Bleeding in anticoagulated patients with atrial fibrillation: practical considerations

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Short title: Bleeding in anticoagulated patients with AF: practical considerations

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Abstract
Major bleeding (especially intracranial hemorrhage) is the most feared adverse event observed in patients with atrial fibrillation (AF) receiving oral anticoagulation. Clinical risk factor-based scores have modest ability to predict major or clinically relevant bleeds, and blood biomarkers are increasingly implemented to improve bleeding prognostication in AF patients on life-long anticoagulation. To improve the safety of anticoagulation in the era of non-vitamin K antagonist oral anticoagulants (NOAC, or direct oral anticoagulants [DOACs], including dabigatran, rivaroxaban, apixaban, and edoxaban), specific demographic, clinical, and laboratory variables should be considered. The current review summarizes practical challenges in the management of oral anticoagulation with emphasis on the risk assessment tools, elderly or underweight patients, cancer patients, impact of chronic kidney disease, liver cirrhosis and thrombocytopenia in the context of bleeding risk in AF patients.

Key words: anticoagulation, atrial fibrillation, biomarkers, bleeding, comorbidities
Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in clinical practice, and it is associated with an increased risk of ischemic stroke and systemic thromboembolism (SE) from <1% to about 20% per year. Of all ischemic strokes, 20-30% are associated with AF and high morbidity and mortality. Oral anticoagulation therapy reduces the risk of stroke and SE by more than 60% in AF patients, yet clinicians and patients need to consider these benefits vs. the risk of major bleeding.

Non-vitamin K antagonist oral anticoagulants (NOAC, or direct oral anticoagulants [DOACs] as recommended by the International Society on Thrombosis and Hemostasis [ISTH], including dabigatran, rivaroxaban, apixaban, and edoxaban), have been shown in landmark phase 3 randomized trials to be at least noninferior to warfarin for the prevention of stroke and SE and are preferred over warfarin in patients with “nonvalvular” AF. When compared to vitamin K antagonist (VKA), the efficacy of NOACs is similar or higher, but they are safer and more convenient. In a meta-analysis of pivotal phase 3 AF randomized controlled trials (RCTs), NOACs reduced the risk of stroke or SE by 19% compared with warfarin (relative risk [RR] 0.81, 95% confidence interval [CI] 0.73-0.91), largely due to a markedly lower rate of hemorrhagic stroke (RR 0.49, 95% CI 0.38-0.64) and intracranial bleeding (ICB) (RR 0.48, 95% CI 0.39-0.59). However, the use of NOACs (in particular, full-dose dabigatran and rivaroxaban), was significantly associated with increased risk of gastrointestinal (GI) bleeding (RR 1.25, 95% CI 1.01-1.55). Of note, the differences in baseline stroke and bleeding risks among different NOAC trials could have affected the reported bleeding rates (Fig. 1).

Residual incidence of stroke or SE despite NOAC use among AF patients is estimated at 1.5-2.5% per year and that of major bleeding at 2-4% per year. As compared with warfarin, NOACs slightly reduced all-cause mortality (RR 0.89, 95% CI 0.85-0.94), vascular mortality (RR 0.88, 95% CI 0.82-0.94), and bleeding-related mortality (RR 0.54, 95% CI 0.44-0.67). Importantly, in the phase 3 AF trials, NOACs were more effective than warfarin in the prevention of stroke or SE among AF patients aged 75 years or older.

A systematic review by Chai-Adisaksopha et al., which comprised 12 RCTs involving 102,607 patients at the average age of 70 to 73 years in the 5 AF trials and 54 to 57 years in the 7 venous thromboembolism (VTE) trials, clearly demonstrated that the incidence of ICB, the most feared hemorrhagic adverse event, in patients receiving NOACs is reduced by >50% compared with warfarin. Of all major bleeding episodes among VKA users, 8.7% were ICB with a 46% to 55% mortality rate. Patients with AF or VTE on NOACs had a lower risk
of overall major bleeding (RR 0.72, number needed to treat [NNT] 156), fatal bleeding (RR 0.53, NNT 454), clinically relevant nonmajor bleeding (RR 0.78, NNT 99), and all bleeding (RR 0.76, NNT 18), without increased risk of GI bleeding (RR 0.94, 95% CI, 0.88-1.34). Several systematic reviews comparing NOACs with standard care demonstrated a 20% higher GI bleeding rates in patients on NOAC. A significant increase in the risk of GI bleeding was observed in the RCTs evaluating dabigatran and rivaroxaban in AF patients. In the RE-LY trial, dabigatran 150 mg bid (but not dabigatran 110 mg bid) was significantly associated with increased risk of major GI bleeding compared with warfarin (RR 1.50, 95% CI, 1.19-1.89), whereas in the ROCKET-AF rivaroxaban 20 mg once daily increased this annual risk by 1% (3.2% vs 2.2%). Of note, NOAC-associated GI bleeding is probably related to the presence of the active drug in GI tract thus facilitating bleeding from vulnerable lesions.

