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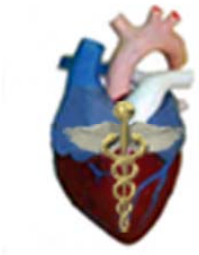

January 2016 • Volume 11 • No 1 (41)

ISSN: 1792-7919 **e-ISSN: 1792-7927**

URL: www.rhythmos.gr / http://rhythmos.info.tm / http://www.evangelismos.dom.gr

EDITORIAL

Management of Major Bleeding with the Non-Vitamin K Oral Anticoagulants: the Role of Antidotes

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Rhythmos 2016;11(1):1-7

ABSTRACT

Over the recent years, new oral anticoagulant agents have been developed and entered the clinical arena, the direct or non-vitamin K oral anticoagulants (NOACs). Although more expensive, these agents have been proven as equivalent or superior to vitamin K antagonists in the treatment of non-valvular atrial fibrillation (AF) and venous thrombo-embolism with a lower incidence of intracerebral hemorrhage. Nevertheless, occurrence of major or life-threatening bleeding events is still quite possible. Thus, there is a major concern regarding the lack of a specific antidote and rapid reversal agent in such disastrous situations. Fortunately, the development of effective specific NOAC antidotes has recently made great advances, which are herein briefly reviewed.

Key Words: atrial fibrillation; anticoagulation; non-vitamin K anticoagulants; dabigatran; rivaroxaban; apixaban; edoxaban; intracerebral hemorrhage; bleeding; antidotes; idarucizumab; andexanet; aripazine

Abbreviations
AF = atrial fibrillation; aPTT = activated partial thromboplastin time; dTT = dilute thrombin time; ECT = ecarin clotting time; NOACs = non-vitamin K oral anticoagulants; PCC = prothrombin complex concentrates; TT = thrombin time; VNAs = vitamin K antagonists; VTE = venous thromboembolism

INTRODUCTION

Over the recent years, new classes of oral anticoagulant agents have been developed and entered into the clinical arena, the direct or non-vtamin K oral anticoagulants (NOACs). These agents belong to two classes, the direct thrombin inhibitor, dabigatran (the -gatrans), and the factor Xa inhibitors, such as rivaroxaban, apixan, edoxaban and betrixaban (the -xabans).[1-4] These agents have been proven as equivalent or superior to vitamin K antagonists (VKAs) in the treatment of non-valvular atrial fibrillation (AF) and venous thromboembolism (VTE),[4-6] albeit at an upfront increased cost. NOACs confer equivalent or better protection from thromboembolic events in these patient groups with lessened occurrence of intracerebral hemorrhage. However, there still remains, albeit decreased, a possibility of such a disastrous cerebral bleeding event, while an increased risk of other site or major bleeding events has been reported.[7] Thus, there is a major concern regarding the lack of a specific antidote and

rapid reversal agent in case of emergence of a life-threatening bleeding event. The shorter half-life of these agents, and hence a quicker dissipation of their anticoagulant effect, is not always entirely reassuring, particularly in emergency and menacing situations.

The risk of hemorrhage-related mortality associated with NOACs in patients requiring long-term anti-coagulation was evaluated by a systematic review and meta-analysis of 11 studies (5 on AF and 6 on VTE) comprising a total of 100,324 patients receiving rivaroxaban (4 studies), dabigatran (3 studies), apixaban (2 studies) and edoxaban (2 studies).[8] NOAC-treated patients had a 47% odds reduction compared with VKA (OR 0.53) and 64% odds reduction compared with low-molecular weight heparin–VKA (OR 0.36) regarding fatal bleeding risk. Case fatality due to major bleeding was lower in NOAC-treated patients both in AF (OR 0.68) and VTE (OR 0.54) patients. AF survivors of major bleeding events treated with NOACs had lower mortality compared with patients treated with VKAs (OR 0.57). The authors concluded that NOACs decrease the mortality risk related to major bleeding events, particularly in AF patients. Similarly, another meta-analysis of 13 randomized trials involving 102,707 patients receiving NOACs for the treatment of VTE or prevention of stroke/systemic embolism due to AF compared with warfarin or other VKAs administered to a target INR 2.0 - 3.0, indicated that the case-fatality rate of major bleeding was 7.57% in patients taking NOACs vs 11.04% in patients taking VKAs.[5] When compared with warfarin, NOACs were associated with significant reductions in fatal bleeding (relative risk-RR, 0.53), cardiovascular mortality (RR, 0.88) and all-cause mortality (RR, 0.91).

