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Recommendations of Polish Cardiac Society expert regarding the use of andexanet alpha in the Polish context. An interdisciplinary protocol

Short title: Recommendations of Polish Cardiac Society expert regarding the use of andaxanet alpha in the Polish context

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ABSTRACT

Andexanet alfa (AA) is a recombinant, inactive analog of human factor Xa (FXa), effectively reversing the effects of its inhibitors — rivaroxaban and apixaban, which are available in Poland. The drug was granted registration after the publication of the ANNEXA-4 trial (Andexanet Alfa, a Novel Antidote to the Anticoagulation Effects of FXA Inhibitors 4), in which its efficacy in restoring hemostasis in life-threatening hemorrhages in a group of patients using the aforementioned anticoagulants was proven. Hence, AA is now recommended for patients receiving apixaban or rivaroxaban therapy with massive and uncontrollable hemorrhages, including hemorrhagic strokes (HS) and gastrointestinal bleeding.

Drug-specific chromogenic anti-Xa assays are generally best suited for estimating rivaroxaban and apixaban plasma levels, aside from direct assessment of their concentrations. The absence of anti-Xa activity, determined using these assays, allows to outrule the presence of clinically relevant plasma concentrations of the FXa inhibitor. On the other hand, the dose of AA should not be modified based on the results of hemostasis tests, as it depends solely on the time elapsed since the last dose of FXa inhibitor, and on the dose and type of long-term medication used.

AA is administered as an intravenous (i.v.) bolus, followed by an i.v.infusion of the drug. The maximum reversal of anti-Xa activity occurs within two minutes of the end of the bolus treatment, with the continuation of the continuous i.v. infusion allowing the effect to be maintained for up to two hours afterwards. Because anticoagulant activity can reappear after the infusion is completed, it is currently unclear at what point after AA administration FXa inhibitors or heparin should be readministered.
Keywords: andexanet alfa, antidotum, bleeding, rivaroxaban, apixaban, non-vitamin K antagonist oral anticoagulants

INTRODUCTION

In recent years, non-vitamin K antagonist oral anticoagulants (NOACs) or direct oral anticoagulant inhibitors (DOACs) have mostly replaced vitamin K antagonists (VKAs) due to their efficacy, safety and predictable therapeutic effects. The use of NOACs, compared to VKAs, is associated with a lower risk of minor, clinically significant hemorrhages, as well as major hemorrhages, including those resulting in death. However, there is a greater risk of gastrointestinal bleeding in patients taking NOACs, probably due to the presence of the active
Due to the increasing number of users of the aforementioned agents, we encounter them more frequently among trauma patients and those referred to surgical wards. The presence of overt, acute bleeding, or the need for immediate surgical intervention, implies the need to reverse the anticoagulant effects of previously taken medications. Up until recently, for in-hospital use, the only previously available drug of this type was idarucizumab, reversing the activity of dabigatran. In the recent years, it was joined by a product that reverses the action of factor Xa (FXa) inhibitors, such as rivaroxaban and apixaban available in Poland, introduced to clinical practice after the success of randomized clinical trials. It is a recombinant, modified and inactive analog of FXa — andexanet alfa (AA) [1, 2].

FXa INHIBITOR ACTION MECHANISMS

The use of NOACs is an effective, safe and recommended in:

- prevention of stroke and peripheral embolism in patients with established permanent or paroxysmal atrial fibrillation;
- treatment and prevention of venous thromboembolism (VTE).

The NOACs available in Poland include dabigatran, a thrombin inhibitor, and FXa inhibitors, namely rivaroxaban and apixaban. FXa inhibitors are selective, direct inhibitors of FXa, which catalyzes the conversion of prothrombin to thrombin, with the effect of the drugs directly

proportional to their concentration. The bioavailability of rivaroxaban is 80%–100%, with a half-life of 7–11 hours, while that of apixaban is 50% and 12 hours, respectively. Both drugs are excreted in 1/3 by the kidneys in an unchanged form, while 2/3 are metabolized by CYP3A4. Unlike dabigatran, FXa inhibitors show a higher percentage of plasma protein binding, hence dialysis does not significantly reduce the concentration of these drugs [3, 4].

One of the many significant advantages of NOACs is the lack of need for routine monitoring of blood clotting parameters, as is the case with VKA therapy. However, it is important to remember that these drugs significantly affect the results of most hemostasis tests (Table 1). Routine monitoring of plasma NOAC concentrations for the purpose of dosage adjustment is not recommended, as it has not yet been investigated if such approach has any positive effects on the outcomes of long-term treatment. The dosage of most FXa inhibitors is currently determined solely by the indication for their use and renal function, while the dose of apixaban is additionally determined by the patient's age and weight. The recommended dosages for each clinical indication are shown in the following Tables 2 and 3 [1, 5].

Table 1. The influence of NOACs on hemostasis results

Test	**Dabigatran**	**Rivaroxaban**	**Apixaban**	**Comments**
A. Routine testing (screening for NOAC)				**Interference vs. measurement**
PT	–/↑	↑/↑↑	–/↑	Different reagents show different sensitivity; order of sensitivity: rivaroxaban > dabigatran > apixaban; only a few reagents are sensitive to apixaban
APTT	↑/↑↑	–/↑	–/↑	Different reagents show different sensitivity; order of sensitivity: dabigatran > rivaroxaban > apixaban
B. Quantitative tests (measurement of NOAC concentration)				
dTT/DTI	↑↑	–	–	Tests sensitive to dabigatran; insensitive to anti-Xa inhibitors
ECT/ECA	↑↑	–	–	Tests sensitive to dabigatran; insensitive to anti-Xa inhibitors

Anti-Xa	–	↑↑	↑↑	Insensitive to dabigatran. Sensitive to anti-Xa inhibitors

Based on: Favaloro E, Lippi G. Blood Transfus. 2017; 15(6): 491–494

Abbreviations: APTT, activated partial thromboplastin test; dTT, diluted thrombin time; ECT, ecarin clotting time; ECA, ecarin chromogenic assay; PT, prothrombin time; TGA, thrombin generation assay; TT, thrombin time

Table 2. Non vitamin K antagonist oral anticoagulants dosage for stroke prevention in patients with atrial fibrillation

	Rivaroxaban	**Apixaban**	**Dabigatran**
Standard dose	20 mg 1 × per day	5 mg 2 × per day	150/110 mg 2 × 1
Reduced dose	15 mg 1 × per day *Dose reduction at CrCl ≤15–49 ml/min	2.5 mg 2 × per day *Dose reduction when 2 of the criteria are met: 1. body weight ≤60 kg, 2. age ≥80 years, 3. serum creatinine level ≥133 μmol/L (1.5 mg/dl), or based on a single criterion: when CrCl 15–29 ml/min	110 mg 2 × 1, if: age ≥80 years, patient treated with concurrent verapamil, increased risk of gastrointestinal bleeding.

Based on: [1]

Abbreviation: CrCl, creatinine clearance

Table 3. Treatment of deep vein thrombosis and pulmonary embolism

	Rivaroxaban	**Apixaban**	**Dabigatran**
Initial treatment	15 mg 2 × per day for 21 days	10 mg 2 × per day for 7 days	UFH or LMWH

Continued treatment	20 mg 1 × per day (without dose reduction, unless the risk of bleeding outweighs the risk of recurrent thromboembolism)	5mg 2 x per day (without dose reduction)	150 mg 2 × 1 (without dose reduction)
Prolonged anticoagulant treatment after pulmonary embolism in patients without malignancies (after 6 months of anticoagulant treatment at therapeutic doses) — recommendation class IIa	10 mg 1 × per day	2,5 mg 2 × per day	150 mg 2x1 (dose reduction criteria as in AF)

Based on: [1]

Abbreviations: AF, atrial fibrillation; LMWH, low-molecular-weight heparin; UFH, unfractionated heparin

THE ROLE OF BIOCHEMICAL EXAMINATIONS IN ASSESSING INDICATIONS FOR ANDEXANET ALFA ADMINISTRATION TIMING

At 2–3 hours (± 1) after NOAC administration, both the plasma drug concentration and the effect on coagulation parameters are at their highest. Unfortunately, routine determination of baseline coagulation parameters does not accurately assess anticoagulant effect, adherence to drug intake recommendations, let alone the time elapsed since the last drug dose.