Scoring systems to predict bleeding in AF

The most commonly used definition of major bleeding in non-surgical patients according to the ISTH includes:
1) fatal bleeding, and/or
2) symptomatic bleeding in a critical area or organ e.g. intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular bleeding with compartment syndrome, and/or
3) bleeding accompanied by a decrease in the hemoglobin level of ≥2 g/dL or leading to transfusion of ≥2 units of whole blood/packed red blood cells.

The annual rates of major bleeding range from 1.3 to 7.2% in patients with AF on VKA treatment. Various bleeding risk scores (Table 1) have been developed to assess the risk of bleeding in patients with AF taking oral anticoagulant therapy. All these scores have a relatively modest ability to predict bleeding events (as reflected by the c-statistic values 0.50-0.65), and numerous studies comparing two or more bleeding risk scores yielded conflicting results. In a PCORI-commissioned systematic review of 38 studies of bleeding risk prediction, the HAS-BLED score had the best evidence for predicting bleeding risk (moderate strength of evidence), consistent with other systematic reviews and meta-analysis comparing bleeding risk prediction scores.

The latest AF guidelines issued by the ESC in 2016 were focused on modifiable risk factors and their elimination if possible, including the use of antiplatelet agents, alcohol abuse, unstable anticoagulation with VKA, and uncontrolled hypertension (to reduce the risk of
ICB). However, non-modifiable bleeding risk factors such as prior major bleeding or stroke, cancer, or advanced age should not be ignored. Whereas modifiable bleeding risk factors should be identified and managed, the important interaction between these and non-modifiable bleeding risk factors should be acknowledged, and such high-risk patients should be scheduled for an earlier and more frequent clinical follow-up after oral anticoagulant therapy has been initiated. Indeed, a formal bleeding risk assessment using the HAS-BLED score has been shown to be superior to the less well-structured approach of addressing modifiable bleeding risk factors only.\textsuperscript{37–39}

**Potential new biomarkers in bleeding prediction**

Most risk prediction models for bleeding in patients with AF, including HAS-BLED, ATRIA and ORBIT-AF score, do not incorporate biomarkers, although they may improve discrimination of traditional risk scores. In the ARISTOTLE trial comparing apixaban with warfarin, blood biomarkers, namely high-sensitivity cardiac troponin T, growth differentiation factor-15, and hemoglobin/hematocrit showed stronger association with bleeding than most of clinical parameters.\textsuperscript{40} The ABC-bleeding score comprising those three biomarkers was validated in the population of the RE-LY trial and performed better than the HAS-BLED and ORBIT scores.\textsuperscript{41} However, these biomarkers are also non-specifically associated with other cardiovascular outcomes (e.g., stroke, death, heart failure, etc.)\textsuperscript{42} and some are not readily available in routine clinical practice.

Other biomarkers reflecting cardiovascular physiology, coagulation and fibrinolysis, are promising candidates for development of new bleeding risk scores in AF.

We tested characteristics of plasma fibrin clot structure as potential new biomarkers which might help predict bleeding in AF patients, given evidence indicating that fibrin clots composed of thinner fibers, which are more compact and less permeable, are less susceptible for fibrinolysis.\textsuperscript{43} Recently, dense fibrin fiber networks, characterized by low plasma clot permeability, has been found an independent predictor of both thromboembolic events and major bleedings in AF patients on VKA.\textsuperscript{44} We reported that patients with lower clot permeability had increased risk of ischemic stroke or TIA (hazard ratio [HR] 6.55; 95% CI, 2.17-19.82) and major bleeds (HR 10.65; 95% CI, 3.52-32.22), while patients with high permeability had elevated risk of minor bleeding compared with the remainder (11.63% per year vs. 3.55% per year).\textsuperscript{45} Hypofibrinolysis as reflected by prolonged clot lysis time, resulted in 8-fold increase in stroke or TIA rate in AF patients on VKA (8.67% per year vs 1.1% per year).\textsuperscript{46} It has also been observed that in patients with AF on rivaroxaban lower plasma clot
permeability, determined 24 to 30 hours since the intake of rivaroxaban predicted ischemic cerebrovascular events (HR 6.64; 95% CI, 2.2-20.1) and major bleedings (HR 7.38; 95% CI, 2.58-21.10), but not deaths, during follow-up.\textsuperscript{47,48} Minor persistent bleeding was associated with increased clot permeability in AF patients on rivaroxaban.\textsuperscript{47} Recently, association between higher ORBIT bleeding risk score along with enhanced fibrinolysis, and looser clot structure in AF was reported \textsuperscript{33}. Despite still poorly understood mechanisms underlying the above observations, it might be speculated based on experimental work that denser clot meshwork within thrombi in vessels impair wound healing and adversely affect cell adhesion, migration, proliferation, which might enhance bleeding in particular from the GI tract.\textsuperscript{49} It remains to be established whether assessment of abnormalities in fibrin network structure in AF may be helpful in predicting bleeding events during treatment with VKA and NOAC.