Nevertheless, the need for a drug-specific antidote with rapid reversal properties remains dire despite these encouraging results, particularly when urgent surgery with a high hemorrhagic risk is needed or in cases of intracerebral hemorrhage or serious bleeding in another critical organ, or even in cases of accidental overdose, where the effect of anticoagulant therapy should be promptly reduced. Fortunately, the development of effective specific NOAC antidotes has recently made great advances,[9-13] which are herein briefly reviewed.

RISK OF MAJOR BLEEDING WITH NOACs

According with the original studies of each NOAC, the risk of major bleeding is not negligible. In the RE-LY trial, the rate of major bleeding was 2.71% per year in the group receiving 110 mg of dabigatran and 3.11% per year in the group receiving 150 mg of dabigatran.[14] A higher rate of major bleeding with dabigatran 150 mg bid (3.74%) in comparison with 110 mg (2.99%) was further confirmed in the RELY-ABLE trial (hazard ratio -HR 1.26).[15] In the ROCKET trial, rate of major bleeding with rivaroxaban was 3.6% (similar to warfarin group, 3.4%), rate of intracranial hemorrhage was 0.5% (significantly lower compared with warfarin, 0.7% per year; HR, 0.67; P = 0.02).[16] However, major gastrointestinal (GI) bleeding was more common in the rivaroxaban group (3.2% as compared with 2.2% in the warfarin group; P<0.001). A subanalysis of the same trial indicated that a significantly higher rate of major or non-major clinical GI bleeding was encountered in rivaroxaban- vs warfarin-treated patients (3.61 events/100 patient-years vs 2.60 events/100 patient-years; HR: 1.42).[17] In the ARISTOTLE trial, major bleeding was observed in 2.13% per year in the apixaban group, with fatal bleeding (including fatal hemorrhagic stroke) occurring in 34 patients.[18, 19] In the ADOPT trial, among 4495 acutely ill patients with cardiac or respiratory failure and/or other medical disorders and risk factors for venous thromboembolism, receiving thromboprophylaxis with apixaban or subcutaneous enoxaparin, by day 30 major bleeding had occurred in 0.47% of patients in the apixaban group and in 0.19% of patients in the enoxaparin group (relative risk, 2.58; P = 0.04).[20] In the ENGAGE-AF TIMI 48 trail, the annualized rate of major bleeding was 2.75% with high-dose (60 mg) edoxaban and 1.61% with low-dose (30 mg) edoxaban.[21] The annualized rate of major GI bleeding was higher with high-dose edoxaban than with warfarin (1.51% vs. 1.23%), but the rate was lowest with low-dose edoxaban (0.82%). In the Explore-Xa trial, major or clinically relevant non-major bleeding was assessed among 508 AF patients randomized to one of 3 doses (40, 60, or 80 mg once daily) of betrixaban (another factor Xa inhibitor mostly excreted unchanged in the bile) or unblinded warfarin.[22] Over a mean of ~5 months, the rate of bleeding was lowest on betrixaban 40 mg (1 event); rates of bleeding with betrixaban 60 or 80 mg were similar to those of warfarin (5, 5 and 7 events).

According with a meta-analysis of all 71,683 participants included in the RE-LY, ROCKET AF, ARISTOTLE, and ENGAGE AF-TIMI 48 trials, NOACs significantly reduced stroke or systemic embolic events by 19% compared with warfarin (relative risk - RR 0.81; p<0.0001), mainly driven by a reduction in hemorrhagic stroke (RR 0.49; p<0.0001), as well as all-cause mortality (RR 0.90; p=0.0003) and intracranial hemorrhage (0.48; p<0.0001), but had similar major bleeding as with warfarin, and increased GI bleeding (RR 1.25; p=0.04).[6] Another meta-analysis of 50 trials including 155,537 patients, showed that the risk of major bleeding with NOACs varies with their indication for use.[23] Significantly higher major bleeding was noted after hip surgery (odds ratio – OR 1.43), in patients with acute coronary syndrome (compared against placebo) (OR 2.89), and for medically

ill patients (OR 2.79). Less bleeding was observed with treatment of acute venous thromboembolism or pulmonary embolism (OR 0.63). No significant difference in bleeding was found during treatment of AF and for extended treatment of venous thromboembolism.