In the event of bleeding in patients treated with FXa inhibitors, in addition to routine laboratory tests (blood count, activated partial thromboplastin time [APTT], prothrombin time [PT], fibrinogen, aminotransferases, creatinine clearance), evaluation of plasma drug levels is advised, and an immediate action should be taken as dictated by clinical evaluation, without waiting for laboratory test results.

Based on the results of observational studies, the International Commission for Standardization in Hematology, in its 2021 recommendations, has expanded the indications in which NOAC

measurements may be useful, to determine appropriate strategies to reverse the anticoagulant effects of the drugs and/or required dosing and guide further treatment. Urgent indications for laboratory evaluation of NOAC levels generally include severe bleeding, urgent surgery and acute ischemic stroke, with consideration of thrombolysis. Planned indications for such evaluations are helpful in the long-term care of patients with extreme weight, renal/liver disease, suspected malabsorption syndrome or drug interactions. Tests evaluating NOACs (over a wide range of concentrations) are covered by most international external quality control programs. Despite the lack of standardization, good correlation between different testing systems was demonstrated, with rivaroxaban and apixaban assays showing low coefficients of variation.

The minimum NOAC concentration that can contribute to bleeding is not known. Expert-based guidelines from the International Society on Thrombosis and Hemostasis (ISTH) suggest considering NOAC reversal in patients with severe bleeding and NOAC concentrations >50 ng/ml, and in preoperative patients at high risk of bleeding and NOAC concentrations >30 ng/ml [1, 6–8].

Methods for evaluating the anticoagulant activity of FXa inhibitors

While routine clotting times (PT and APTT) cannot be used to accurately assess the effect of rivaroxaban and apixaban, the results of both clotting times are prolonged in the presence of anti-Xa inhibitors in a drug type- and dose-dependent manner. However, the test results do not demonstrate sufficient linearity, are not very accurate, and depend on the sensitivity of the reagents and the type of coagulometer. PT is considered only as a screening test for the use of rivaroxaban, which, with adequate sensitivity, will result in PT prolongation at the time of therapeutic drug concentration. On the other hand, this parameter should not be used to assess the concentration of apixaban, since in this case PT prolongation can only occur at the maximum concentration. It is also worth mentioning that the result of the assay depends on the reagent used. Thus, a normal PT does not necessarily exclude a therapeutic concentration of rivaroxaban, let alone apixaban. Hence, we should not rely on the PT result in the course of clinical management.

The usefulness of POCTs (point-of-care tests) for assessing NOAC activity (including thromboelastography/thromboelastometry, surface acoustic wave, dry blood spot and microsampling techniques, and urine strip tests) is unproven. The tests show low sensitivity at low NOAC concentrations, while urine determinations do not correlate with plasma drug concentrations. Currently, none of the POCT methods meet the parameters of in vitro device

clinical trials, as they use an animal model or data from a small sample of patients, include a limited number of NOACs, or are based on NOAC-enriched blood in vitro. Portable analyzers designed to monitor VKA treatment also do not accurately reflect the coagulation parameters of patients treated with NOACs. The research to implement rapid NOAC testing is still ongoing.

According to the literature, the most clinically useful method for determining the concentration of rivaroxaban and apixaban is the chromogenic “anti-Xa” method, adjusted using drug-specific calibrators. The method is simple to perform, has adequate sensitivity, a wide range of linearity and good correlation with NOAC reference mass spectrophotometry methods. Until recently, the anti-Xa method was considered highly specialized and expensive. Today, due to the availability of commercial reagent kits, it can be performed around the clock using virtually any coagulography analyzer, with the result obtained in 30–60 minutes. The principle of the method is to add a reagent with a high concentration of factor Xa to citrated plasma. Factor Xa binds to the FXa inhibitor present in the patient's plasma, and the “free” FXa remaining in the reaction mixture is measured using the amidolytic chromogenic method. The reaction with the chromogenic substrate produces a yellow product (p-nitroaniline), and the measured increase in optical density is inversely proportional to the NOAC concentration. The results are read from a calibration curve plotted using a reagent of known concentration. The test showed a strong correlation with serum concentrations of rivaroxaban and apixaban, hence can be used as a clinically reliable monitoring tool. The absence of anti-Xa activity determined using these assays excludes clinically relevant plasma concentrations of the drug. Based on the available literature, it has been determined that anti-Xa activity <0.50 IU/ml corresponds to a plasma concentration of rivaroxaban or apixaban <30 ng/ml, which is the cutoff for safely undertaking rescue procedures. In contrast, dose adjustment and the use of anticoagulant reversal therapies based on anti-Xa level results are still an area of interest. Firstly, therapeutic ranges have still not been established, and long-term data on the efficacy and safety of interventions targeting the anti-Xa levels are still lacking. Moreover, the value of the anti-Xa index, based on which we could select a higher or lower dose of AA, is also unknown. Moreover, in clinical practice, measuring the change of anti-Xa activity is also not useful for predicting clinical response following AA administration. In fact, the results of the ANNEXA-4 study showed that no significant relationship between hemostatic efficacy and reduction in anti-Xa activity [1, 2, 6, 8, 9].

Conclusions

Quantitative NOAC measurements may be useful in detecting overexposure to these drugs at risk of bleeding (also in terms of drug reversal strategies), under-exposure to NOACs at risk of thrombosis, and identification of drug interactions, which should be confirmed by studies in larger cohorts. The fact that personalized NOAC dosing can improve the benefit-risk ratio in some patients is confirmed by the high inter-individual variability observed in phase III clinical trials, and the numerous factors affecting pharmacokinetics and the dose–response relation.

At present, it is believed that drug-specific chromogenic anti-Xa assays are the most suitable for measuring NOAC plasma concentrations. The cost of performing an anti-Xa test (about PLN 100) is higher than PT/APTT, but comparable to many specialized hemostasis tests. Given their use is limited to specific situations, the burden on healthcare systems should be lower than that currently incurred when treating patients using VKAs.

In Poland, only a handful of laboratories undertake measurement of anti-Xa activity, to the disadvantage of patients in whom NOAC measurement is indicated, especially considering the limitations of the analytical and clinical value of screening tests. With the automation of assays and the availability of stable, liquid reagents, as well as the increasing use of NOACs, laboratories should enable clinicians to measure concentrations of these drugs while defining the sensitivity of measurement systems and participating in international quality control programs that include assessing the impact of NOACs on quantitative and qualitative hemostasis diagnostic tests.

There is a need to establish target therapeutic ranges and standardize NOAC assays, which will improve the safety of these drugs and ensure inter-laboratory reproducibility of results.

Increasing the availability and performance of NOAC concentration assays is essential for the development and implementation of guidelines for the optimal management of patients treated with NOACs, as well as for determining strategies for the administration and monitoring of the effects of reversal agents for these drugs.

To date, neither the NOAC concentration nor the anti-Xa index value, based on which we could select a higher or lower AA dose, is known. Therefore, in most cases of unknown timing of the last NOAC dose, such as in unconscious patients, it is recommended to administer a higher (if the patient is continuously taking 20 mg of rivaroxaban and 5 mg of apixaban) or lower dose of the drug (patients continuously treated with reduced dose of rivaroxaban and apixaban).

ANDEXANET ALFA

Registered and unregistered indications

Andexanet alfa is a recombinant inactive human factor Xa analogue that, through non-specific binding, prevents the action all known FXa inhibitors, including low-molecular-weight heparin (LMWH) and unfractionated heparin (UFH).