**Specific AF patient populations at risk of bleeding on anticoagulation**

**Advanced age**

Older patients have a higher risk of bleeding, however in the age group above 75 years reduced ICB and increased GI bleeding on NOAC as compared to VKA share the same pattern as that observed in younger AF patients.\textsuperscript{9} In phase 3 AF trials, there were some differences in bleeding risk in patients aged 75 years or more depending on the specific anticoagulants (Fig. 2). Assessing NOACs in elderly AF patients, an increased rate of extracranial major bleeding in such patients receiving both doses of dabigatran was observed,\textsuperscript{50} while similar rates of the bleeding regardless of age were reported in RCTs with apixaban, edoxaban, or rivaroxaban.\textsuperscript{51–53} Compared with warfarin, only apixaban was associated with a lower risk of major bleeding among patients above 75 years.\textsuperscript{53,54}

**Low body mass**

The risk of all-cause death, stroke and SE, and major bleeding is higher in anticoagulated patients with lower weight compared to normal weight.\textsuperscript{55} Low body weight may increase exposure to any NOAC and as such increases the risk of bleeding.\textsuperscript{56} Body weight of 60 kg or less is a dose-reduction criterion for apixaban.\textsuperscript{57} In the largest study evaluating NOACs in relation to body weight in the AF patients, apixaban was at least as efficacious as warfarin but safer across the range of weight, with the greatest reduction in the risk of bleeding and hemorrhagic stroke in the group with body weight of $\leq$60 kg.\textsuperscript{55} In patients with very low body weight (<50 kg) on dabigatran the drug’s efficacy and safety were similar to those observed in the remainder of the study cohort.\textsuperscript{58} However, observational studies have suggested that low
body mass index (<23.9 kg/m²) may predict bleeding in patients on dabigatran. Of note, frequently co-existing renal insufficiency may make dabigatran a less preferably option for the underweight older AF patients. Patients with low body weight on oral anticoagulation should be under closer surveillance in terms of bleeding risk.

**Chronic kidney disease**

Patients with AF and chronic kidney disease (CKD) have an increased morbidity and mortality due to their excessive risk for both thromboembolic and severe bleeding events, and risk stratification and treatment of patients with AF and CKD may be challenging. All NOACs are eliminated by the kidneys, albeit to a different extent, with the maximum value for dabigatran (80%), whereas 50%, 35%, and 27% of edoxaban, rivaroxaban, and apixaban, respectively, are cleared via the kidneys in unchanged form. In all patients on NOACs, renal function needs to be monitored at least yearly. Importantly, intercurrent acute illness (e.g. infections, acute heart failure, etc.) may transiently affect renal function. Of note, renal function may be overestimated in underweight patients due to their reduced muscle mass (especially when calculated with the Modification of Diet in Renal Disease (MDRD) formula). Compared with warfarin, all four NOACs showed consistent efficacy and safety in patients with mild to moderate CKD compared with non-CKD patients in the respective subgroup analyses of pivotal NOAC trials. The ARISTOTLE trial data analysis suggests that the bleeding benefit with apixaban compared with warfarin becomes significantly more prominent at lower creatinine clearance (CrCl) values, while the stroke reduction benefit is maintained. In contrast, the bleeding benefit of 110 mg twice a day dabigatran over warfarin cannot be observed in patients with CrCl <50 mL/min while a similar stroke risk reduction compared with VKA is maintained. All available NOACs trials essentially excluded patients with a CrCl of <30 mL/min (except for a few patients on apixaban with CrCl 25–30 mL/min in the ARISTOTLE trial). Rivaroxaban, apixaban, and edoxaban (but not dabigatran) are approved in Europe for the use in patients with severe CKD (Stage 4, i.e. a CrCl of 15–29 mL/min), with the reduced dose regimen. In Europe, NOACs should not be prescribed to AF patients with severe renal dysfunction (CrCl <15 mL/min) as well as in patients on dialysis, whereas in the United States of America apixaban was approved for use in hemodialyzed patients in 2014. Since VKA use leads to a high risk of bleeding in this subset of patients, the decision to use a VKA in such patients is challenging and should be based on the individual patient’s risk of stroke, anticipated net benefit and patient’s preferences.
Regarding AF patients after kidney transplantation, high-quality evidence is lacking, but NOACs might be used with the dosing regimen adjusted to the estimated renal function, and consideration of possible drug–drug interactions between the NOAC and immunosuppressive agents.64