Although a lower rate of hemorrhagic stroke has been consistently reported with use of NOACS,[6, 24] admittedly, it also appears that the rate of major GI bleeding related to the use of at least some NOACs is higher than that reported in warfarin users.[25, 26] In general, any major bleeding during oral anticoagulant treatment is associated with a substantially increased subsequent risk of both death and of thrombotic events such as ischemic stroke or myocardial infarction, especially following intracranial hemorrhage, and this risk is similarly elevated regardless of treatment with a NOAC or warfarin.[27]

Of course, concomitant use of antiplatelet drugs clearly increase the risk for major bleeding.[28] Other factors increasing the risk of major bleeding with NOACs may comprise older age, history of smoking, history of prior GI bleeding, mild anemia, renal insufficiency, baseline diastolic blood pressure $\geq$90 mm Hg, history of chronic obstructive pulmonary disease, and prior use of aspirin; while female gender and diastolic blood pressure <90 mm Hg were associated with a decreased risk.[29] The effect of older age was confirmed by another subanalysis of the ROCKET AF trial: although efficacy and safety of rivaroxaban relative to warfarin did not differ with age (supporting rivaroxaban as an alternative for the elderly), elderly patients had higher major bleeding rates than younger patients (4.63% vs 2.74%/100 patient-years; P<0.0001).[30] In another subanalysis, independent clinical factors most strongly associated with GI bleeding were baseline anemia, history of GI bleeding, and long-term aspirin use.[17] Although both ischemic stroke and bleeding outcomes have been correlated with plasma drug (dabigatran) concentrations (trough levels),[31] monitoring of anticoagulation does not appear to be practical neither with this approach, nor with another method (thrombelastography) that has been suggested.[32]

MANAGING BLEEDING WITH NOACs

Although NOACs generally seem to confer a lower bleeding risk compared to VKAs, management of bleeding in patients on NOACs is challenging because there is lack of reliable and readily available laboratory tests of monitoring the anticoagulant effect of NOACs and therapeutic options are few and nonspecific and mostly supportive.[33] Until now there have been several proposals with supportive and other nonspecific measures put forth by working groups and societies to manage such situations until specific and validated antidotes become available.[1, 34] These proposed actions included postponing or delaying the procedure, if at all possible, and monitoring the drug concentration for cases in need for urgent surgery, or if the dosage was not immediately available, propositions were based on laboratory tests, such as prothrombin time (PT) and activated partial thromboplastin time (aPTT), or measuring the anti-Xa activity; otherwise, supportive measures were recommended to be followed, while keeping procoagulant drugs at standby to use if and when abnormal intra- or post-operative bleeding occurred. In cases of bleeding, volume expansion and local hemostatic measures, blood transfusion, as needed, and fresh frozen plasma and off-label use of a non-specific pro-coagulant agent were empirically recommended, such as non-activated or activated prothrombin complex concentrates (PCC), or recombinant human factor VIIa, with its attendant shortcomings.[35, 36] In the case of dabigatran, hemodialysis could also be considered. In patients presenting within 2-6 hours of a suspected overdose with either dabigatran or apixaban, the use of activated charcoal may be a reasonable option.[35]

According with data from the ROCKET AF trial, during a median follow-up of 1.9 years, 779 (5.5%) patients experienced major bleeding at a rate of 3.52 events/100 patient-years with a similar event rate in each arm (n = 395 for rivaroxaban and n = 384 for warfarin).[37] The median number of transfused red packed cells per episode was similar in both arms (2 units). Overall, few transfusions of whole blood (n = 14), platelets (n = 10), or cryoprecipitate (n = 2) were used. Transfusion of fresh frozen plasma was significantly less in the rivaroxaban arm (n = 45 vs n = 81 units; odds ratio - OR 0.43; P < 0.0001). PCC was administered less in the rivaroxaban arm (n = 4 vs n = 9). Outcomes after major bleeding were similar in the 2 groups. The authors concluded that among high-risk patients with AF who experienced major bleeding in ROCKET AF, the use of fresh frozen plasma and PCC was less among those allocated rivaroxaban compared with warfarin; however, use of blood transfusion and outcomes after bleeding were similar.

