REVIEW ARTICLE

# HEMATURIA AND OTHER KINDS OF BLEEDINGS ON NON-VITAMIN K ANTAGONIST ORAL ANTICOAGULANTS IN PATIENTS WITH ATRIAL FIBRILLATION: AN UPDATED OVERVIEW ON OCCURRENCE, PATHOMECHANISMS AND MANAGEMENT

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**ABSTRACT**

Non-vitamin K antagonist oral anticoagulants (NOACs) are currently recommended for oral anticoagulation in patients with non-valvular atrial fibrillation. In the setting, NOACs effectively prevent from stroke and systemic embolic events. In spite of the favorable safety profile of NOACs when compared with vitamin K antagonists, the use of any kind of anticoagulation is associated with an increased risk of bleeding. However, there is still a lack of direct comparisons of effectiveness and safety among NOACs. The results of indirect comparisons and meta-analyses suggest that the risk of various types of hemorrhagic complications differ among the particular NOACs. Management of bleeding in patients under NOAC therapy can be challenging because of limited availability of antidotes and the lack of routine laboratory test monitoring the NOAC anticoagulant effect. In case of life-threatening or critical site bleeding, reversal of NOAC anticoagulant activity is essential together with immediate implementation of causative treatment. Moreover, some patients on chronic NOAC therapy may require urgent surgery or invasive procedures. Specific reversal agents for NOACs have been developed, i.e. more widely available idarucizumab for the factor IIa inhibitor (dabigatran) and andexanet alfa for the factor Xa inhibitors (rivaroxaban, apixaban, edoxaban) with limited availability. This review summarizes the occurrence and management of NOAC-related bleeding complications with a particular emphasis on hematuria.

**KEY WORDS:** bleeding, non-vitamin K antagonist oral anticoagulants, idarucizumab, andexanet alfa

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## INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia [1]. AF is associated with increased risk of thromboembolic events, heart failure, death and hospitalization [2]. In AF patients, OAC (oral anticoagulant) therapy is highly effective for ischemic stroke prevention. However, warfarin and other vitamin K antagonists (VKAs) use can be limited by narrow therapeutic index, variability in dose-response among patients and great number of drug or food interaction.

Non-vitamin K antagonist oral anticoagulants (NOACs) directly inhibit thrombin (dabigatran) or activated factor X (rivaroxaban, apixaban, edoxaban). NOACs have predictable pharmacodynamics and pharmacokinetics and display rapid onset and offset of action. Their use in non-valvular AF therapy is still increasing. According to the guidelines of European Society of Cardiology, NOACs are recommended as the first choice anticoagulants in most of patients with non-valvular AF and one or more stroke risk factors [3]. Four phase III randomized clinical trials showed that NOACs are at least as safe and effective as VKAs [4-7].

The use of OACs, both VKAs and NOACs, is associated with bleeding risk, including major bleeding, intracranial hemorrhage (ICH), gastrointestinal (GI) and urinary bleeding. Generally, NOACs therapy have been shown to significantly reduce the rate of intracranial hemorrhage compared with warfarin. However, these drugs may increase the risk of gastrointestinal bleeding. NOACs differ in their degree of renal excretion, half-life times, bioavailability and metabolism. There are no head-to-head clinical trials comparing NOAC therapies. Evidence from indirect comparisons should be carefully assessed.

## THE AIM

The aim of this review was to describe the occurrence, pathomechanisms and management of hemorrhagic complications in patients with AF treated with NOACs. We decided to pay a particular attention to hematuria as this kind of bleeding complication is common and so far only few papers have addressed this topic.