Liver disease
Patients with significant active liver disease including cirrhosis, or those with persistent (2 values at least 7 days apart) elevation of the liver enzymes or bilirubin [e.g. alanine transaminase or aspartate transaminase ≥2–3 times the upper limit of normal (ULN) or total bilirubin ≥1.5 times the ULN] were excluded from the landmark NOAC trials in AF.13,14,18,58 NOACs are contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk including Child-Pugh C cirrhosis, while rivaroxaban should not be used even in AF patients with Child B liver cirrhosis due to a >two-fold increase in drug exposure in these individuals.65 Dabigatran, apixaban and edoxaban may be used with caution in patients with Child B liver cirrhosis. Reduced dose NOAC should be considered in patients with liver disease at high bleeding risk, and close surveillance is reasonable in this subset. Lee et al.66 in a registry-based study in patients with liver cirrhosis treated predominantly with low-dose dabigatran and rivaroxaban, demonstrated comparable to warfarin risk of stroke/SE and ICB and reduced risk of major bleeding including GI bleeding. The advantage of NOACs over warfarin in the bleeding risk reduction was observed in the groups with nonalcoholic and nonadvanced liver cirrhosis. In patients with advanced cirrhosis, who presented with any complications as ascites, encephalopathy, spontaneous bacterial peritonitis, or prior esophageal varices bleeding, this benefit from NOACs is diminished, presumably due to reduced drug metabolism and impaired hepatobiliary excretion.(59)

Of note, hepatotoxicity has been observed in <1% of AF patients in the NOAC trials at a similar rate to the warfarin arms.67 Usually drug withdrawal normalized liver function markers within a few days. Search for underlying liver pathologies and hepatotoxic drugs, e.g. amiodarone, should be performed.

Prior serious bleeding
In most cases of bleedings due to secondary (e.g. bleeding post-trauma) or reversible causes (e.g. GI bleed due to colon polyps or peptic ulcer) anticoagulation can be resumed once the cause of the bleed has been eliminated. Re-initiation of anticoagulation should be considered
after 4-7 days post-GI bleed if benefits outweigh potential risks of re-bleeding.\textsuperscript{68,69} Factors that need to be taken into consideration before preinitiation or withholding of anticoagulation, include identification of the bleeding site, presence of reversible/treatable cause of bleeding and angiodysplasia in the GI tract, older age, chronic alcohol abuse and need for antiplatelet therapy. Results from observational studies on patients after GI bleeding suggest benefits from resuming anticoagulation, without an increase in recurrent GI bleeding in the majority of AF patients.\textsuperscript{70}

The 2016 ESC guidelines recommend in AF patients at high-risk of GI bleeding, use of VKA or NOAC other than dabigatran 150 mg bid, rivaroxaban 20 mg once daily and edoxaban 60 mg once daily (class IIa, level of evidence B). Elimination of modifiable bleeding risk factors, in particular alcohol abuse and cyclooxygenase-1 inhibitors, is of key importance to minimize bleeding risk on anticoagulation. Importantly, the landmark AF RCTs indicate that compared with warfarin, the risk of GI bleeds is not increased for dabigatran 110 mg bid and apixaban 5 mg bid\textsuperscript{7} (Fig. 3).

Protein pump inhibitors co-therapy is associated with 25 to 51% lower incidence of GI-bleeding hospitalizations during VKA and NOACs use, with the most pronounced reduction observed for dabigatran, as the result of reduced direct mucosal toxicity of the drug and decreased dabigatran bioavailability\textsuperscript{71} (Fig. 4). Approximately 1 in 12 major bleedings in patients receiving warfarin or dabigatran reflects an underlying GI tract cancer, most commonly colorectal cancer. The cancer-related bleeding manifests sooner and is more frequently chronic than this from a nonmalignant or unidentified source. There was no difference observed in the short-term outcome between dabigatran- and warfarin-related bleedings, however the majority of patients required blood transfusions and prolonged hospital stay.\textsuperscript{71} Further prospective studies are required to determine if GI cancer screening before and after initiation of anticoagulation, in particular the most common colorectal cancer, may allow earlier cancer detection and treatment, however baseline screening in high-risk populations should be considered.