Andexanet alfa is registered for use in patients with serious or life-threatening bleeding, treated with apixaban or rivaroxaban. The efficacy and safety of AA has been confirmed in numerous studies. Initially, the effect was evaluated in animal models [10, 11], followed by a phase II study using different doses of the drug in healthy volunteers receiving FXa inhibitors, to establish a dosing regimen [12, 13]. The effects of bolus administration and intravenous (i.v.) infusion of AA on apixaban and rivaroxaban concentrations, anti-Xa activity and thrombin generation were documented in two phase III studies, ANNEXA-A for apixaban and ANNEXA-R for rivaroxaban [14]. In the end, AA was approved after the publication of the results of the ANNEXA-4 trial, a multicenter, prospective, open-label study that recruited 352 patients who experienced acute major bleeding, mainly intracranial and gastrointestinal, treated with FXa inhibitors. Primary endpoints included the percentage change in anti-FXa activity and the percentage of participants who achieved a good or excellent hemostatic effect within 12 hours after the infusion [2].

Based on the available literature, it is also known that AA administration can be considered off-label in life-threatening clinical situations requiring urgent surgical intervention [1, 15, 16].

Dosage regimen and pharmacokinetics

Low dose: Initial i.v. bolus of 400 mg (at 30 mg/min, about 15 min) → continuous i.v. infusion of 4 mg/min over 120 min (480 mg)

High dose: initial intravenous bolus of 800 mg (at 30 mg/min, approx. 30 min) → continuous i.v. infusion of 8 mg/min over 120 min (960 mg).

The choice of AA dose depends on the dose of FXa inhibitor administered and the time elapsed since the last dose (Figures 1 and 2) Maximum reversal of anti-Xa activity occurs within two minutes of the end of the bolus. In contrast, the follow-up continuous i.v. infusion allows the reduction in anti-Xa activity to be maintained until two hours after it ends. Then, the anti-Xa level returns to or exceeds the activity recorded in the placebo group [1, 2, 17].

Treatment monitoring, contraindications, possible side effects

As mentioned, the determination of anti-Xa activity is not applicable for monitoring the reversal of the anticoagulant effect of FXa inhibitors. In fact, commonly available assays are inadequate for determining anti-Xa activity after AA administration. The high dilution of the sample and

the reversibility of AA binding to the Xa inhibitor, leading to dissociation of the inhibitor and AA, result in an overestimation of anti-Xa activity, which can cause a significant underestimation of the drug effect.

Treatment monitoring should be based primarily on clinical parameters, namely the assessment of hemostasis or side effects.

Interactions

Given the lack of clinical data on the safety of the combined use of AA and prothrombin complex concentrate (PCC), activated prothrombin complex concentrate (aPCC), recombinant factor VIIa, fresh frozen plasma (FFP) or whole blood, such use should be avoided unless absolutely necessary. Several case series have been published on this topic, with the results highlighting the potentially increased thrombotic risk associated with the use of AA and PCC combination [18, 19].

The use of AA should also be avoided in the case of planned heparinization during surgery, as it may result in unresponsiveness to heparin. AA, however, has not yet been registered as an antidote to reverse the effects of heparins [20, 21].

In about 10% of patients, non-neutralizing antibodies to AA appear in low concentrations during treatment. However, the clinical consequences of their presence have not been demonstrated.

Contraindications to the use of the drug include hypersensitivity to the active compound or to any of the other components of the formulation, and a known allergic reaction to hamster proteins [17].

Side effects

The most common mild side effects are infusion-related reactions such as hot flashes, facial flushing, chest discomfort or increased sweating.

If such mild side effects are observed, careful monitoring of the patient may suffice. In the case of symptoms of moderate severity, short-term interruption or slowing of the infusion with resumption after the discomfort has subsided may be considered. Antihistamine administration may also be considered [17].

The use of AA is associated with a significant risk of thrombosis. This complication usually results from the underlying disease that is the basis for NOAC therapy (mainly venous thromboembolism, atrial fibrillation), anticoagulant withdrawal, activation of coagulation in the course of bleeding, frequent bed immobilization during hospitalization, as well as the use

of a drugs reversing the anticoagulant effect of the FXa inhibitor. AA has an independent procoagulant effect, related to tissue factor pathway inhibitor (TFPI) inhibition. The period of increased risk in AA-treated patients remains unknown, but described thromboembolic events can occur up to 30 days after infusion. In the ANNEXA-4 study, thromboembolic complications affected 10.4% of patients with a median time of occurrence of 9 days. These included cerebrovascular incidents, deep vein thrombosis, pulmonary embolism and even acute myocardial infarction. Importantly, these did not occur in any patient after NOAC was restarted. Of the 50 patients who developed thromboembolic complications, 34 either did not resume anticoagulant treatment or suffered from thrombosis before it was resumed.

Hence, it is extremely important to monitor patients for signs of thrombosis and to consider resuming anticoagulant treatment as early as possible after a bleeding event. To date, however, there is a lack of results from randomized trials regarding the optimal time to re-initiate anticoagulant treatment. The clinical decision should therefore be made on an individual basis, considering the benefit/risk ratio [2, 17].

As for laboratory tests, increases in D-dimer and prothrombin fragments 1 + 2 above 2 times the upper normal limit were often observed after AA infusions in healthy subjects. The changes lasted from a few hours to a few days but were not related to the occurrence of thromboembolic complications.

Andexanet alfa exhibits modest renal clearance and there is no need to adjust the drug dose according to renal and hepatic function. It is rapidly degraded in plasma by endogenous proteases, which results in its relatively short half-life (one hour) [17].

PATIENT POPULATIONS WITH SEVERE BLEEDING AND INDICATIONS FOR ANDEXANET ALFA

Patients with hemorrhagic stroke/hemorrhage to the CNS

Stroke is caused by restriction of blood supply to the brain or extravasation of blood, and classifieds as ischemic stroke (80%), HS (15%) or subarachnoid stroke (5%) on this basis. The incidence of HS increases sharply with age and is therefore expected to remain high due to the aging of the population, even with improvements in blood pressure treatment [22, 23]. Another growing source of HS is the increasing use of oral anticoagulants for treatment [22, 24]. The incidence of intracranial bleeding associated with oral anticoagulants in phase III trials (comparing NOACs with warfarin and aspirin therapy) ranged from 0.2 to 0.5 per 100 person-years. It is worth noting, however, that the risk of such a complication during NOAC treatment is still about twice as low as with chronic warfarin therapy [25]. In multicenter randomized

trials comparing warfarin with rivaroxaban 20 mg (ROCKET-AF) or apixaban 2 × 5 mg (ARISTOTLE), intracranial hemorrhage incidence was estimated at 0.8% over a median of 707 days of follow-up (0.5/100 person-years) in the ROCKET-AF trial, and 0.33% per year in the ARISTOTLE trial. In comparison, the rates for warfarin treatment were, respectively: 1.2% (0.7/100 person-years) (hazard ratio [HR], 0.67) and 0.8%/year (HR, 0.42) [26, 27].

Known risk factors for intracerebral hemorrhage, despite adequate NOAC therapy, include advanced age, concomitant use of antiplatelet drugs, history of stroke or transient ischemic stroke, history of bleeding, decreased serum albumin levels, thrombocytopenia, race (Asian, Latin American or black) and, especially, hypertension [25–28].

Hemorrhagic stroke, which occurs more often in patients taking oral anticoagulants, is associated with increased hematoma volume and expansion, as well as increased morbidity and mortality [22, 29]. The mortality rate in HS associated with taking oral anticoagulants is about 60% [30]. The use of NOACs is associated with a lower but still significant risk of stroke than with VKA drugs [31].

There is no doubt that reversal of NOACs should reduce the risk of hemorrhagic foci emergence. Therefore, therapy should consider the possibility of using fast-acting specific inhibitors of these compounds' action [22].

