classified as:

1. MB: 1) fall in hemoglobin of 2 g/dL or transfusion of 2 or more units of blood; 2) symptomatic bleeding in critical organs (intra-cranial, intra-spinal, intra-ocular, retroperitoneal, intra-articular, pericardial, or intra-muscular with compartment syndrome) or fatal.
2. CRNMB: all bleeding episodes that were clinically relevant but did not qualify as MB (i.e., epistaxis that required intervention or spontaneous macroscopic hematuria).
3. Minor bleeding: all bleeding episodes that cannot be defined as MB or CRNMB.

Antidotes are essential in all cases of major or life-threatening bleeding or in case of urgent intervention with a high risk of bleeding (e.g., emergency surgery, neurosurgery, hepatic or other major organ surgery). Differently, they are not required in cases of gastrointestinal (GI) bleeding that responds to supportive measures, supratherapeutic levels of anticoagulant drugs without bleeding, elective surgery, or need for surgery that can be delayed long enough to permit anticoagulant drug clearance[16,17].

EMERGENCY SCENARIOS

Among emergency scenarios during anticoagulant therapy, ICH and GI bleeding not responding to supportive measures are indubitably the most noxious situations.

ICH is a serious complication of anticoagulant therapy with a 30- to 90-day mortality rate of 40-65%. The

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annual incidence of ICH during anticoagulant therapy is 0.3 to 1%, corresponding to a relative risk 3-10 times higher than in the general non-anticoagulated population. In most cases, ICH is fatal if there is a rapid hematoma expansion, and unfortunately, oral anticoagulants are associated with high rates of hematoma expansion. Therefore, anticoagulant reversal needs to be very timely. In AF patients, DOACs have shown a lower risk of bleeding complications, obtaining a 50% risk reduction of ICH[18]. However, the need for protocols to manage such a rare but challenging clinical situation remains high.

All the most recent guidelines recommend the use of idarucizumab for the prompt reverse of anticoagulation in patients with ICH taking dabigatran, while for those taking an anti-FXa agent, before andexanet alpha approval, 4F-PCCs were used. Today, for apixaban and rivaroxaban, the first recommended antidote is andexanet alpha, whereas the 4F-PCCs are considered in case of unavailability of andexanet[7,8,19].

The overall risk of GI bleeding in patients receiving anticoagulant therapy is approximately 1,5-5% per year. Emergency physicians generally start volume resuscitation for stabilization, assessing the need for blood transfusion based on hemoglobin level, extent of bleeding, and clinical presentation[20]. GI bleeding is the most common site of major bleeding associated with DOACs. In a sub-analysis of the ANNEXA-4 study, there was a 12% mortality rate due to anticoagulant-related major GI bleeding[21].

In patients with life-threatening GI hemorrhages, anticoagulation should be discontinued, and the use of reversal agents must be considered. All principal guidelines suggest, in case of GI bleeding on VKA, the use of 4F-PCC and vitamin K; in case of DOACs, the use of a specific reversal agent (i.e., idarucizumab or andexanet) or PCC[22-24].

Management of bleeding in emergency settings is usually multidisciplinary, with emergency physicians as first-line actors, but in consultation with other specialists, including neurologists, gastroenterologists, cardiologists, intensive care specialists, surgeons, transfusionists, and hemostasis experts, the latter one having a crucial role in guiding decisions in areas of uncertainty.

CONCLUDING REMARKS

For AVK the decennial experience makes reversal standardized all over the world. For dabigatran, the simple scheme of use, clear effectiveness, and relatively low cost of idarucizumab make its use easy. There are some uncertainty areas as regards andexanet, such as its cost that limits diffusion to tertiary hospitals, the in-label indication only for two of FXa inhibitors, lack of data for emergency surgery, the prolonged inhibition of tissue factor pathway inhibitor and risk of thrombotic events on rebound.

Due to the complexities of managing emergency conditions in patients taking oral anticoagulants, it is advisable that each institution develops specific policies based on locally available reversal agents and involving a multidisciplinary team.

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