A history of a spontaneous ICB constitutes a contraindication against anticoagulation according to labelling of VKAs and NOACs, unless the cause of the bleeding (like uncontrolled hypertension, aneurysm or arteriovenous malformation, or triple antithrombotic therapy) has been reversed.\textsuperscript{7,72} Arguments for not resuming or initiating anticoagulation in ICB patients with AF should be assessed on an individual basis.\textsuperscript{73} Patients with (probable) cerebral amyloid angiopathy have a very high risk of recurrent ICB and should not be anticoagulated.\textsuperscript{74} Adequate blood pressure control is of paramount importance in all patients
post ICB. Left atrial appendage occlusion (LAAO) may be considered in some AF patients post ICB as well as after recurrent intractable or untreatable major bleeding, although evidence on the role of LAAO in such patients is lacking. However, antiplatelet treatment for at least 1 month post LAAO is associated with increased bleeding risk in such patients, which should be taken into account especially in elderly AF patients.

**Thrombocytopenia**

It is estimated that up to 3\% of AF patients have thrombocytopenia, defined as a platelet count below 100,000 / µL. Although thrombocytopenia does not protect against thromboembolic events, in the landmark phase 3 NOAC trials, AF patients with the platelet count below 90,000-100,000 / µL were excluded. The current guidelines for the management of patients with AF do not provide any recommendations for the use of NOACs in thrombocytopenic patients.

In a retrospective study, VKAs use in patients with moderate thrombocytopenia of 50,000-100,000/µL (mean platelet count, 87,900/ µL), who had AF or VTE, was associated with 3-fold higher incidence of minor bleeding (5.55 vs. 1.84 per 100 patient-years) and a tendency toward a higher risk of major bleeding. All the recorded bleeding complications occurred at INRs above 2.5, suggesting using narrower INR targets and lower intensity oral anticoagulation. Sadowska et al. demonstrated the acceptable safety and effectiveness of anticoagulation with NOAC at reduced doses in a cohort of AF patients with moderate thrombocytopenia (mean platelet count, 78,000/ µL). The risk of bleeding was unaffected by the type of NOAC (rivaroxaban 15 mg once daily, dabigatran 110 mg bid, or apixaban 2.5 mg bid), and was predicted only by age. Despite reduction in a NOAC dose, similar rates stroke or TIA, and death was observed in thrombocytopenic and normocytopenic patients. Of note, several cases of NOAC-induced thrombocytopenia have been reported in the literature, that supports platelet count monitoring during treatment.

In patients with severe thrombocytopenia (<50,000 / µL) and AF the anticoagulation should be individualized and closely monitored given the lack of evidence from trials.

**Cancer patients**

AF is present in approximately 5\% of patients with cancer at the time of diagnosis or within the first months of treatment. Based on the current guidelines about 80\% of AF patients with cancer, had indications for chronic anticoagulation. Of note, cancer is associated with an increased risk of bleeding, related to presence of thrombocytopenia, metastases, kidney and
liver damage, damage to the vessel by a tumor infiltrating its wall, invasive procedures, and radiation therapy. 

Regarding cancer patients with AF, most data are from observational studies. Randomized studies of cancer patients with VTE, including the Hokusai VTE Cancer trial with edoxaban and SELECT-D trial with rivaroxaban, showed that NOACs use compared to dalteparin was associated with reduction in the recurrence rate of VTE and increased risk of major bleeding, mainly GI bleeding. The highest bleeding risk was observed in the patients with esophageal, gastroesophageal, and urologic cancer.

Shah et al. in a registry-based study on population of AF patients with cancer reported lower or similar rates of bleeding and stroke, and a lower rate of VTE in NOACs users compared to VKAs users. Although limited by a sample size, the lowest rates of VTE and severe bleeding were observed for apixaban. The data from registries suggested an increase in hemorrhagic complications in cancer patients with AF and metastatic disease, advanced CKD, recent bleeding (<30 days), and longer immobility.

The 2019 ISTH guidelines regarding the use of NOACs in patients with AF and cancer receiving chemotherapy recommend individualized anticoagulation, based on risk of stroke, bleeding, and patient preferences. NOACs should be considered in patients with clinically relevant interactions between VKAs and anticancer medications, that are not expected with NOACs, or in those with inability to comply with INR monitoring. The use of a NOACs over VKAs or heparins is suggested in patients on chemotherapy with newly diagnosed AF, with the exception of patients with luminal GI cancer and an intact primary tumor or active GI mucosal abnormalities. In a recent study in patients with colorectal cancer after surgery and the first-line chemotherapy, treated with NOAC, mainly rivaroxaban 20 mg daily, the rate of TIA and stroke and major bleeding was relatively low, 4.0% and 1.9%, respectively. A reduced dose of NOAC was associated with higher risk of thromboembolic events. Real-world data on the effectiveness and safety of NOACs in oncological patients suggest a clear benefit, especially in patients with favorable prognosis, however the safety in specific subgroups of cancer patients remains to be clarified.

