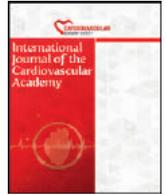




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Review

Novel oral anticoagulants in non-valvular atrial fibrillation: Pharmacological properties, clinical trials, guideline recommendations, new antidote drugs and real-world data☆

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ABSTRACT

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia. Ischemic stroke and systemic thromboembolism are the most fatal complications of AF. Vitamin K antagonists (VKA) are used in the prevention of AF-related stroke and systemic thromboembolism. However, the use of VKAs is associated with limitations such as their narrow therapeutic index, the need for monitoring, and numerous food-drug interactions. Novel oral anticoagulants (NOACs) developed by researchers do not have those limitations and are better tolerated in patients with non-valvular atrial fibrillation. In this review, the pharmacological properties of NOACs, the results of NOAC clinical trials, the guideline recommendations, the important aspects of patient selection and clinical practice, new antidote drugs for NOACs and real-world data of NOACs in patients with non-valvular atrial fibrillation have been discussed.

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Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and is seen in 1–2% of the general population.¹ The number of patients with AF in the United States was 2.2 million in 2010 and is expected to rise to 12 million by 2050.² Ischaemic stroke and systemic thromboembolism are the most severe and fatal complications of AF. AF is responsible for 15% of the ischaemic stroke cases among all age groups and this rate increases up to 30% in people older than 80 years.³ Warfarin is a vitamin K antagonist (VKA) that has been used in the prevention of AF for over 50 years. Randomised trials have shown that warfarin is superior to placebo, aspirin and the combination of aspirin–clopidogrel in preventing stroke.^{4,5,6} Warfarin use is challenging due to its narrow therapeutic index and it has many food and drug interactions. Thus, only 50 to 60% of the patients with AF are prescribed warfarin therapy and in 30 to 50% of these patients the international normalised ratio (INR) levels cannot be maintained within the therapeutic index.^{7,8} Although the efficacy of warfarin and other VKAs has been proven, the low and suboptimal use has led to the development of novel oral anticoagulants (NOACs).

Novel oral anticoagulants

Vitamin K antagonists affect the vitamin K dependent factors II, VII, IX, and X of the coagulation cascade and novel oral anticoagulants (NOACs) affect specific steps. They are classified according to their effects as the direct thrombin inhibitors dabigatran and AZD0837, and the direct factor Xa inhibitors rivaroxaban, apixaban, edoxaban, betrixaban, LY-517,717 and ym-150 (Table 1).⁹ This review focuses on dabigatran, rivaroxaban, apixaban and edoxaban that are approved by the American Food and Drug Administration (FDA) for the prevention of stroke and systemic embolism in patients with non-valvular AF.

Dabigatran

Dabigatran etexilate is an oral pro-drug and is converted to its active form dabigatran, a reversible, direct and competitive thrombin inhibitor by serum esterases.¹⁰ Its half-life is 12–17 h, and 80% of the drug is excreted renally.¹¹ The RE-LY (Randomized Evaluation of Long-term Anticoagulation Therapy) trial, is a prospective, randomised controlled and open-labelled trial that compares the efficacy and safety of 110 mg and 150 mg doses of dabigatran to warfarin with respect to stroke and systemic embolisms. The trial was designed as a non-inferiority trial. 18,113 patients with mean CHADS₂ scores of 2.1 were included in the trial and were randomised to receive dabigatran (110 mg or 150 mg, twice a day) or warfarin (INR 2–3). The primary endpoint was stroke or systemic embolism. With respect to the primary endpoint, the dose of 110 mg dabigatran (1.53% events/year) was non-inferior ($p < 0.001$) to warfarin and the dose of 150 mg dabigatran (1.1% events/year) was superior to warfarin ($p < 0.001$).¹² The rate of major and life-threatening bleeding in the group of 150 mg doses of dabigatran was similar to warfarin (3.11% vs. 3.36% events/year

respectively, $p = 0.31$) and the 110 mg dose of dabigatran was associated with a 20% risk reduction (2.7% vs. 3.4% events/year, $p = 0.003$). When the major bleedings were evaluated independently according to their locations, the rate of intracranial haemorrhages was seen to be significantly lower in both of the dabigatran arms (110 mg BID and 150 mg BID) than it was in the warfarin arm (0.23%, 0.35% and 0.74% events/year respectively, $p < 0.001$ for both groups). On the other hand, it was seen that the 150 mg dose of dabigatran increased the risk for gastrointestinal bleeding when compared to warfarin (1.51% and 1.02% respectively, $p < 0.001$), and the 110 mg dose of dabigatran was similar to warfarin (1.12% and 1.02% respectively, $p = 0.43$).¹³