## REVIEW AND DISCUSSION

### HEMATURIA

One of the most frequent site of bleeding during OAC therapy is genitourinary tract. Macroscopic hematuria occurs in 2-24% of these patients [8]. Previous studies have emphasized the clinical significance of hematuria in patients on OAC therapy. OACs usually do not induce *de novo* hematuria, but they may have a negative effect on the intensity and duration of hematuria from other etiologies. OAC-related bleeding is often diagnosed in individuals with underlying genitourinary pathology (3-82%), such as malignancy, prostate diseases, infection, urolithiasis or congenital anomaly [9]. Among AF patients with hematuria, warfarin use might be associated with a higher prevalence and early detection of genitourinary cancer [10]. In contrast, some authors suggest that warfarin might have a protective effect on some types of cancer development, especially prostate cancer, but not renal or bladder cancer [11].

Moreover, the effect of NOACs versus warfarin on genitourinary bleeding may differ. A meta-analysis of over 175,000 patients on OACs demonstrated that the overall probability of visible hematuria was 26.7%. Warfarin therapy was linked to an increased risk for visible hematuria, but major hematuria was more common in patients receiving NOAC. Among NOACs, dabigatran was the most likely to cause major hematuria compared to warfarin (37% vs. 0.2%). Urologic pathology was found in 44% patients with hematuria, malignancy in 14% [12]. These observations indicate the importance of complete urologic evaluation for hematuria, including upper tract imaging and cystoscopy.

### INTRACRANIAL HEMORRHAGE

Intracranial hemorrhage is one of the most devastating OAC therapy complications associated with high risk of mortality and severe disability. Previous studies confirmed that warfarin therapy is linked with more hematoma expansion and higher mortality than spontaneous ICH [13]. The substantial benefit of NOAC therapy is driven by effective protection against hemorrhagic stroke. A meta-analysis of phase III trials showed that NOACs reduce the risk of ICH by half [14]. Another meta-analysis indicated that higher doses of NOACs might be associated with increased likelihood of ICH [15]. According to the results of the phase III trials, each NOAC was associated with lower rates of intracranial hemorrhage compared with warfarin. However, in these studies there have been only limited data on potential association between prior NOAC use and ICH outcome. Among patients with ICH, prior NOAC or warfarin therapy was associated with higher in-hospital mortality compared with patients with no prior use of anticoagulants. Prior use of NOACs was associated with lower risk of in-hospital mortality and better in-hospital outcome compared with prior use of warfarin [16].

The RE-LY (*Randomized Evaluation of Long-Term Anticoagulation Therapy*) trial showed that dabigatran 150 mg twice daily and dabigatran 110 mg twice daily reduced the relative risk of ICH (relative risk [RR] 0.26; 95% confidence interval [CI] 0.14-0.49 and RR 0.31; 95% CI 0.17-0.56, respectively). The risk of ICH was lower with both dabigatran doses compared with warfarin group irrespective of age [17]. This observation indicates that the relationship between age and anticoagulant treatment is not only a pharmacokinetic interaction. This findings support hypothesis that the lack of NOAC interference of VIIa-Tissue Factor (TF) complex formation might be associated with lower incidence rates of ICH compared with warfarin. Warfarin and other VKAs inhibit the synthesis of vitamin K-dependent clotting factors, including factor II (prothrombin), VII, IX and X. Plasma clotting factor VII is the natural ligand of TF (the cellular transmembrane receptor for factor VIIa). Factor VIIa-TF complex formation triggers the coagulation cascade. High TF expression in vital organs, such as the lungs, brain, heart, testis, uterus, and placenta provides addition protection against hemorrhage.

Some data suggest potential role of cerebral microbleeds neuroimaging in identifying patients who might net harm from oral anticoagulation. In the CROMIS-2 trial, in 1447 patients with AF anticoagulated after ischemic stroke or transient ischemic attack, cerebral microbleeds were independent risk factor for symptomatic intracranial hemorrhage [18]. In a meta-analysis of cohort studies including individuals with recent ischemic stroke and documented AF, the presence of at least 5 cerebral microbleeds was associated with high ICH risk. However, it remains uncertain how this knowledge might impact clinical practice [19].