Reversal agents

The use of specific and non-specific reversal agents in AF patients on NOACs should be restricted to life-threatening situations predominantly ICB or posttraumatic bleeding.
Idarucizumab is a humanized monoclonal antibody fragment which is a specific reversal agent for dabigatran. It binds with 350 times higher affinity than thrombin to free and thrombin-bound dabigatran within minutes. This reaction is irreversible.\textsuperscript{90} Idarucizumab was approved in November 2015 in Europe. It has become the standard of care for the reversal of dabigatran when it is available. The RE-VERSE AD (Reversal Effects of Idarucizumab on Active Dabigatran) study assessed the safety and efficacy of 5 g idarucizumab (administered as 2 rapid 2.5 g intravenous boluses) in dabigatran-treated patients who present with uncontrolled or life-threatening bleeding (group A) or nonbleeding patients who require emergent surgery or intervention (group B). The primary outcome of the Re-VERSE AD study was maximum percentage reversal of the anticoagulant effect of dabigatran. The RE-VERSE AD study published as an interim analysis of the first 90 patients in 2015\textsuperscript{91} and then the final analysis of 503 patients in 2017,\textsuperscript{92} showed the utility of idarucizumab in the two groups of patients. Now idarucizumab is the best therapeutic option for AF patients on dabigatran who experience life-threatening bleeding.

Andexanet alpha, which binds with high affinity to direct FXa inhibitors and also low-molecular-weight heparins and fondaparinux,\textsuperscript{93} is a modified human recombinant FXa decoy protein that lacks catalytic activity following replacement of an active-site serine with alanine and with removal of the membrane-binding domain, which precludes this protein to participate in the formation of the prothrombinase complex.\textsuperscript{15,92} Because of its pharmacodynamic half-life of 1-hour, andexanet was administered as a bolus followed by an infusion with anti-FXa activity returning to placebo levels within 2 hours.

Results of two RCTs (ANNEXA [Andexanet Alfa, a Novel Antidote to the Anticoagulation Effects of FXA Inhibitors trials]) performed in healthy volunteers aged 50 to 75 years who received apixaban (ANNEXA-A) and rivaroxaban (ANNEXA-R),\textsuperscript{93} demonstrated the efficacy and safety of andexanet alpha. The ANNEXA-4 phase 3b to 4 study confirmed the efficacy and safety of andexanet alpha in patients treated with FXa inhibitors with acute major bleeding.

In May 2018 andexanet alpha, which is a specific reversal agent for oral FXa inhibitors, was approved in the United States and in 2019 in Europe, but currently it is unavailable in many countries. For this reason, the available Xa inhibitor reversal strategies rely on non-specific strategies of unknown effectiveness in particular prothrombin complex concentrates (PCCs). PCCs are plasma-derived products that contain 3 (factors II, IX, and X) or 4 (addition of factor VII) clotting factors in addition to variable amounts of heparin and the natural
coagulation inhibitors protein C and protein S, which are used among others to reverse anticoagulants effects of VKA in severely bleeding patients. Activated PPC, aPCC (also known as factor VIII inhibitor bypassing activity) contains mostly activated factor VII along with mainly nonactivated factors II, IX, and X. A dose of 50 U/kg of PCC or aPCC is recommend in patients treated with rivaroxaban or apixaban if life-threatening bleeding occurs.16,19

A prospective multicenter observational study showed that in the real world reversal strategies in bleeding patients on rivaroxaban or apixaban differ largely. A Swedish case series of 84 bleeding patients (75% with AF) who required reversal of FXa inhibition after 9-16 hours since the last dose of the anticoagulant showed that in most cases (70% ICB and 16% GI bleeds) PCC at a dose of 2000 units was used in patients 65 kg or more, while 1500 units were administered in patients weighted below 65 kg.95 No hemostatic effect of PCC was observed in 30.9% of patients, largely in those with ICB. Of note, 15 patients died, including 13 patients following ICB (30-day mortality rate, 32%), whereas 2 patients suffered from fatal ischemic stroke at 5 and 15 days after the index bleeding.96

Analysis of 460 bleeds observed in patients on NOACs showed that almost 20% of those patients received vitamin K, which is useless in such clinical situations.94 It has absolutely no possibility of any effect, but was given probably because many of these patients had a prolonged INR due to the rivaroxaban.97

Tranexamic acid, an antifibrinolytic agent effective in trauma or postpartum hemorrhages, acts a lysine analog that impairs plasminogen activation on fibrin. In patients on NOACs its efficacy is uncertain, however it might be used.

Fresh frozen plasma (FFP) is ineffective in patients bleeding on NOACs but was used in about 10% of patients reported by Xu Y et al.94 FFP may be used as a plasma volume expander in patients following transfusions, however its shortcomings are numerous, including risk of transfusion reactions, and acute heart failure.