Rivaroxaban

Rivaroxaban is a direct factor Xa inhibitor. Its half-life is 5–9 h (9–13 h in the elderly) and 60–70% of the drug is excreted renally.¹¹ 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 is a prospective, randomised, double-blind trial comparing rivaroxaban and warfarin in patients with non-valvular AF. Total of 14,264 patients with non-valvular AF with mean CHADS₂ scores of 3.48 were included in the trial. Patients were randomised to receive 20 mg/day doses of rivaroxaban (15 mg/day if the creatinine clearance is 30–49 mL/min) or warfarin (target INR: 2–3). The primary end points were stroke and systemic embolism. When the trial was completed, it was shown that rivaroxaban was non-inferior to warfarin with respect to the primary endpoint (2.1% vs. 2.4% respectively, for non-inferiority $p < 0.001$). There was no difference between the rates of major and clinically significant non-major bleeding rates between rivaroxaban and warfarin groups (14.9% vs. 14.5% events respectively, $p =$ non-significant). In addition, the rate of intracranial haemorrhages was significantly lower in the rivaroxaban group (0.5% and 0.7% events/year, $p = 0.02$).¹⁴

Apixaban

Apixaban is an oral drug and is a direct competitive factor Xa inhibitor. It is absorbed rapidly, has a half-life of 10–14 h and 27% of the drug is excreted renally.¹⁵ The AVERROES trial (Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment) is a double-blind randomised trial including 5599 patients with AF for whom vitamin K antagonist therapy is inappropriate. The patients were randomised to receive apixaban (5 mg, twice a day) or aspirin (80–325 mg). The mean follow-up was 1.1 years. The rate of stroke or systemic embolism was 1.6% in the apixaban group and 3.7% in the aspirin group (HR 0.45, 95% CI 0.32–0.62, $p < 0.001$). It was recommended to terminate the trial early because a significant benefit in favour of apixaban was demonstrated. There was no significant difference in major bleeding rates between apixaban and aspirin groups. In addition, it was shown that apixaban was tolerated better than aspirin as more cases in the aspirin group discontinued their treatment.¹⁶

Table 1
Comparison of pharmacokinetic profiles for the novel oral anticoagulants.^{12,14,15,20}

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Mechanism of action	Direct thrombin (factor IIa) inhibition	Direct factor Xa inhibition	Direct factor Xa inhibition	Direct factor Xa inhibition
Dosing	110 mg oral, twice daily 150 mg oral, twice daily	20 mg oral daily 15 mg oral daily (if CrCl 30–49 mL/min)	5 mg oral, twice daily 2.5 mg oral, twice daily (if creatinine > 133 mmol/L)	60 mg oral daily 30 mg oral daily
Elimination	80% renal	~66% renal	~27% renal	50% renal
Pro-drug	Yes	No	No	No
Half-life (h)	12–17	5–9 (9–13 h in the elderly)	10–14	9–11
Tmax (h)	1	2–4	3–4	1–4

CrCl: creatinine clearance.

Table 2
Comparison of data from major trials for the novel oral anticoagulants.^{12,14,15,20}