### MAJOR BLEEDING

The comparison of major bleeding events from the clinical trials between particular NOAC and VKA is limited by differences in the definition of major bleeding. The RE-LY trial enrolled 18,133 patients. The rate of major bleeding (defined as a reduction in the hemoglobin concentration of at least 20 g per liter, transfusion of at least 2 units of blood or symptomatic bleeding in a critical area or organ) among the patients in the warfarin group was 3.36% per year, compared with 2.71% in the group receiving 110 mg dabigatran (p=0.003) and 3.11% per year in the group receiving 150 mg dabigatran (p=0.31). Life-threatening bleeding occurred more frequently (1.8% per year) in patients in the warfarin group as in those receiving dabigatran 110 mg (1.22% per year, p≤0.001) and dabigatran 150mg (1.45% per year, p=0.04) [6]. In the ROCKET-AF (*Rivaroxaban Once-daily oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation*) trial, the rates of major bleeding (defined as clinically overt bleeding associated with any of following: fatal outcome, involvement of a critical anatomic site, fall in hemoglobin concentration ≥2 g/dL, transfusion of ≥2 units of whole blood or packed red blood cells, or permanent disability) in the warfarin and

**Table 1.** Comparison of pharmacological characteristics of NOACs.

| Target | Dabigatran | Rivaroxaban | Apiksaban | Edoxaban |
|---|---|---|---|---|
| Prodrug | Yes | No | No | No |
| Oral bioavailability (%) | 7 | 66 | 50 | 68 |
| Mean half-time (h) | 14-18 | 7-13 | 12 | 50 |
| Renal clearance (%) | 85 | 33 | 27 | 50 |
| Plasma protein binding (%) | 33 | 95 | 87 | 99 |
| Potential interactions | P-glycoprotein drug modulating drugs | CYP3A4, P-glycoprotein modulating drugs | CYP3A4, P-glycoprotein modulating drugs | CYP2C9, CYP2C8, 2C18, 2C19, 1A2, 3A4 modulating drugs |
| Metabolism | Conjugation | Oxidation and hydrolysis | Oxidation and conjugation | Hydrolysis, unchanged (70%) |
| Dosing in AF | 150 mg twice daily or 110 mg twice daily (patients ≥80 years old / >75 years old (ESC) or concomitant use of verapamil or amiodarone) | 20 mg once daily or 15 mg once daily (patients with CrCl 30-49 mL/min) | 5 mg twice daily or 2.5 mg twice daily (if at least two of following: age≥80 years, body weight≤60 kg or serum creatinine level ≥1.5 mg/dL (133 µg/L) | 60 mg once daily or 30 mg once daily (patients with CrCl 30-50 mL/min, body weight≤60 kg or concomitant use of verapamil or quinidine or dronedarone) |

Note: AF – atrial fibrillation; CrCl – creatinine clearance; CYP – cytochrome P450; ESC – European Society of Cardiology; NOACs – non-vitamin K antagonist oral anticoagulants

rivaroxaban groups were similar (5.6% vs 5.4%, p=0.58) with significantly lower rates of fatal bleeding in the rivaroxaban group (0.4% vs 0.8%, respectively; p=0.003) [5]. In the ARISTOTLE (*Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation*) trial, apixaban reduced the risk of major hemorrhage by 31% compared with warfarin (hazard ratio [HR] 0.69; 95% CI 0.60-0.80; p<0.001). Major hemorrhage occurred more common in older patients, those with history of prior myocardial infarction, prior hemorrhage, prior stroke or transient ischemic attack, systemic embolism, diabetes or hypertension. Renal function impairment and lower hematocrit level were also more frequent among patients who sustained a major bleeding [4].