The ANNEXA-4 trial showed that 79% of patients with an indication for reversal of factor Xa inhibitors related to HS achieved excellent or good hemostatic efficacy, defined as <35% increase in hematoma volume after 12 hours [2, 32]. Other retrospective studies have shown comparable results of AA hemostatic efficacy, ranging from 64.7 to 88.9% [33–35].

Current retrospective studies or case series have directly compared the risks and benefits of AA and prothrombin complex clotting factor concentrate (PCC) in patients with traumatic and spontaneous intracerebral hematomas (sICH). However, these studies have yielded conflicting results regarding the superiority of any of these medications in achieving hemostasis and decreasing the risk of death or thromboembolic events. Thus, the currently available evidence does not unequivocally support the clinical efficacy of AA or PCC in reversing factor Xa inhibitor-related acute major bleeding, nor does it allow for a conventional meta-analysis of potential superiority [36–42]. Further clinical trials are underway that will hopefully clarify the role of each agent in the treatment of sICHs [43].

Hemorrhagic stroke is a complex clinical event requiring multidisciplinary care. A patient with HS taking oral anticoagulants should be provided with medical care including clotting compensation, anticoagulation reversal, intensive blood pressure lowering, the possibility of neurosurgical intervention, and should be treated in a stroke unit or intensive care unit. Brain

imaging is essential to distinguish HS from ischemic stroke and to determine the hematoma volume. Computed tomography of the head is the most widely used imaging method for confirming HS, due to its widespread availability, speed and ease of performance, and high diagnostic accuracy. Imaging of the brain during the acute phase of HS can provide prognostic information and help monitor the evolution of the focus, the development of hydrocephalus, and cerebral edema, especially in patients whose neurological condition has deteriorated, as well as those with impaired consciousness. The therapeutic goal in HS is to minimize the risk of hematoma expansion that results in rapid neurological deterioration. Hematoma expansion tends to occur early (usually within the first 24 hours) and is associated with poor prognosis and mortality. The risk of hematoma expansion is increased in patients taking oral anticoagulants.

In addition, most patients with acute HS have elevated blood pressure, which is also associated with a higher risk of hematoma expansion and requires close monitoring.

Therefore, if HS is found to be associated with FXa inhibitor therapy, the use of such drugs should be halted, and efforts should be made to restore clotting function as soon as possible. In these patients, immediate administration of a specific antidote or, possibly, PCC should be considered. Treatment should be administered when clinically significant anticoagulant levels are suspected, based on the type and timing of FXa inhibitor administration. The decision to administer AA is made by the neurologist in conjunction with the neurosurgeon after deciding on conservative or surgical treatment. When considering the use of drugs to restore clotting function, it is important to consider the patient's performance status prior to the HS, the extent of the hemorrhagic focus, the patient's general and neurological condition, and chances of survival. Cost, hospital formulary status and drug availability may limit the choice of reversal agent, especially in small local hospitals.

The consensus of the European Stroke Organisation recommends immediate reversal of dabigatran anticoagulation with idarucizumab in the case of HS, and immediate administration of AA (Grade C) in the case of HS related to factor Xa inhibitors. If AA is not available, high-dose 4-factor PCC (50 IU/kg) is recommended (Grade C) [1]. Due to the lack of high-level recommendations for reversal strategies for NOAC-related sICH treatment, further clinical trials are needed. The choice of anticoagulation reversal agents in HS will continue to evolve, as will our understanding of their efficacy, safety and risk of thromboembolism.

Patients with gastrointestinal bleeding

The management of patients with gastrointestinal bleeding resulting from overdose/abuse of factor Xa inhibitors is regulated by guidelines of research societies. Since FXa inhibitors, similarly to other NOACs, are characterized by a relatively short half-life (12–24 hours), in most cases of gastrointestinal bleeding resulting from their use, temporary withholding the supply of the preparations in question constitutes sufficient management. Joint recommendations published in 2021 by the British Society of Gastroenterology (BSG) and the European Society of Gastrointestinal Endoscopy (ESGE) [44] recommend the use of AA (considering its prothrombotic risk) as a reversal agent for factor Xa inhibitors only in hemodynamically unstable gastrointestinal bleeding patients (weak recommendation, low data quality).

Regarding specific sources and etiologies of gastrointestinal bleeding, ESGE guidelines for upper gastrointestinal (UG) bleeding of non-variceal etiology [45] recommend temporarily withholding anticoagulants, including FXa inhibitors. This management should not delay UG endoscopy. In cases of severe, persistent bleeding, reversal agents should be considered (strong recommendation, low data quality). However, the cited guidelines refer to agents that reverse the effects of FXa inhibitors, including AA, as compounds of limited availability [46].

The ESGE guidelines for UG bleeding of variceal etiology [47] recommend the use of FXa inhibitor reversal agents exclusively in the absence of hemodynamic stabilization of the patient. The decision to use AA should be made in conjunction with a hematologist, taking into account the risk of thromboembolic complications that may occur as a result of the drug in question (strong recommendation, low quality data). In other cases, it is recommended that FXa inhibitor therapy be temporarily withheld until its effect ceases on its own.

The ESGE guidelines for lower gastrointestinal bleeding [48] suggest the use of AA for bleeding that persists despite the implementation of endoscopic treatment and for persistent hemodynamic instability of the patient (weak recommendation, low data quality). In such a situation, hemodynamic evaluation of the patient is once more suggested. In addition, the guidelines note the limited availability of the agent, its high cost and possible complications due to prothrombotic activity [2].

The joint 2022 guidelines of the American College of Gastroenterology (ACG) and the Canadian Association of Gastroenterology (CAG) do not recommend the use of AA in patients with suspected gastrointestinal bleeding resulting from FXa inhibitors (conditional recommendation, very low-quality data) [49]. The above position is based on the very low quality of available literature data (including lack of a control group and methodological inconsistency in terms of the endoscopic treatment implemented), high costs and possible side

effects of the compound in question. Nevertheless, the cited ACG and CAG guidelines allow the use of AA in cases of life-threatening gastrointestinal bleeding, in patients who have taken rivaroxaban or apixaban in the prior 24 hours.

Summarizing the recommendations of the scientific societies presented above, in the case of gastrointestinal bleeding resulting from FXa inhibitors, the use of AA is reserved for hemodynamically unstable patients and those with persistent bleeding despite implemented endoscopic treatment. Regardless of the etiology and source of gastrointestinal bleeding, measures to reverse the effects of FXa inhibitors, i.e., administration of AA, should not delay gastrointestinal endoscopy and should be preceded by a hematological consultation.

Patients hospitalized in the Emergency Department

The statutory tasks of the Emergency Department are specified as the delivery of health care services, consisting of preliminary diagnosis, and undertaking treatment to the extent necessary to stabilize the vital functions of persons in a state of sudden danger to life or health, from internal or external causes, and in particular in the event of an accident, trauma, and poisoning in adults and children [50]. Among the victims of traffic accidents and patients who have suffered injuries in other circumstances, patients with head injuries are the biggest concern in the Emergency Department. NOAC-associated intracranial hemorrhages are characterized by rapid deterioration of the patient's condition within 24–48 hours, as the hematoma volume increases, while the poor prognosis is related to the extent of the hematoma and intraventricular bleeding. In these cases, rapid reversal of NOAC effects prevents hematoma enlargement and facilitates appropriate surgical intervention. In general, the NOAC should be discontinued, the time of the last dose should be established, and the time of elimination of the drug from the body should be determined. Other measures include morphology evaluation, clotting tests, and the measurement of creatinine/estimated glomerular filtration rate levels. A normal hemodynamic compromise should be reached, and if possible, surgery should be postponed, and bleeding should be controlled.

Andexanet alfa should be used in patients taking FXa inhibitors who are victims of traffic accidents, or trauma victims in other circumstances with life-threatening post-traumatic bleeding.