	RE-LY	ROCKET-AF	ARISTOTLE	ENGAGE AF-TIMI 48
Treatment arms	Dabigatran (110 mg or 150 mg, twice a day) vs. warfarin (target INR: 2–3)	Rivaroxaban 20 mg/day (15 mg/day if the creatinine clearance is 30–49 mL/min) vs. warfarin (INR: 2–3)	Apixaban (5 mg, twice a day) vs. warfarin (target INR: 2–3)	Edoxaban (30 mg/d or 60 mg/d) vs. warfarin (target INR: 2–3)
Trial design	Randomised, open-label	Randomised, double-blind	Randomised, double-blind	Randomised, double-blind
Number of patients	18,113	14,264	18,201	21,105
Mean age	71.5	73	70	72
TTR of warfarin (%)	64	55	62	68
Mean CHADS ₂ score	2.1	3.48	2.1	2.8
Primary endpoint: stroke/systemic embolism (%/year)	1.53 in 110 mg dabigatran group, 1.11 in 150 mg dabigatran group, 1.69 in warfarin group (p < 0.001 for non-inferiority for both dabigatran groups)	2.1 in rivaroxaban group and 2.4 in warfarin group (p < 0.001 for non-inferiority)	1.27 in apixaban group and 1.6 in warfarin group (p < 0.001 for non-inferiority and p = 0.01 for superiority)	1.61 in 30 mg edoxaban group, 1.18 in 60 mg edoxaban group and 1.50 in warfarin group (p = 0.005, p < 0.001 for non-inferiority respectively)

INR: international normalised ratio; TTR: time-in-therapeutic range.

Another trial ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) compared apixaban to warfarin. This trial was a double-blind, randomised, controlled non-inferiority trial and included 18,201 patients with non-valvular AF with CHADS₂ scores of 2.1 from 39 countries. The mean follow-up was 1.8 years. Patients were randomised to receive apixaban (5 mg, twice a day) or warfarin. Patients who met two or more of the following criteria were administered half doses of apixaban: being over 80 years of age, weighing 60 kg and less or having serum creatinine levels higher than 1.5 mg/dL. The primary composite endpoint, stroke or systemic embolism occurred in 212 (1.27%) patients in the apixaban arm and 265 (1.6%) patients in the warfarin arm (p < 0.001 for non-inferiority, p = 0.01 for superiority).

According to the results, apixaban was superior to warfarin in preventing stroke and systemic embolisms in patients with non-valvular AF. Apixaban was also superior to warfarin with respect to all-cause mortality rates (3.52% vs. 3.94%, p = 0.047). Regarding the safety endpoints, major bleeding occurred less in the apixaban arm (2.13%) than the warfarin arm (3.09%) (p < 0.001). The rate of intracranial haemorrhages was 0.33% event/year in the apixaban group and 0.80% event/year in the warfarin group (p < 0.001).¹⁵

Edoxaban

Edoxaban is a direct, specific and reversible inhibitor of factor Xa, delivered orally. Edoxaban has a half-life of approximately 9–11 h and its absolute oral bioavailability is 62%. It quickly reaches peak plasma concentrations in 1.5 h and 50% of drug elimination is via the kidneys.¹⁷ The Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48 (ENGAGE AF-TIMI 48) is a randomised, double-blind, multicentre trial comparing warfarin and edoxaban for thromboembolism and stroke prophylaxis in non-valvular atrial fibrillation. From 1393 hospitals in 46 countries, 21,105 subjects with a average CHADS₂ score of 2.8 were randomized to edoxaban high dose (60 mg daily), edoxaban low dose (30 mg daily), or warfarin titrated to an international normalised ratio of 2.0 to 3.0. The primary compound endpoint was systemic embolism and stroke. Annual rate of the primary end point was 1.50% with warfarin (time-in-therapeutic range (TTR), 68%), when compared to 1.18% with 60 mg edoxaban (p < 0.001 for non-inferiority) and 1.61% with 30 mg edoxaban (p = 0.005 for non-inferiority). Annual rate of major bleeding was 3.43% in warfarin, 2.75% and 1.61% for 60 mg and 30 mg edoxaban treatment respectively (p < 0.001 for both doses). Both doses of edoxaban were shown to be as efficient as warfarin for systemic embolism and stroke prophylaxis in non-valvular AF and were associated with significantly lower rates of bleeding and death from cardiovascular causes. On the other hand gastrointestinal bleeding rates were significantly higher in edoxaban 60 mg group compared to warfarin therapy (1.51% vs 1.23%; p = 0.03).¹⁸

We can summarise the four randomised controlled novel oral anticoagulant trials as follows:

- 1- In patients with non-valvular AF, novel oral anticoagulants are at least as effective as warfarin for the prevention of stroke and systemic embolism.^{12,14,15,18}
- 2- When compared to warfarin, 150 mg doses of dabigatran reduced the relative risk by 34% and apixaban reduced it by 21%. Both of these drugs were superior to warfarin in preventing the primary endpoint.^{12,15}
- 3- The rates of intracranial haemorrhages and haemorrhagic stroke were significantly lower with novel oral anticoagulants. However, only 150 mg doses of dabigatran were proven to be superior to warfarin in preventing ischemic stroke (relative risk reduction 24%).^{12,14,15,18}
- 4- Only apixaban is superior to warfarin with respect to mortality of all causes (p = 0.047).¹⁵
- 5- With respect to other major bleedings except gastrointestinal bleeding, apixaban, 110 mg doses of dabigatran and both doses of edoxaban are safer than warfarin (superior). Rivaroxaban and 150 mg doses of dabigatran are at least as safe as warfarin (non-inferior).^{12,14,15,18}
- 6- Rivaroxaban, 150 mg doses of dabigatran and 60 mg doses of edoxaban increase the risk of gastrointestinal bleeding when compared to warfarin. Apixaban, 110 mg doses of dabigatran and 30 mg doses of edoxaban are similar to warfarin (Table 2).^{12,14,15,18}

Limitations to NOACs

The novel oral anticoagulant drugs have become popular in patients with non-valvular AF for the prevention of stroke and ischaemic embolisms because they do not require monitoring, they are easy to use and they cause fewer drug and food interactions. However, the different designs and inclusion criteria of the trials comparing NOACs, and the lack of trials comparing all three NOACs with each other raise controversy. The four large phase III trials (RE-LY, ROCKET-AF, ARISTOTLE and ENGAGE AF-TIMI 48) were all designed as non-inferiority trials. The RE-LY trial was an open-labelled trial but the ROCKET-AF, ARISTOTLE and ENGAGE AF-TIMI 48 trials were double-blind.^{12,14,15,18} In current guidelines, effective warfarin therapy is defined as an “INR level between 2.0 and 3.0 and the TTR as at least 70% of the entire treatment duration”.¹ The TTR in these trials differs significantly, the TTR is 55% in the ROCKET-AF trial, 62% in the ARISTOTLE trial, 64% in the RE-LY trial and 68% in the ENGAGE AF-TIMI 48 trial. Due to suboptimal time-in-therapeutic range the efficacy of warfarin could have been calculated lower than it should have been, thus, NOACs may have been determined as relatively non-inferior and/or superior to warfarin.¹⁹ Another important topic for discussion is the inclusion of patients from different risk groups for stroke. The mean CHADS₂ scores in the

RE-LY, ARISTOTLE, ENGAGE AF-TIMI 48 and ROCKET-AF trials were 2.1, 2.1, 2.8 and 3.5 respectively. This may be one of the reasons why rivaroxaban was not superior to warfarin with respect to the primary endpoints although apixaban and 150 mg doses of dabigatran were superior. Another discussion topic is the association of dabigatran therapy with ischaemic myocardial events. This discussion was raised because the number of myocardial infarctions (MI) was higher in the dabigatran arm of the RE-LY trial than the warfarin arm. Due to this, MI, unstable angina, cardiac arrest and cardiac death rates on dabigatran treatment were analysed and published. The annual MI rates in the arms receiving 110 mg or 150 mg of dabigatran or apixaban were 0.82%, 0.81% and 0.64% respectively and there was no statistically significant difference. There was no significant difference between the rates of the primary composite endpoints unstable angina, MI, cardiac arrest and cardiac death either.²⁰