In the ENGAGE AF-TIMI 48 (*Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48*) study, the rate of major bleeding (as defined by the International Society of Thrombosis and Haemostasis) was 3.4 % with warfarin versus 1.61% (p<0.001) with low-dose edoxaban and 2.75% (p<0.001) with high dose edoxaban [7]. The risk of major bleeding in clinical trials was significantly lower with dabigatran 110 mg twice daily, apixaban twice daily and edoxaban once daily compared with warfarin. Similar observations were made by other authors. In real-world data, Yao e*t al.* using a large US insurance database found that in patients with AF apixaban was associated with lower risks of both stroke and major bleeding, dabigatran was associated with similar of stroke and lower risk of major bleeding, and rivaroxaban was associated with similar risks of both stroke and major bleeding in comparison to warfarin [20]. Also in a cohort of 19,713 newly anticoagulated AF patients, a significantly lower rate of major bleeding were observed on dabigatran or apixaban therapy when compared with warfarin treatment [21]. This results are worth emphasizing because the risk of major bleeding is higher in the early phase of anticoagulation therapy.

## GASTROINTESTINAL BLEEDING

In general, NOAC therapy is associated with an increased risk of GI bleeding compared with warfarin, with apixaban being the exception. Several local and systematic mechanisms lead to gastrointestinal complications of NOAC treatment. That might be the consequence of differences in bioavailability between these drugs and warfarin and longer NOACs persistence in the gastrointestinal tract (Table 1). The bioavailability of warfarin is 97%, while the mean bioavailability of NOACs is substantial lower (dabigatran 7%, rivaroxaban 66%, apixaban 50% and edoxaban 68%) [22]. Moreover, the NOACs may also inhibit GI mucosal healing. Old age, concomitant use of antiplatelet drugs, hepatic or renal dysfunction are additional risk factors of NOAC-related GI bleeding.

Some data suggest that dosing of novel anticoagulants can affect the incidence of bleeding. Once daily administration of rivaroxaban offer higher peak level than apixaban 5 mg twice daily and may lead to higher risk of bleeding despite the fact that both these drugs inhibit factor Xa, are administrated in active form, and have comparable bioavailability. The annual incidence of GI bleeding in patients receiving NOACs is up to 2% with rivaroxaban which is associated with highest risk. In the ROCKET-AF trial, the rate of major bleeding from a gastrointestinal site was significantly higher among the patients receiving rivaroxaban once daily compared with the warfarin group (3.2%, n=224 *vs.* 2.2%, n=154; p<0.001) [5]. In the RE-LY trial, the rate of major GI

bleeding was 1.12% per year in the warfarin group, compared with 1.51% per year in the patients receiving 150 mg dabigatran (p<0.001) and 1.02% in patients receiving 110 mg dabigatran (p=0.43) [6]. In the ARISTOTLE trial, there was no significant difference between the rates of major GI bleeding in the apixaban group and the warfarin group (n=121 *vs*. n=133, p=0.35). Digestive tract was the most frequent location of major hemorrhage (31%, n=171) [4]. In the ENGAGE-AF TIMI 48 study, edoxaban 60 mg once daily was associated with increased risk of GI bleeding than warfarin (1.51% *vs*. 1.23% per year, p=0.03), while edoxaban 30 mg once daily reduced the rate of GI bleeding compared with warfarin (0.82% *vs*. 1.23% per year, p<0.001) [7].

The risk of GI bleeding varies among different NOAC regimens. A meta-analysis of phase III randomized controlled trials showed that rivaroxaban and high dosage of dabigatran and edoxaban significantly increased the number of GI bleeding in patients with non-valvular AF [23]. The rate of GI bleeding was similar in patients receiving apixaban, low-dose dabigatran and warfarin. This results suggest that rivaroxaban and high dosage of dabigatran and edoxaban should be avoided in patients at elevated risk of GI bleed.

In a recent network meta-analysis, rivaroxaban, but not apixaban, edoxaban and dabigatran, was associated with increased risk of major GI bleeding [24]. The highest probability of being the safest option had apixaban with regard to the major GI bleeding risk.