Detailed management of hemorrhagic side effects of FXa inhibitors

Breakdown of bleeding severity and management approaches

The management of bleeding in patients treated with NOACs should be dictated by the severity of the bleeding, as well as be based on the patient's clinical condition and risk factors. To date, numerous scales for assessing the severity of bleeding have been developed, with the most common being the TIMI, ACUITY and GUSTO scales or the ISTH, frequently used in studies of anticoagulant reversal agents (Table 4). The BARC scale (Bleeding Academic Research Consortium), which is recommended for use in cardiac intensive care units, is a standardization of these various classifications [51, 52] (Table 5).

Patient-related risk factors include:

- anticoagulant treatment used, including the time elapsed since the last dose of the drug;
- age;
- renal and hepatic function;
- comorbidities (e.g., coexisting cancer that increases the risk of bleeding or thrombosis);
- drugs that affect NOAC metabolism (this mainly refers to P-gp inhibitors and CYP3A4 inhibitors), concomitant use of antiplatelet drugs and non-steroidal anti-inflammatory drugs (NSAIDs);
- thromboembolic risk, which is important in the context of returning to anticoagulant treatment [1].

Table 4. Definition of major bleeding in non-surgical patients according to the International Society of Thrombosis and Hemostasis

1	Fatal bleeding and/or
2	Symptomatic bleeding in a critical area or organ (e.g., intraspinal, intracranial, intraocular, articular, pericardial, retroperitoneal or intramuscular bleeding with fascial compartment syndrome) and/or
3	Bleeding accompanied by a decrease in hemoglobin concentration of ≥2 g/dl (or to an absolute concentration of ≤8 g/dl with no previous result) or requiring transfusion of ≥2 units of whole blood or red blood cell concentrate

Based on: Schulman S, Kearon C. Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. Thromb Haemost. 2005; 3: 692–694.

Table 5. BARC — Bleeding Academic Research Consortium scale

0	No bleeding

1		Inactive bleeding, not requiring specialized assistance, which may only contribute to discontinuation of antiplatelet or anticoagulant therapy
2		Overt, active bleeding that does not meet the criteria for types 3–5, but meets one of the three following criteria: 1) requires medical non-surgical intervention; 2) leads to hospitalization; 3) requires immediate evaluation
3	a	Overt bleeding associated with a decrease in Hb concentration of 3–5 g/dl or requiring blood transfusion
	b	Overt bleeding associated with a decrease in Hg of ≥5 g/dl or cardiac tamponade or bleeding requiring surgical intervention
	c	Intracranial or intraocular bleeding
4		CABG-related bleeding
5	a	Probably fatal bleeding (clinical suspicion without confirmation by autopsy or imaging)
	b	Fatal bleeding (overt or confirmed by imaging/autopsy)

Abbreviation: CABG, coronary artery bypass grafting

The European Society of Cardiology (ESC) guidelines differentiate bleeding into:

- mild (usually BARC 2);
- severe, non-life-threatening (BARC 3a);
- life-threatening or critical organ bleeding (BARC 3b).

General recommendations for bleeding during NOAC treatment include assessment of baseline hemostatic parameters (hemoglobin, hematocrit, platelet count, PT, TT, APTT) and renal function. As mentioned earlier, the effect of FXa inhibitors should not be assessed and the time of the last dose should not be estimated on the basis of coagulation parameter results. It should be kept in mind that such parameters can be abnormal for a number of other reasons, especially in cases of massive bleeding or intravascular coagulation syndrome. Only normal anti-Xa activity, evaluated using methods with adequate sensitivity, excludes therapeutic levels of Xa inhibitors.

The following are the recommendations for bleeding management according to its severity:

Mild bleeding:

- delay or skip the next NOAC dose;

- the dose and type of NOAC used should be carefully reviewed before restarting treatment, and the need to take other medications that increase the risk of bleeding should be verified.

Severe, non-life-threatening bleeding:

- it is important to stop bleeding and maintain adequate vascular volume: mechanical surgical or endoscopic compression to achieve hemostasis, fluid therapy, transfusion of red blood cell concentrate when Hb is reduced to under <7–8 g/dl, transfusion of platelet cell concentrate if platelet count is ≤50 G/l or patient was taking antiplatelet drugs, administration of tranexamic acid, causal treatment of bleeding;
- the timing of the last NOAC dose should be determined;
- activated charcoal may be considered within 3–4 h of taking the NOAC;
- in patients treated with dabigatran, consider idarucizumab or hemodialysis.

Life-threatening bleeding or bleeding into a critical organ

In patients treated with NOACs who experience such bleeding, in addition to implementing standard bleeding management (as above), it is advisable to reverse the anticoagulant effect. According to the recommendations of the European and American clinical societies, the first-line management should be idarucizumab 5 g i.v. for patients treated with dabigatran, or AA for patients treated with apixaban and rivaroxaban (dosage above).

PCC or aPCC, on the other hand, are recommended as NOAC reversal drugs in the absence of an available antidote. PCC is used at a dose of 25 IU/kg body weight, and the dose can be repeated 1–2 times, if necessary, up to a dose of 50–75 IU/kg body weight. aPCC is used at a dose of 50 IU/kg body weight, up to a maximum of 200 IU/kg body weight.

Although the reversal of the anticoagulant effect of NOACs is sometimes insufficient by itself to stop bleeding, it may allow for other needed invasive interventions. Neither vitamin K nor protamine sulfate is effective in treating bleeding in patients treated with NOACs. Similarly, FFP is not applicable in controlling bleeding in such patients. This is mainly due to the NOACs present in the plasma, which inhibit the activity of clotting factors after FFP administration. Hence, a transfusion of a large volume of FFP would be needed to achieve a clinically relevant effect [1, 51].

Figure 3 presents the American College of Cardiology recommendations for the management of bleeding in patients treated with NOACs [53].

Andexanet alfa vs. PCC (current therapeutic standard)

Based on ESC guidelines, PCC or aPCC are recommended as NOAC reversal drugs for life-threatening bleeding in the absence of an available antidote, and the choice between the two agents should depend on the availability and experience of the individual center [1].

For major bleeding, AA has more evidence of effective and safe anticoagulant reversal than PCC. Several cohort studies of bleeding patients treated with anti-Xa agents who received PCC have been published, with somewhat conflicting results [54–57]. While Schulman and Majeed reported similar efficacy of PCC to AA, the study group sizes were quite small (66 and 84 patients, respectively). AA, on the other hand, underwent an extensive preclinical program on animal models followed by cohorts of non-bleeding patients treated with various anti-Xa agents [58, 59]. Its effectiveness was finally confirmed in the ANNEXA-4 trial, which recruited patients with severe bleeding (intracranial or gastrointestinal) treated with various anti-Xa agents [2].

Studies comparing the Food and Drug Administration approved AA and off-label PCC, such as the Costa et al. study [36], argue in favor of AA due to its greater potential to achieve hemostasis. Schmidt et al. [59], on the other hand, documented similar efficacy of both agents, with a higher incidence of thrombotic events after AA. Evaluation of both products head-to-head is attempted in the ongoing ANNEXA-I trial (NCT03661528), comparing the use of AA with “usual care” in patients with intracranial hemorrhage taking Xa antagonists, with usual care in many situations consisting of PCC. However, the trial began in early 2019 and is still ongoing.

Resumption of anticoagulant treatment

It is unclear at what time after AA administration factor Xa inhibitors or heparin can be re-administered. The effect of AA ceases about 2 hours after the drug infusion is stopped, at which time the reappearance of low concentrations of rivaroxaban and apixaban in the bloodstream can be observed.

Returning to anticoagulant therapy after a history of severe bleeding is associated with a better prognosis, a reduction in the risk of death and thromboembolic complications, but increased risk of bleeding [60]. In contrast, the risk of bleeding, especially hematoma expansion in the HS, is highest within the first 72 hours. Hence, the timing of NOAC reintroduction is a crucial but currently unclear issue. Current retrospective studies, expert opinions and clinical practice regarding the timing of resumption of anticoagulant treatment vary widely. ESC guidelines recommend resuming NOAC treatment after 4–8 weeks following intracranial bleeding, after

considering the benefits and risks and taking imaging results into account. For gastrointestinal bleeding, NOACs should be started as soon as clinically feasible [1, 2, 60].