Novel oral anticoagulants in light of guidelines

In the AF guideline and updates published by the European Society of Cardiology (ESC) in 2010 and 2012 it is stated that AF patients must undergo risk classification for stroke and the anticoagulant treatment requirements should be determined accordingly. For this purpose, instead of the CHADS₂ score it is recommended to use the CHA₂DS₂-VASc score that allows better differentiation of the “real low risk” cases.¹ The ESC guideline does not recommend anticoagulant treatment for non-valvular AF patients in the real low-risk groups – i.e. patients under 65 years of age with no risk factors (with a CHA₂DS₂-VASc score of 0). Oral anticoagulants are offered as the single treatment option for cases with CHA₂DS₂-VASc scores ≥ 1 . Female patients are given 1 point for gender under any circumstance, however, they are not suitable candidates for anticoagulant therapy if they are under 65 years and have no risk factors. In other words, anticoagulant treatment is indicated for all patients with AF over the age of 65. If the patient has a rheumatoid heart disease (especially mitral stenosis), a history of prosthetic valvular operations or mitral valve repair, and if the creatinine clearance is under 30 mL/min the only suitable oral anticoagulant (OAC) is warfarin. In the rest of the patients with non-valvular AF, warfarin and all three NOACs are suitable for the same indications and have equivalent proof levels.²¹

The American College of Cardiology and the American Heart Association (ACC/AHA) have updated the guidelines they published in 2014 to recommend using the CHA₂DS₂-VASc score for risk classification instead of the CHADS₂ score in a similar fashion to the ESC guidelines.²² The common aspects and differences between the guidelines important for clinical practice issued by the ESC and ACC/AHA can be summarised as follows:

- * The ESC guidelines recommend OAC treatment for patients with CHA₂DS₂-VASc scores of 1, the ACC/AHA guidelines state that treatment may not be necessary, OAC treatment can be administered or treatment with aspirin may be considered.^{21,22}
- * In patients with CHA₂DS₂-VASc scores of 0 both guidelines state that treatment is not required.^{21,22}
- * The ESC guidelines do not recommend using NOACs in patients who have renal failure with CrCl (creatinine clearance) <30 mL/min, the ACC/AHA guidelines state that NOACs should not be used in end-stage chronic renal failure patients (CrCl < 15 mL/min) or in cases in haemodialysis programs and that warfarin is the drug of choice for these patients.^{21,22}
- * The ESC guidelines recommend using a 110 mg dose of dabigatran twice a day for patients with renal failure and CrCl = 30–49 mL/min. The ACC/AHA guidelines state that 150 mg or 75 mg BID doses of dabigatran can be used in this patient group.^{21,22}
- * The ACC/AHA guidelines state that 75 mg doses of dabigatran twice a day or 15 mg/day doses of rivaroxaban can be used in renal failure patients with CrCl = 15–30 mL/min. However, it is stated that this recommendation is not based on data from prospective studies.²²

Monitoring novel oral anticoagulants

Unlike warfarin, the novel oral anticoagulants do not require routine monitoring. It may be necessary to assess the efficacy of NOACs in some specific clinical situations such as bleeding, newly developed or deteriorating renal failure, stroke or systemic embolism.²³ However, there is no specific coagulation test that can be used to determine the efficacy of the NOAC drugs in these clinical conditions. The most useful approach used for this purpose is measuring the thrombin or ecarin clotting times. Especially during emergencies, the activated partial thromboplastin time is another measure that can be used during dabigatran treatment. However, it must not be forgotten that high blood levels of the drugs may lead to erroneous activated partial thromboplastin time readings.²⁴ The coagulation test used for rivaroxaban patients is the prothrombin test.²⁵ The factor Xa levels can also be used to monitor rivaroxaban, apixaban and edoxaban.^{25,26}

Bleeding management

There are a few novel antidotes used to antagonise drug effects in bleedings induced by NOACs. Treatment with plasma is ineffective because the bleeding is not due to factor deficiency; thrombin and factor Xa inhibitors are already present in the patient's blood. It is thought that cryoprecipitate may be useful in dabigatran-induced bleedings and that prothrombin concentrates may be useful in apixaban or rivaroxaban-induced bleedings. The only emergency approach proven to be useful in the treatment of dabigatran-induced bleeding is the use of activated charcoal followed by haemodialysis to remove the drug from the body.²⁷ Currently, there is a few new specific antidote drugs to treat major bleedings associated with new generation oral anticoagulants. Thus, the most important point that needs to be considered by the physician is the selection of the most suitable drug and dose regimen.

Converting from anticoagulant treatment to NOACs and the perioperative approach

The use of novel oral anticoagulants is increasing as they have advantages over warfarin. Their onset of effect is rapid, they do not cause significant food and drug interactions and they do not require monitoring. If a patient on NOAC therapy is going to have surgery the most important question is when to stop the drug before the surgery. The definitive issue is the functional capacity of the patient's kidneys. According to current consensus reports it is recommended to assess the creatinine clearance at least seven days before the surgery before making a decision. Important aspects to consider when deciding when to stop NOAC therapy before surgery are given in Table 3.