Experts strongly recommend that an institutional policy concerning bleeding management is defined in every hospital. In patients on NOAC, including a protocol containing the availability and indications of specific and nonspecific reversal agents, should be developed by among cardiologists, hemostasis experts, intensivists and others, and this policy should be easily accessible for all physicians in a given institution.31,68

**Patient preferences and knowledge in reducing bleeding risk**
Optimal stroke prevention treatment strategies incorporate patient preferences and values, which may differ from those of the physician. Results from a survey suggest that AF patients who initiate oral anticoagulation are willing to sustain four major bleeds to avoid one serious stroke. About half of the patients, mainly older, with minor or major bleeds on anticoagulation and without history of cerebrovascular events, accepts a low number of bleeds (0-3). Our recent findings confirmed that AF patients fear more of major stroke than bleeding, but they are less willing to accept such adverse events after serious bleed in the past as well as in the presence of persistent minor bleeding e.g. easy bruising. From a practical point of view, it is important to remember that only one out of two patients with AF treated with NOAC or VKA is aware that the safest painkiller is paracetamol, and 1 out of 4 patients knows what to do when an anticoagulant dose is missed. Among patients with AF, women, patients with diabetes, prosthetic heart valve and minor bleedings were found to be better informed about those issues. Better education of AF patients about the disease itself and anticoagulation is likely to improve compliance and therapy outcomes, and activities aiming at improving knowledge should be strongly supported in everyday practice.

**Monitoring**

Patients treated with NOAC are likely to undergo a less frequent follow-up, compared with VKA patients, due to absence of a need for routine monitoring of NOAC plasma levels. The 2018 European Heart Rhythm Association guidelines on the use of NOAC in patients with AF, recommended regular follow-up assessment during NOAC use, particularly in high-risk groups with older age, renal failure, multiple comorbidities and frailty. At each visit adherence to treatment, co-medications, presence of thromboembolic and bleeding complications, and other side effects should be evaluated. Particular attention should be directed to minimize modifiable bleeding risk factors and to assess optimal NOAC and its correct dosing. In patients on NOACs, without renal impairment, CrCl using the Cockcroft–Gault method should to be monitored at least yearly. In case of kidney failure, a more frequent evaluation should be performed (recheck interval in months may be calculated from equation CrCl /10). Hemoglobin concentration and liver function should be measured at least once every 6 months in patients ≥75 years (especially if on dabigatran) or with frailty, and yearly in other patients. Limited data support plasma level measurement of NOAC in emergencies, before elective procedures and during long-term exposure. There are several special situations in which assessment of drug exposure and anticoagulant effect may support clinical decisions. They...
include: 1) thrombolytic therapy in stroke, 2) surgery or invasive procedure, 3) a need for immediate reversal of anticoagulation, 4) extreme body weight, 5) substantial drug–drug interactions (e.g. after transplantation, anti-HIV treatment), 6) suspected non-compliance or overdosage in case of thrombosis or hemorrhage, respectively.97

Conclusions
Overall, NOACs were comparable or superior to VKAs in most patients with AF as shown in RCTs and observational studies. Individualization of anticoagulant therapy based on benefit and safety profiles as well as patient characteristics should be considered in particular in AF patients at elevated risk of bleeding, such as the elderly patients with several co-morbidities and those with cancer (Table 2). Given a high risk of stroke in most AF patients as compared to bleeding risk, appropriate dosing regimen should be used and reduced-dose regimen should be restricted to the recommended settings. Modifiable bleeding risk factors such as use of non-steroidal anti-inflammatory drugs available over the counter should be eliminated whenever feasible.

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Contribution statement:
AU, LD, TP - the concept and design of the study, analysis and interpretation of data, revising article for important intellectual content, final manuscript approval

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3. Potpara TS, Mujovic N, Lip GYH. Meeting the unmet needs to improve management


15. Lu G, Deguzman FR, Hollenbach SJ, et al. A specific antidote for reversal of


**Figure 1.** Differences in thromboembolic and bleeding risk in seminal randomized controlled trials on non-vitamin K antagonist oral anticoagulants in atrial fibrillation. CHADS₂, congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke/transient ischemic attack history. HAS-BLED, see Table 1.
Figure 2. Major bleeding rates among atrial fibrillation patients aged ≥75 years treated with non-vitamin K antagonist oral anticoagulants and warfarin based on landmark randomized controlled trials.