Factors associated with increased risk of recurrent gastrointestinal bleeding:

- no identified source of bleeding and no reversible cause;
- bleeding during a break in NOAC use/ while on non-therapeutic doses of NOACs;
- multiple angiodysplasia-like lesions in the gastrointestinal tract;
- chronic alcohol abuse;
- old age.

Factors associated with increased risk of recurrent CNS bleeding:

- lack of reversible cause;
- bleeding during interruption of NOAC use/during use of non-therapeutic doses of NOACs;
- concomitant antiplatelet treatment;
- modifiable risk factors:
    - uncontrolled hypertension,
    - alcohol/nicotine/sympathomimetic drug dependence,
    - low low-density lipoprotein/triglycerides,
    - concomitant antiplatelet treatment;
- non-modifiable:
    - older age,
    - Asian race,
    - male sex,
    - renal failure,
    - small vessel disease,
    - cerebral amyloid angiopathy,
    - microbleed presence in brain imaging.

Currently, there are no randomized trials on the timing of NOAC resumption after bleeding. Four phase III trials on resumption of anticoagulant treatment after intracranial bleeding are ongoing (ENRICH AF, ASPIRE, PRESTIGE-AF and Restart TICrH) [2].

At present, the decision to resume anticoagulant treatment should be based on the patient's clinical condition, his thromboembolic risk, and whether the bleeding site has been identified and treatment to stop the bleeding has been successfully implemented.

In the case of bleeding resulting from reversible causes or post-traumatic bleeding, anticoagulant treatment can usually be initiated after the cause has been identified and eliminated. There are aspects of both gastrointestinal bleeding and intracranial hemorrhages that support the reintroduction of anticoagulant treatment or its discontinuation.

For major bleeding without an identified, reversible cause, the decision on anticoagulant treatment should depend on the possible net benefit of treatment and an assessment of the risk of recurrent bleeding. Another option, in case of contraindications to anticoagulant therapy in atrial fibrillation, is percutaneous closure of the left atrial appendage (recommendation grade IIb). However, even in this case, the patient requires continuation of antiplatelet therapy. [1]

PATIENTS BEFORE SURGICAL PROCEDURES

Non-cardiac surgical procedures performed on an elective and expedited basis require only that anticoagulants are discontinued at the appropriate time. NOAC drugs, with normal creatinine clearance, should be discontinued more than 24 hours before low-risk surgery and 48 hours before high-risk surgery (e.g., procedures on the aorta, visceral and iliac arteries). The longest, over 72 and 96 hours of withdrawal is required for dabigatran in patients with impaired renal function (Table 6).

The exact timing of discontinuation should depend primarily on the type of treatment and the patient's renal function. In contrast, there is no evidence that the timing of withdrawal of NOACs before surgery depends on their residual plasma concentrations. In addition, the concentrations of NOACs that allow the safe performance of particular surgical procedures are not known [61].

Table 6. The amount of time that should pass since the last non-vitamin K antagonist oral anticoagulants (NOACs) dose before planned surgical procedures

	Apixaban/rivaroxaban		Dabigatran	
Bleeding risk	Low	High	Low	High
CrCl ≥80 ml/min	≥24 h	≥48 h	≥24 h	≥48 h
CrCl 50–79 ml/min			≥36 h	≥72 h
CrCl 30–49 ml/min			≥48 h	≥96 h
CrCl 15–29 ml/min	≥36 h		Contradicted in the MPI	
CrCl < 15 ml/min	Contradicted in the MPI			

For procedures with a very low risk of bleeding, the procedure should be performed during the period of minimum plasma concentrations of NOACs (12 or 24 hours after the last dose for twice-daily or once-daily administration, respectively)

Based on: [1]

Abbreviations: CrCl, creatinine clearance; MPI, Medication Package Insert

The situation is different for procedures with immediate and urgent indications. In these cases, according to the recommendations of the ESC, it is recommended that NOACs be discontinued immediately, and a full blood clotting panel (PT, aPTT, anti-Xa, *etc*.) and plasma NOAC determination, if available, should be performed. Surgery or intervention, if possible, should be delayed until at least 12 hours, and optimally until 24 hours after the last NOAC dose. If the patient requires immediate life-saving surgery associated with intermediate or high risk of bleeding, and the last dose of anticoagulant was taken earlier, it is advisable to use reversal agents (Figure 4) [1, 61].

Studies of NOAC reversal in urgent surgery situations, part of the process to register AA and idarucizumab, are difficult to compare.

A phase IIIb to IV study (ANNEXA-4) evaluated the efficacy and safety of AA in patients with acute major bleeding treated with factor Xa inhibitors, but did not include patients receiving anticoagulant therapy, requiring surgery and emergency invasive procedures [2]. In addition, the exclusion criteria for ANNEXA-4 included planned surgery within 12 hours. Nevertheless, off-label administration of AA is allowed in exceptional situations when there is a need for immediate life-saving surgical intervention in patients treated with an FXa inhibitor. The effectiveness of such a post-treatment strategy has been proven repeatedly in clinical cases and retrospective studies [15, 16, 62]. Unfortunately, because of AA's ability to non-specifically bind all factor Xa inhibitors, the treatment is problematic for interventions requiring the administration of UFH or LMWH [20]. AA treatment should not be monitored based on anti-Xa activity. Commercially available anti-Xa activity assays are inadequate for its measurement after AA administration, as the resulting anti-Xa activity assay results are overestimated, leading to a significant underestimation of the change in AA activity [63]. If NOAC reversal agents are unavailable, PCC or aPCC should be considered, despite the lack of clear evidence of their safety and efficacy in this indication (Table 5). An additional option is the use of recombinant activated factor VII [1].

The composition of PCC includes clotting factors: II, VII, IX, X, with less protein C and protein S, and a small amount of heparin. In aPCC, on the other hand, there are both activated and non-activated factors II, VII, IX and X. PCC preparations supplied by different manufacturers vary slightly in the amount of clotting factors and their inhibitors.

To minimize the risk of supratentorial hematoma, it will also be advised, to preferentially choose general anesthesia, not spinal anesthesia in cases requiring urgent or immediate surgery, In vascular surgery departments, immediate and urgent procedures are primarily performed to treat:

- ruptured aneurysms of the abdominal aorta, thoracoabdominal aorta, iliac arteries or visceral arteries;
- traumas in which large vessels were damaged, including those responsible for limb vitality;
- acute ischemia of the upper or lower extremities.

Ruptured aneurysm surgery carries a very high risk of hemorrhagic complications. This is influenced by the condition of the patient admitted with such a diagnosis — most often with symptoms of hemorrhagic shock and coagulation disorders already present. Classic surgery with opening of the peritoneal cavity and retroperitoneal space, with active anticoagulants, is fraught with a major risk of uncontrollable bleeding and, thus, a substantial risk of death. Nowadays, it is possible to perform surgery for ruptured aortic aneurysms using an endovascular approach, which can potentially reduce the risk of hemorrhagic complications. However, this should not change the surgical approach in this group of patients, as conversion from endovascular to conventional surgery may be necessary during the course of the procedure. Large vessel injuries in the abdominal or thoracic cavity, absolutely require the use of FXa inhibitor reversal drugs. This is primarily related to the extent of the surgery, and the need to supply the injured vessels.

Surgeries for acute ischemia of the upper and lower extremities are very common procedures performed as part of the vascular Emergency Department. Despite the fact that these procedures are much less burdensome for the patient, usually with little vascular access and skin incision, NOAC inhibition should also be considered in such cases. Some of these procedures can be performed percutaneously, in the form of mechanical thrombectomy. In cases of both open and endovascular procedures, there is a risk of iatrogenic perforation of the vessel, and, consequently, uncontrolled bleeding. In cases of acute, long-lasting ischemia of the limb, compartment syndrome may occur. This symptom should absolutely be treated surgically by performing a fasciotomy, usually in a three-compartment open approach. This procedure involves decompressing the swollen and, in high probability, necrotic muscle groups of the ischemic limb by cutting through the fascia and skin, which involves the risk of major bleeding.