Typically, patients treated with warfarin, aspirin or non-steroidal anti-inflammatory drugs bleed from the upper GI tract. Similarly, the most frequent site of major bleeding among patients receiving rivaroxaban in the ROCKET AF trial was the upper GI tract [5]. On the other hand, in the RE-LY trial, the most common location for major bleeding in patients on dabigatran therapy was the lower GI tract [6]. In the ENGAGE-AF TIMI 48 participants, the rate of lower GI bleeding was significantly lower with low-dose edoxaban than with warfarin and the rates of upper GI bleeding were similar in both groups [7]

## AF PATIENTS UNDERGOING PERCUTANEOUS CORONARY INTERVENTIONS

Triple antithrombotic therapy (TAT) with OAC plus two antiplatelet agents (aspirin and P2Y12 inhibitor) in patients with AF after an acute coronary syndrome (ACS) or undergoing elective percutaneous coronary intervention (PCI) is associated with a 2- to 4- fold increase in the risk of major bleeding [25]. Clinical decision making in these patients requires the evaluation of patient's stroke and bleeding risks. In this setting, the European Society of Cardiology guidelines recommend the preference of NOACs over VKAs and minimizing the duration of triple antithrombotic therapy (e.g. ≤1 week) [26]. Novel P2Y12 inhibitors (i.e. ticagrelor and prasugrel) should be avoided as a part of TAT. In patients with AF after ACS and/or PCI, absolute bleeding risk may be also reduced by using a radial approach, adding a proton pomp inhibitor to limit GI bleeding, and avoiding the use of non-steroidal anti-inflammatory drugs.

Several recent studies have evaluated the efficacy and safety of double *vs*. triple antithrombotic therapy in patients with AF and ACS or undergoing PCI. In the WOEST (*What is the Optimal Antiplatelet & Anticoagulant Therapy in Patients with Oral Anticoagulation and Coronary Stenting*) trial, the use of clopidogrel alone compared with aspirin plus clopidogrel in the patients on VKA therapy reduced the number of all bleeding events as well as all-cause mortality without any increase in ischemic events [27].

In the ISAR-TRIPLE (*Triple Therapy in Patients on Oral Anticoagulation After Drug Eluting Stent Implantation*) trial, patients receiving concomitant aspirin and VKA were randomized to 6-week clopidogrel therapy or 6-month clopidogrel therapy. There was no significant differences in the combined ischemic endpoint (cardiac death, myocardial infarction, definite stent thrombosis, and ischemic stroke) or in the bleeding endpoint of TIMI major bleeding between the groups [28]. These findings suggests that TAT may be minimized in patients with elevated bleeding risk.

The results of recent randomized controlled trials clearly indicate that the use of NOACs instead of VKAs in AF patients undergoing PCI is associated with a reduction of bleeding risk. In the PIONEER AF-PCI (*A Study Exploring Two Strategies of Rivaroxaban and One of Oral Vitamin K Antagonist in Patients With Atrial Fibrillation Who Undergo Percutaneous Coronary Intervention*) trial, participants undergoing PCI with placement of stents were randomized in a 1:1:1 ratio to rivaroxaban 15 mg plus P2Y12 inhibitor for 12 months, very low-dose rivaroxaban (2.5 mg twice daily) plus DAPT for 1, 6 or 12 months, and standard therapy with a dose-adjusted vitamin K antagonist plus DAPT for 1, 6 or 12 months. All groups had a similar efficacy rates but broad CIs were observed. The administration of low-dose rivaroxaban plus P2Y12 inhibitor for 12 months or very-low-dose rivaroxaban plus DAPT for 1,6 or 12 months reduced the rates of clinically significant bleeding compared with standard VKA plus DAPT for 1, 6, or 12 months therapy [29].