Of course, a most dreaded complication with any anticoagulant is intracranial hemorrhage. According to a study of 55 patients on NOACs with this complication, the 30-day mortality rate was 20%.[38] Neurosurgical procedures were carried out in 37 patients (67%). Renal function was significantly lower in non-survivors. Pro-hemostatic therapy with PCC had no effect. The authors concluded that successful neurosurgical management of patients with intracranial hemorrhage and NOAC intake was feasible, but drastic deterioration was observed in some patients, particularly when impaired renal function was present, findings which underscore the urgent need of improving treatment modalities for these patients.[38]

Several groups have attempted to provide practical guidance for the use of NOACs, either in the form of advice given in reviews and tabular data or proposing checklists, in an attempt to help optimize the risk-benefit ratio of NOAC therapy. [1, 3, 4, 39] A European Heart Rhythm Association group has listed 15 topics of specific clinical scenarios and formulated as practical answers as possible based on available evidence.[1] A Canadian group proposed an evidence-based point-of-care tool—a 1-page NOAC ABCD checklist available online: A (adherence), B (bleeding), C (creatinine clearance), D (drug interactions), E (examination), and F (follow-up).[39] The checklist is accompanied by quick-reference tables summarizing dosing, interactions, and periprocedural management. However, when all these safe-keeping proposals have failed and one is faced with a threatening situation like major bleeding, a contingency plan with effective reversal strategies should be in place.[33-36] This can only be complete with the availability of specific antidotes, which are now becoming available,[10, 12, 13] as detailed in the next section.

ANTIDOTES (Table 1)

Idarucizumab (Praxbind®), a humanized antibody fragment, is a specific antidote for *dabigatran*, developed by Boehringer Ingelheim.[9, 40] This is the first antidote of NOAC to receive approval by the FDA (October 16, 2015) (http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm467300.htm) and the European Medicines Agency (EMA) (20/11/2015) (http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/003986/human_med_001938.jsp&mid=WC0b01ac058001d124). This molecule binds to dabigatran with an affinity about 350 times greater than thrombin, preventing it from binding to thrombin and thus cancelling its anticoagulant effect.[41] Idarucizumab is specific for dabigatran and does not bind thrombin or its substrates, nor does it activate platelets. In animal and human studies, idarucizumab did not promote or reduce thrombin generation, thus it has no intrinsic anticoagulant or procoagulant effects.

In a porcine trauma model, idarucizumab reduced dabigatran-associated bleeding and mortality.[42] It stopped bleeding within 15 minutes and was associated with an immediate decrease in dabigatran anticoagulant effects. There was no evidence of safety concerns associated with the administration of idarucizumab.

In a phase 1 randomized, placebo-controlled, double-blind study, comprising 47 healthy volunteers (aged 18–45 years) who received dabigatran 220 mg bid for 3 days and a final dose on day 4, and then idarucizumab (1 g, 2 g, or 4 g 5-min infusion, or 5 g plus 2.5 g in two 5-min infusions given 1 h apart) administered (each dose to 12 men) about 2 hours after the final dabigatran dose, idarucizumab immediately and completely reversed dabigatran-induced anticoagulation in a dose-dependent manner.[43] Drug-related adverse events were all of mild intensity and reported in 7 participants (1 infusion site erythema and hot flushes, 2 epistaxis, 1 infusion site hematoma, and 3 hematuria). No serious or severe adverse events were reported, no adverse event led to discontinuation of treatment, and no clinically relevant difference in incidence of adverse events was noted among the groups.

Table 1. Antidotes for Non-Vitamin K Oral Anticoagulants

Antidote	**Idarucizumab (Praxbind®)**	**Andexanet alfa**	**Aripazine, Ciraparantag (PER977)**
Manufacturer	Boehringer Ingelheim	Portola Ph.	Perosphere Inc.
Type	humanized monoclonal antibody fragment (Fab)	Recombinant human Factor Xa variant (39 kDa)	small synthetic, cationic water-soluble molecule (512 Da)
NOAC	Dabigatran	Oral Factor Xa inhibitors	All NOACs
Cleared by	Kidney	?	?
Dose	5 g: 2 doses of 2.5 g IV over 5-10 min at 15 min apart (2.5 g/50 ml vial)	400/800 mg followed by 2-h infusion of 4-8 mg/min / Lower doses for apixaban & higher for rivaroxaban	100-300 mg IV
Half-life	47 min (initial / 10.3 h (terminal)	1 h	Onset of action: 10 min / Duration of action: 24 h
Studies	REVERSE-AD	ANNEXA-4	Phase 1 study