Although there are no publications on fibrinolytic treatment in patients treated with NOACs, it seems that thrombolytic treatment of acute limb ischemia should be contraindicated in this group of patients.

The current position regarding open and endovascular procedures with vascular access preventing complete control of bleeding (e.g., femoral access) for immediate and urgent vascular surgery, practically requires the use of NOAC reversal in all cases.

Unfortunately, the effect of AA persists only until about 2 hours after the end of the infusion, which is a significant problem for patients undergoing surgical procedures that last several hours. In such cases, inhibition of anti-Xa activity by AA may not be sufficient to maintain hemostasis [17].

Given the above, in the absence of life-threatening bleeding, AA administration should be delayed until immediately before surgery to ensure maximum anticoagulant reversal and avoid repeated doses. However, there are examples in the literature of double administration of a standard dose of AA [64] or a single standard dose of AA with prolonged infusion of the drug at a half-reduced rate during prolonged surgery [65].

Hence, it remains necessary to create multidisciplinary guidelines for determining the risk of perioperative bleeding, as well as the timing of AA administration for specific procedures. As new data emerge, we expect that the use of AA in the perioperative setting will evolve.

CARDIOLOGIST-THE IMPORTANCE OF COORDINATING INTERDISCIPLINARY COLLABORATION IN DECISIONS TO USE ANDEXANET ALFA

The decision to reverse the action of a NOAC and administer an antidote in the form of an AA is difficult and requires an assessment of the possible benefits over risks. Such a decision can only be made possible through interdisciplinary cooperation of specialists from different fields. Depending on the type of side effects of NOAC use, this will include neurologists, surgeons or emergency medicine physicians. However, cardiologists definitely have the most experience in the use of NOACs, due to the fact that these drugs are mostly administered for cardiac indications. It would, therefore, be advisable for cardiologists to coordinate these multispecialty teams, and for AA to be located in cardiology departments.

DETERMINATION OF ANDEXANET ALFA FINANCING CONDITIONS

Currently, the only substance registered in Europe and the United States for the specific reversal of the anticoagulant effect of apixaban and rivaroxaban is AA (ATC code: V03AB38 — all

other drugs, antidotes). The US Food and Drug Administration registered the drug as a breakthrough designation in November 2013. In May 2018, the drug received accelerated approval [66, 67]. In Europe, including Poland, the European Medicine Agency, in April 2019, granted AA conditional approval, which is used for drugs of particular public health importance and to address population health needs when the clinical benefits outweigh the risks of their use [17].

Thus, AA is currently recommended for reversal of rivaroxaban and apixaban in patients with life-threatening or unmanageable hemorrhages, i.e. for use in emergency and life-threatening conditions in the hospital setting, and in Poland there is currently no dedicated public funding for this drug in the hospital lump sum system (Table 7). Thus, there is an urgent need to create a billing product for this drug, e.g. by including it in the aggregated product catalog (pol. *katalog produktów do sumowania*) allowing it to be summed-up with other procedures performed within the existing diagnosis-related groups (pol. *Jednorodne Grupy Pacjentów*) dedicated to the treatment of hemorrhage, or the catalog of separate products (pol. *katalog produktów odrębnych*): 5.52.01.0001384 — hospitalization for reasons not covered elsewhere (pol. *hospitalizacja z przyczyn nieujętych gdzie indziej*). Before this can happen, however, there is an urgent need for hospitals to seek alternative methods of financing in individual patients.

Table 7. Recommendations for the use of andexanet alfa in patients with life-threatening or unmanageable hemorrhages

Anticoagulation Forum 2018	Suggested	[68]
American Society of Hematology 2018	Suggested	[69]
European Stroke Organisation 2019	Recommended in the first line treatment	[70]
American College of Cardiology 2020	Recommended in the first line treatment	[71]
Japanese Circulation Society/Japanese Heart Rhythm Society 2022	For consideration	[72]
American College of Emergency Physicians 2020	Recommended	[73]
American Heart Association/American College of Cardiology/Heart Rhythm Society 2019	Potentially useful	[74]
Asia Pacific Heart Rhythm Society 2021	Potentially useful	[75]

European Heart Rhythm Association 2021	Recommended	[76]
Deutsche Gesellschaft für Neurologie 2022	For consideration	[77]
American College of Chest Physicians 2018	Recommended	[78]
Spanish Society of Digestive Pathology/Spanish Society of Thrombosis and Haemostasis 2022	Recommended, if available	[79]

CONCLUSIONS

Andexanet alfa is recommended for patients with life-threatening and unmanageable hemorrhages (major bleeding according to ISTH or BARC 3b), including HS and post-traumatic bleeding, in patients using FXa inhibitors. Prothrombin complex factor concentrate or aPCC, on the other hand, are recommended as reversal agents for all NOACs in the absence of an available antidote.

Management of patients with severe bleeding includes determining the type and dose of NOAC used and the time elapsed since its last administration. A full panel of clotting parameters should be performed, including plasma NOAC concentrations, if the test is available. The ISTH suggests considering NOAC reversal in patients with severe bleeding and NOAC levels >50 ng/ml. Currently, it is believed that drug-specific chromogenic anti-Xa assays are most appropriate for estimating rivaroxaban and apixaban plasma levels. The absence of anti-Xa activity determined using these assays excludes clinically relevant plasma NOAC levels.

In contrast, the AA dose should not be modified based on the results of hemostasis tests. Rather, it should depend solely on the time elapsed since the last dose of the FXa inhibitor and the long-term dosage of the anticoagulant. When using rivaroxaban >10 mg, apixaban >5 mg, or when the dose is unknown, it is recommended to administer a high dose of AA when the drugs were taken within 7 hours, or a low dose when a minimum of 8 hours has passed. When using rivaroxaban ≤10 mg and apixaban ≤5 mg, a low dose of AA is recommended. When the time of the last NOAC dose is unknown, high dose should be administered to long-term users of higher doses of NOACs, and a low dose for long-term users of lower doses.

Andexanet alfa is administered as an i.v. bolus of 400 mg (low dose) or 800 mg (high dose) at a rate of 30 mg/min. An i.v. infusion of the drug is then introduced, at a rate of 4 mg/min (low dose) or 8 mg/min (high dose) for 120 minutes. Maximum reversal of anti-Xa activity occurs within two minutes of the end of the bolus, and continued continuous i.v. infusion allows the effect to be maintained until 2 hours afterwards.

Measuring anti-Xa has no use in monitoring of the FXa anticoagulant effect reversal. Treatment monitoring should be based mainly on clinical parameters — evaluation of hemostasis or side effects, including thromboembolic events.

Due to the high and multifactorial thromboembolic risk in patients requiring AA administration, resumption of anticoagulant treatment should be considered as early as possible after the bleeding is contained.

Based on the available literature, it is also known that the use of AA can be considered off-label in life-threatening clinical situations requiring urgent surgical intervention. Surgery or intervention, if possible, should be delayed until at least 12 hours, and optimally until 24 hours, after the last NOAC dose. When a patient requires immediate life-saving surgery associated with intermediate or high risk of bleeding, and the last dose of anticoagulant has already been taken, antidote administration is indicated. Unfortunately, the short duration of AA action after the end of the infusion poses a significant problem for patients undergoing surgical procedures lasting many hours. Formulating definitive recommendations on the use of AA for this indication requires further research. The ISTH suggests the need to reverse FXa inhibitors before surgery in patients with a high risk of bleeding and NOAC levels >30 ng/ml.

Unfortunately, in Poland there is no dedicated public funding for AA in the hospital lump sum funding system. Thus, there is an urgent need to create a billing product for this drug and to seek alternative methods of financing in individual patients within hospital procedures.