In the REDUAL-PCI (*Evaluation of Dual Therapy With Dabigatran vs. Triple Therapy With Warfarin in Patients With AF That Undergo a PCI With Stenting*) trial, dabigatran 150 mg twice daily or 110 mg twice daily plus P2Y12 inhibitor *vs*. standard TAT was associated with significantly lower rate of major or clinically relevant non-major bleeding among AF patients after PCI [30]. A numerical increase in MI and definite stent thrombosis in the dual therapy dabigatran 110 mg group was observed. Adverse cardiac events were similar between study groups. The AUGUSTUS (*An Open-label, 2 Factorial, Randomized Controlled, Clinical Trial to Evaluate the Safety of Apixaban vs. Vitamin K Antagonist and Aspirin vs. Aspirin Placebo in Patients With Atrial Fibrillation and Acute Coronary Syndrome or Percutaneous Coronary Intervention)* investigators found that an antithrombotic regimen that included apixaban without aspirin among patients with AF and a recent ACS or PCI treated with P2Y12 was associated

**Table 2.** Available reversal agents and suggested use ([37] – modified).

| Reversal Agent | Factor IIa inhibitor (dabigatran) | Factor Xa inhibitors (apixaban, edoxaban, rivaroxaban) |
|---|---|---|
| 4F-PCC | second line | first line |
| aPCC | second line | second line |
| Idarucizumab | first line | not indicated |
| Andexanet alfa | not indicated | first line |
| Plasma | not indicated | not indicated |

Note: aPCC – activated prothrombin complex concentrate; 4F-PCC – the 4-factor prothrombin complex concentrate

with lower rate of bleeding and hospitalizations without significant differences in the number of ischemic events compared with VKA, aspirin or both therapy [31]. In AF patients undergoing PCI in the ENTRUST-AF PCI trial, the edoxaban-based regimen (edoxaban 60 mg daily plus P2Y12 inhibitor) was non-inferior in terms of bleeding events compared with VKA in combination with a P2Y12 inhibitor and aspirin, without significant differences in the rates of ischemic events [32].

## SAFETY *VS*. EFFICACY

Anticoagulation therapy should be administrated carefully and individually. Indirect comparisons and network meta-analyses showed generally similar efficacy and differences in safety profiles of NOACs [33]. In the ARISTOPHANES *(Anticoagulants for Reduction in Stroke: Observational Pooled Analysis on Health Outcomes and Experience of Patients)* study, apixaban was superior to warfarin in preventing stroke/systemic embolism, major bleeding and intracranial hemorrhage. Rivaroxaban was associated with significantly lower risk of stroke/systemic embolism and higher rate of major bleeding compared with warfarin [34].

In clinical practice, decision to prescribe standard or reduced dose of NOACs should be made of the basis of specific considerations (age, renal function and use of concomitant medications). However, some data suggest that a substantial number of patients are receiving reduced dose of NOACs without fulfillment Food and Drug Administration (FDA) dosing recommendation for such dosing. Inappropriate dosing of NOAC may have important clinical implications for treatment effectiveness.

In a propensity weighted nationwide study of reduced doses of NOAC, apixaban 2.5 mg twice daily was related with a trend towards higher risk of ischemic stroke/systemic embolism compared with warfarin [35]. In the ORBIT-AF II (*Outcomes Registry for Better Informed Treatment of Atrial Fibrillation II*) registry, a reduced NOAC dose was prescribed to 16% patients which was consistent with FDA labeling in 43% cases. Moreover, patients receiving inappropriately reduced-dose NOACs had higher rates of thromboembolic events (2.11 versus 1.35 events per 100 patient years; HR 1.56; 95% CI 0.92-2.67) and death (6.77 versus 2.60; HR 2.61; 95% CI 1.86-3.67) compared with individuals appropriate receiving standard dosing [36].

## MANAGEMENT OF NOAC-RELATED BLEEDING

Currently, we dispose limited therapeutic options in patients with bleeding during NOAC therapy (Table 2) [3, 37]. An obligate first step in the initial evaluation of such individuals is to determine hemodynamic status, blood pressure, coagulation parameters, blood count and renal function. In cases of minor hemorrhage mechanical compression or minor surgery ought to be sufficient. Delay NOAC for one dose or one day should be considered. Due to NOACs short half-life time, after 12-24 hours after the last dose we may expect improvement of the coagulation.

Management of moderate to severe bleeding may include fluid replacement, blood transfusion and a procedure to control bleeding (e.g. endoscopy). Oral activated charcoal can be used if NOAC was recently ingested. Owing to low protein binding, hemodialysis reduces the plasma concentration of dabigatran.