A Phase 3 prospective cohort study, the RE-VERSE AD (A Study of the Reversal Effects of Idarucizumab on Active Dabigatran), was conducted to determine the safety of 5 g of IV idarucizumab and its capacity to reverse the anticoagulant effects of dabigatran in patients who had serious bleeding (group A) or required an urgent procedure (group B). According to an interim analysis of 90 patients who received idarucizumab (51 patients in group A and 39 in group B),[12] among 68 patients with an elevated dilute thrombin time test and 81 with an elevated ecarin clotting time at baseline, reversal was 100%. Idarucizumab normalized the test results within minutes in 88-98% of the patients. Concentrations of unbound dabigatran remained low (<20 ng/ml) at 24 h in 79% of the patients. Among 35 assessed patients in group A, hemostasis was restored at a median of 11.4 hours. Among 36 patients in group B who underwent a procedure, normal intraoperative hemostasis was reported in 33, and mildly or moderately abnormal hemostasis in the other 3 patients. One thrombotic event occurred within 72 h after idarucizumab administration in a patient in whom anticoagulants had not been reinitiated.

Idarucizumab is available as a ready-to-use solution of 50 mg/ml (two 2.5g/50-ml vials, kept in the refrigerator and having a 24-month shelf life) (see package insert: http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/ 761025lbl.pdf). Before use, the unopened vials may be maintained at room temperature for up to 48 h if they are stored in the original package to protect them from light or for up to 6 h if exposed to light. A total IV dose of 5 g is administered as 2 consecutive 2.5-g infusions over 5-10 min at ≤15 min apart, expected to reverse all of the available dabigatran (i.e., all unbound and protein-bound dabigatran and its active metabolites).[41] Drug plasma concentrations decline in a biphasic manner with a rapid, initial half-life of ≈45 min with only 4% of the peak concentration remaining in plasma after 4 h. The drug is eliminated mainly renally. However, there should be no concern in patients with renal insufficiency, since these patients often have elevated dabigatran plasma concentrations, and thus the higher idarucizumab exposure may be advantageous. The drug normalizes dabigatran-induced prolongation of the dTT (dilute thrombin time), ECT (ecarin clotting time), aPTT (activated partial thromboplastin time), TT (thrombin time), and activated clotting time within minutes in a dose-dependent manner. If the dTT or ecarin-based assays are not available, the aPTT or TT can be used to monitor dabigatran reversal with idarucizumab.

The short half-life of idarucizumab in patients with normal renal function allows resumption of dabigatran therapy within 24 h in order to avoid the potential risk of thrombosis, provided that hemostasis has been secured.[41] The effect of idarucizumab is very rapid and sustained for 12 h, meaning that surgery or other procedures can be started shortly after administration. A pre-procedural normal aPTT and TT confirms reversal of the anticoagulant effect. Post-procedurally and after adequate hemostasis is restored, in patients at high risk for bleeding, treatment can start with a low dose of an anticoagulant for thromboprophylaxis, and the dose can then be increased to a therapeutic level once the bleeding risk abates. Since idarucizumab is specific for dabigatran, the anticoagulant activity of other anticoagulants will not be affected. In patients with renal impairment, the half-life of idarucizumab is prolonged, hence reinitiation of dabigatran may need to be delayed or an alternative anticoagulant may need to be considered.

Andexanet alfa is another antidote, in injectable form, recently developed by Portola Pharmaceuticals for factor Xa inhibitors. This recombinant protein is a modified form of factor Xa that is catalytically inactive but retains high-affinity binding to factor Xa inhibitors. In animal models, andexanet reversed immediately and in a dose-dependent manner the anticoagulant effect of factor Xa inhibitors, restored hemostasis and reduced bleeding.[9, 44] In Phase 1 and 2 studies in healthy volunteers, the antidote reversed antifactor Xa activity in a dose-dependent manner and no thrombotic events were reported.[9] In these studies, it was observed that anticoagulation returned to pre-treatment levels within few hours after a bolus of the antidote and therefore a constant infusion of the drug is recommended to reverse anticoagulation for longer periods of time.