Article information

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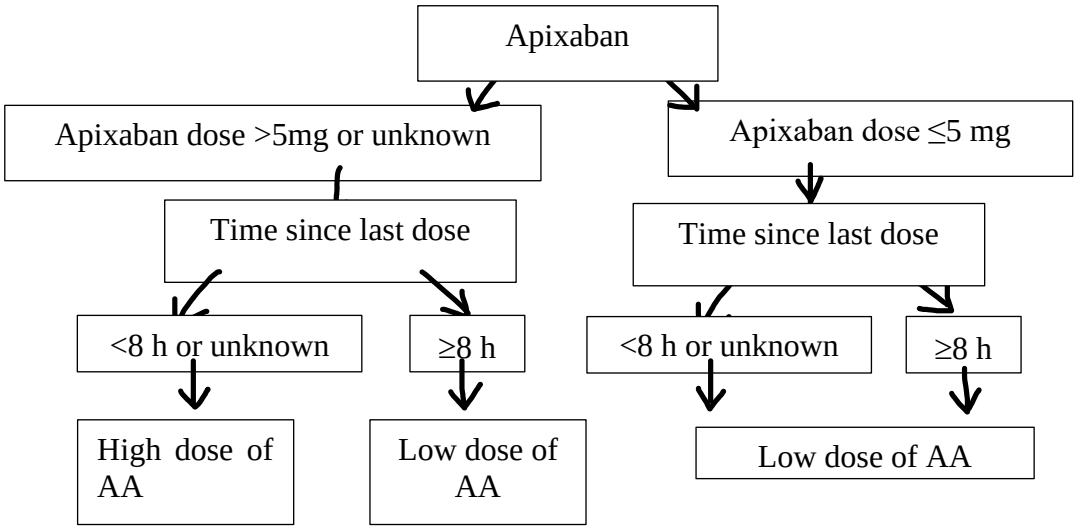

Figure 1. Dosage of andexanet alfa (AA) when using apixaban (based on: [17])

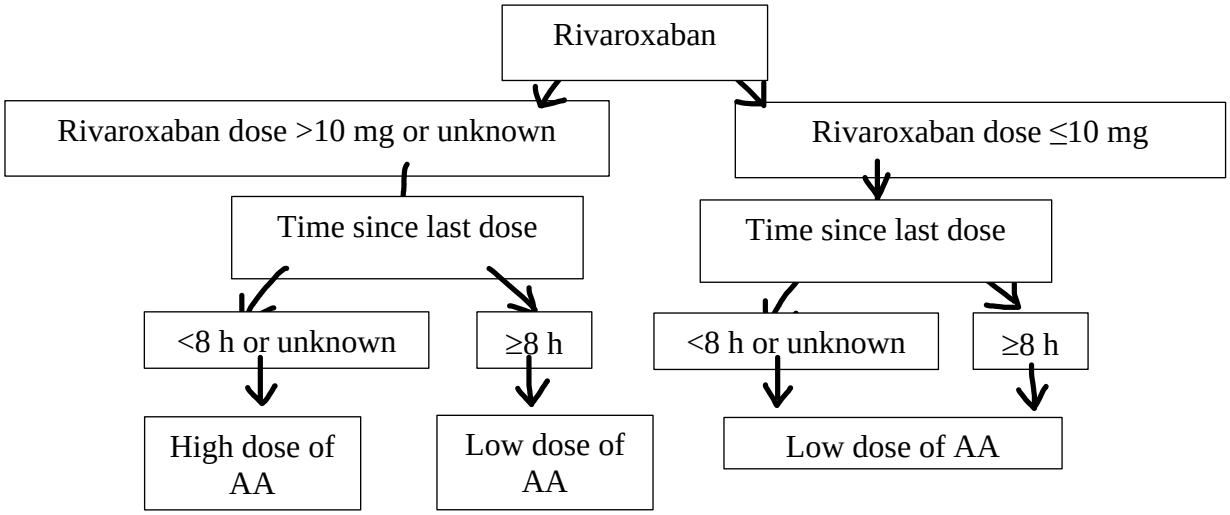

Figure 2. Dosage of andexanet alfa (AA) when using rivaroxaban (based on: [17])

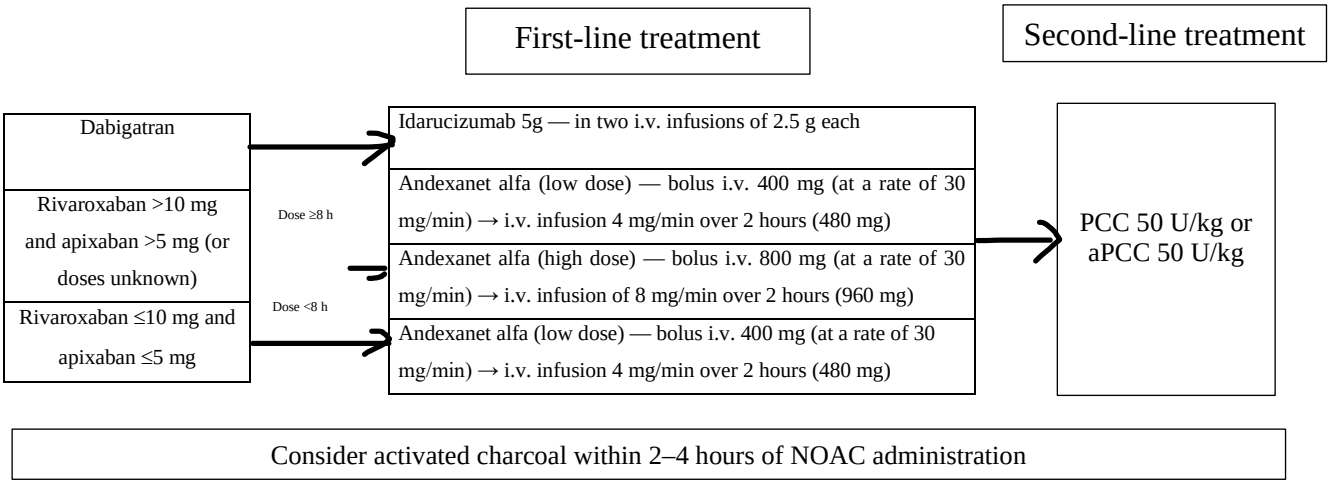

Figure 3. Reversal of non-vitamin K antagonist oral anticoagulants action

Based on: Tomaselli GF, Mahaffey KW, Cuker A, et al. 2017 ACC expert consensus decision pathway on management of bleeding in patients on oral anticoagulants: a report of the American College of Cardiology Task Force on expert consensus decision pathways. J Am Coll Cardiol. 2017; 70: 3042–3067

Abbreviations: aPCC, activated prothrombin complex concentrates; i.v., intravenous; PCC, prothrombin complex concentrates

1. Determine the urgency of the medical procedure:

Immediate (a few minutes)	Urgent (a few hours)	Expedited (several days)

2. A full panel of blood clotting parameters should be performed: PT, APTT, anti-Xa, *etc*. + plasma NOAC concentration, if available

3. The time of the last NOAC dose should be determined

Last dose >12 hours *>24 hours in case of impaired renal function, e.g., eGFR <50 ml/min	Last dose ≤12 hours *≤24 hours in case of impaired renal function, e.g., eGFR <50 ml/mi		
	Immediate NCS	Urgent NCS	Expedited NCS
NCS can be performed	NOAC reversal depending on antidote availability and risk of bleeding associated with the procedure	Postpone the procedure for 12 hours (24 hours in patients with kidney disease) or until clotting parameters normalize	Postpone surgery, as for elective procedures, provided it is safe to do so

Figure 4. Proposed regimen for patients treated with NOACs before NCS (based on: [61])

Abbreviations: eGFR, estimated glomerular filtration rate; NCS, non-cardiac surgery' NOAC, non-vitamin K antagonist oral anticoagulants; other — see Table 1