In a life-threatening, critical site bleed, or in situations in which bleeding cannot be controlled, reversal of NOACs is indicated. The rational use of antidotes is crucial. Relative short half-times of NOACs reduce the need for use of an antidote in clinical practice.

Administration of prothrombin complex concentrates (PCC) should be consider for NOAC related bleeding if specific reversal agents are not available.

Idarucizumab is a humanized monoclonal antibody fragment designed to reversal the effect of dabigatran. Idarucizumab and dabigatran form complexes cleared by the kidneys. In the RE-VERSE (A Study of the RE-VERSal Effects of Idarucizumab on Active Dabigatran) AD study, in over 500 patients intravenous infusion of 5 g of idarucizumab rapidly, durably and safely reversed the anticoagulant effect of dabigatran in patients who had uncontrolled bleeding or were about to undergo an urgent major procedures [38]. Idarucizumab is widely available almost all over the world. Andexanet alfa is a recombinant modified factor Xa molecule for reversal of factor Xa inhibitors. This first and only available antidote was approved by the Food and Drug Administration in patients treated with rivaroxaban or apixaban when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding. Andexanet alfa acts as a decoy of Xa, that binds factor Xa inhibitors without enzymatic activity. In the ANNEXA-4 study, andexanet alfa was administrated as a bolus injection, followed by a 2-hour infusion. In 352 patients with acute major bleeding within 18 hours after receiving apixaban, rivaroxaban, edoxaban at any dose or enoxaparin at a dose of at least 1 mg per kilogram of

body weight per day, treatment with andexanet alfa substantially reduced anty-Xa activity. Most of patients (82%) had excellent or good hemostatic efficacy [39]. Unfortunately, there is still a limited access to andexanet alfa.

Ciraparantag (PER977) is a small synthetic molecule that binds heparin and the oral direct factor Xa (FXa) and factor IIa (FIIa) inhibitors. Ciraparantag in healthy subjects was safe and completely reversed the anticoagulant effects of edoxaban [40]. Unfortunately, this universal antidote has not been studied in major bleeding or patients who needed urgent surgery.

A clinical concern of NOACs antidotes is anticoagulation rebound (reappearance of NOAC anticoagulation activity after reversal). In the RE-VERSE AD study, reappearance of levels above 20 ng per milliliter of dabigatran was observed in 23% patients (n=114), mainly after 12 hours, and was associated with continued or recurrent bleeding in 20 patients. Three patients required administration of additional dose of idarucizumab [38]. In the ANNEXA-4 (*Prospective, Open-Label Study of Andexanet Alfa in Patients Receiving a Factor Xa Inhibitor Who Have Acute Major Bleeding)* study, rivaroxaban level above 50 ng/mL was documented 4 hours after andexanet alfa infusion. Further studies are needed to determinate the role played by anticoagulation rebound in the clinical practice [39].

## CONCLUSIONS

Scientific evidence from both randomized clinical trials and registries indicates favorable risk to benefit profile of NOACs compared with warfarin in patients with non-valvular AF. Substantial benefits of NOACs include: a reduced risk of ICH, faster onset and offset of action and fewer drug and food interactions. In randomized clinical trials, dabigatran 110 mg, apixaban, and edoxaban have been associated with lower risk of major bleeding compared with VKA. The risk of major bleeding was similar with warfarin for patients taking 150 mg dabigatran or rivaroxaban. NOACs except apixaban and low-dose dabigatran may increase the risk of gastrointestinal bleeding. Visible hematuria during NOAC therapy should be a red flag and underlines the importance of upper urinary tract imaging and cystoscopy to exclude neoplasia. Management of bleeding in anticoagulated patients who experience major bleeding, trauma or undergoing emergency surgery may require antidote administration.

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## Conflict of interest

*Anna Tomaszuk-Kazberuk – lectures and consultations for Boehringer–Ingelheim and consultation for Bayer.*
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