More recently the combined results of ANNEXA-A and ANNEXA-R trials were reported.[13] These trials evaluated the efficacy and safety of andexanet for the reversal of anticoagulation with apixaban or rivaroxaban in older healthy volunteers (mean age 58 years), who were given 5 mg of apixaban bid or 20 mg of rivaroxaban daily. Among the apixaban-treated individuals, anti–factor Xa activity was reduced by 94% among those who received an andexanet bolus (n=24), as compared with 21% among those who received placebo (n=9) (P<0.001), and unbound apixaban concentration was reduced by 9.3 ng/ml vs 1.9 ng/ml (P<0.001); thrombin generation was fully restored in 100% vs 11% of the participants (P<0.001) within 2 to 5 min. Among the rivaroxaban-treated individuals, anti–factor Xa activity was reduced by 92% among those who received an andexanet bolus (n=27), as compared with 18% among those who received placebo (n=14) (P<0.001), and unbound rivaroxaban concentration was reduced by 23.4 ng/ml vs 4.2 ng/ml (P<0.001); thrombin generation was fully restored in 96% vs 7% of the participants (P<0.001). These effects were sustained when andexanet was administered as a bolus plus an infusion. No serious adverse or thrombotic events were reported. Another study, the ANNEXA-E (Andexanet Alfa a Novel Antidote to the Anticoagulant Effects of FXA Inhibitors-Edoxaban), is going to assess the effect of this antidote in patients receiving edoxaban. An ongoing trial (ANNEXA-4; NCT02329327) is evaluating the efficacy and safety of andexanet in patients (estimated to be enrolled: n=270) with factor Xa inhibitor–associated acute major bleeding (https://clinicaltrials.gov/ct2/show/NCT02329327).[13]

Aripazine or ciraparantag or PER977, has been introduced as a universal antidote binding and inhibiting all NOACs;[10, 11] however, it has so far only been studied in volunteers taking edoxaban and the mechanism of action remains unknown. Aripazine is a small, synthetic, water-soluble, cationic molecule developed by Perosphere Inc. that binds to unfractionated heparin, low-molecular-weight heparin, fondaparinux, dabigatran and to the new factor Xa inhibitors through hydrogen bonding and charge–charge interactions. Preliminary data are promising. The molecule effectively reverses bleeding associated with factor Xa inhibitors in animal models of

external and internal bleeding. In addition, the results of the first human, Phase I study have been recently published. In this study, the effect of single IV doses of aripazine (5-300 mg) administered alone and after a 60-mg oral dose of edoxaban was examined in 80 healthy persons.[45] After edoxaban, the mean whole-blood clotting time increased by 37% over the baseline value. In patients receiving a single IV dose of aripazine (100-300 mg) 3 hours after the administration of edoxaban, the whole-blood clotting time decreased to within 10% above the baseline value in $\leq$10 min, whereas in patients receiving placebo, this occurred much later (12-15 h). The whole-blood clotting time remained within 10% above or below the baseline value for 24 h after the administration of a single dose of aripazine. Edoxaban anticoagulation significantly reduced the mean fibrin-fiber diameter (determined by scanning electron micrographs of clots) relative to baseline, which was restored to normal 30 min after administration of aripazine; there was no evidence of procoagulant activity after administration of aripazine (assessed by measuring levels of d-dimer, prothrombin fragment 1.2, and tissue factor pathway inhibitor and by whole-blood clotting time). Potentially related adverse events were transient mild perioral and facial flushing and dysgeusia; 1 person reported a moderate headache. In addition, 1 person had a moderate muscle cramp and elevation in creatinine kinase levels, events that were not considered to be related to aripazine. Thus, in this study, baseline hemostasis was restored from the anticoagulated state within 10-30 min after administration of 100-300 mg of aripazine and was sustained for 24 hours. Additional phase 2 clinical studies are ongoing.[45]

Conclusion

NOACs have been proven equivalent or superior to VKAs in the treatment of non-valvular AF and VTE, conferring protection from thromboembolic events with lessened occurrence of intracerebral hemorrhage. However, occurrence of major or life-threatening bleeding events is still quite possible; it has even been suggested that the rate of GI or other site major bleeding related to the use of at least some NOACs is higher than that reported in warfarin users. Thus, there is a major concern regarding the lack of a specific antidote and rapid reversal agent in case of a life-threatening bleeding event. The quicker dissipation of the anticoagulant effect of these agents due to their shorter half-life is not always entirely reassuring, particularly when urgent surgery with a high hemorrhagic risk is needed or in cases of intracerebral hemorrhage or serious bleeding in another critical organ, or even in cases of accidental overdose, where the anticoagulant effect should be promptly reversed. Fortunately, the development of effective specific NOAC antidotes has recently made great advances, with one having already gained FDA and EMA approval and another two agents already in the pipeline.

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