Figure 3. Major gastrointestinal (GI) bleeding rates in patients with atrial fibrillation treated with non-vitamin K antagonist oral anticoagulants versus those on warfarin. Based on 12
Figure 4. The incidence of hospitalizations for upper gastrointestinal (GI) bleeding in relation to oral anticoagulants and proton-pump inhibitor (PPI) co-therapy. IRR, incidence rate ratio; RR, risk difference per 10,000 person-years. Based on 71
Table 1. The most commonly used clinical bleeding scores used in patients with atrial fibrillation

<table>
<thead>
<tr>
<th>Scale</th>
<th>Risk factors</th>
<th>Scoring point</th>
<th>Bleeding risk stratification</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAS-BLED</td>
<td>Hypertension (SBP&gt;160 mmHg)</td>
<td>1</td>
<td>Low risk 0–2</td>
</tr>
<tr>
<td></td>
<td>Abnormal renal and/or liver function</td>
<td>1 point each</td>
<td>High risk 3–9</td>
</tr>
<tr>
<td></td>
<td>Stroke</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bleeding history</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Labile INR</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Elderly (&gt;65 years)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Drugs (antiplatelets/NSAIDS)/concomitant/≥8 units alcohol/week</td>
<td>1 point each</td>
<td></td>
</tr>
<tr>
<td>HEMORR_HAGES</td>
<td>Hepatic or renal disease</td>
<td>1</td>
<td>Low risk 0–1</td>
</tr>
<tr>
<td></td>
<td>Ethanol abuse</td>
<td>1</td>
<td>Intermediate risk 2–3</td>
</tr>
<tr>
<td></td>
<td>Malignancy</td>
<td>1</td>
<td>High risk 4–12</td>
</tr>
<tr>
<td></td>
<td>Older (aged &gt;75)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Reduced platelet count</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Re-bleeding risk</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hypertension (uncontrolled)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Anemia</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Genetic CYP 2C9 polymorphisms</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Excessive fall risk</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stroke/TIA history</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>ATRIA</td>
<td>Anemia</td>
<td>3</td>
<td>Low risk 0–3</td>
</tr>
<tr>
<td></td>
<td>CKD with eGFR</td>
<td>3</td>
<td>Intermediate risk 4</td>
</tr>
<tr>
<td></td>
<td>Age ≥75 years</td>
<td>2</td>
<td>High risk 5–10</td>
</tr>
<tr>
<td></td>
<td>Previous bleeding</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hypertension</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>ORBIT-AF</td>
<td>Age (75 years or older)</td>
<td>1</td>
<td>Low risk 0–2</td>
</tr>
<tr>
<td>ABC-bleeding score</td>
<td>Reduced hemoglobin (&lt;13 mg/dL in men and &lt;12 mg/dL in women)</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hematocrit (&lt;40% in men and &lt;36% in women) or history of anemia</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bleeding history</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Insufficient kidney function (eGFR &lt; 60 mg/dL/1.73 m²)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Treatment with an antiplatelet agent</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Medium risk 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>High risk ≥ 4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Age | Biomarkers (differentiation factor-15, high-sensitivity cardiac troponin T, hemoglobin/hematocrit) | digitally calculated |
| History of previous bleeding | | low risk |
| SBP- Systolic Blood Pressure; INR – International Normalized Ratio; NSAID - Non-Steroidal Anti-Inflammatory Drug; TIA - transient ischemic attack; CKD - chronic kidney disease; GFR - Glomerular filtration rate | <1%/year | moderate 1-2%/year | high >2%/year |
| | | | |
Table 2. NOACs and approved/studied doses in stroke prevention in atrial fibrillation. Based on 54,68

<table>
<thead>
<tr>
<th></th>
<th>Standard dose</th>
<th>Dose reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban</td>
<td>2 x 5mg</td>
<td>2 x 2.5 mg if two out of three:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- weight ≤60 kg,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- age ≥80 years,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- serum creatinine ≥133 mmol/(1.5 mg/dL) [or if CrCl 15–29 mL/min],</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>2 x150 mg</td>
<td>No pre-specified dose-reduction criteria.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Based on SmPC, 2 x110 mg if:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- age ≥80 years,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- concomitant verapamil,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- increased risk of gastrointestinal bleeding</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>1 x 60mg</td>
<td>1 x30 mg if:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- weight ≤60 kg,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- CrCl ≤50 mL/min,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- concomitant therapy with strong P-Gp inhibitor</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>1 x 20mg</td>
<td>1 x15 mg if CrCl ≤50 mL/min</td>
</tr>
</tbody>
</table>

Based on clinical and pharmacokinetic data, dose adjustment or NOAC change should be considered if: age ≥75 years, cancer, concomitant antiplatelet drugs or significant drug-drug interactions, frailty/fall risk, chronic kidney disease stage 4, hepatic, history of bleeding or predisposition, recent surgery on critical organ and thrombocytopenia. SmPC, summary of product characteristics.