When converting from warfarin to one of the novel oral anticoagulants, the novel oral anticoagulant must be started when the INR is below 2, in the opposite case double-treatment must be continued until INR reaches efficient levels. When converting from low molecular weight heparin (LMWH) to new generation oral anticoagulants heparin must be discontinued after delivering the final dose, and the new generation oral anticoagulant must be started 2 h before the time of the next dose of heparin that was to have been administered. In the opposite case, the first dose of heparin must be delivered 12 or 24 h after the last dose of the novel oral anticoagulant.²⁷ When it is desired to convert to NOACs from infusions of unfractionated heparin the first NOAC dose should be administered at the time of the discontinuation of the infusion.

In the postoperative period it is recommended to restart the NOAC therapy as soon as possible once haemostasis is maintained. Intravenous heparin or LMWH bridge treatment is not required in the postoperative period as the effects of NOACs end rapidly and once restarted they rapidly reach therapeutic efficacy within 2 h.²⁸

Table 3
Preoperative interruption of novel oral anticoagulants.^{45,46,47}

Drug	Renal function	Low bleeding risk surgery (last dose)	High bleeding risk surgery (last dose)
Dabigatran (150 mg twice daily)	Normal or mild impairment (CrCl ≥ 50 mL/min)	24 h before surgery	48–72 h before surgery
	Moderate impairment (CrCl 30–49 mL/min)	48–72 h before surgery	96 h before surgery
Rivaroxaban (20 mg once daily)	Normal or mild impairment (CrCl ≥ 50 mL/min)	24 h before surgery	48–72 h before surgery
	Moderate impairment (CrCl 30–49 mL/min)	48 h before surgery	72 h before surgery
Apixaban (5 mg twice daily)	Normal or mild impairment (CrCl ≥ 50 mL/min)	24 h before surgery	48–72 h before surgery
	Moderate impairment (CrCl 30–49 mL/min)	48 h before surgery	72 h before surgery

CrCl: creatinine clearance.

Drug interactions

The drug interactions of NOACs are another important issue. Although NOACs cause less drug interactions than warfarin, the drug interactions of NOACs must be known and a detailed pharmaceutical history of the patient must be obtained before prescribing these drugs.

Dabigatran requires an acidic medium for absorption because it contains tartaric acid. While antacids and H₂ receptor antagonists do not affect the absorption of dabigatran; pantoprazole, a proton-pump inhibitor prevents the formation of an acidic medium and reduces the absorption of dabigatran.²⁹

The inhibition and induction of P-glycoprotein (P-gp) play an important role in the metabolism of dabigatran and also affect its blood levels. In patients using drugs like amiodarone, verapamil, quinidine, ketoconazole that inhibit P-gp, dabigatran must be avoided or used with caution at low doses. On the other hand, it must not be forgotten that concomitant use of the P-gp inducer rifampicin may reduce the therapeutic efficacy of dabigatran. In patients using ketoconazole, clarithromycin, ritonavir and other protease inhibitors that inhibit CYP3A4, apixaban and rivaroxaban must be used with caution because the blood levels and efficacy of the drugs may increase.²⁹

New antidotes for novel oral anticoagulants

Life-threatening bleeding is the most important complication of NOACs. Lack of antidotes for NOACs is another crucial point when urgent intervention or surgery is needed.³⁰ That brings the necessity of a fast-affecting and specific antidote for reversal of anticoagulation. Clinical trials in progress are evaluating the efficacy and safety of idarucizumab and andexanet alpha.³¹

Dabigatran and idarucizumab

Idarucizumab (aDabi-Fab, BI 655075) which is a human monoclonal antibody is the first specific dabigatran antidote. Binding specifically to dabigatran, idarucizumab antagonises its effects. Compared to thrombin it has a 350-fold increased affinity to dabigatran.³² The Study of the REVERSAL Effects of Idarucizumab in Patients on Active Dabigatran (RE-VERSE AD) is a phase 3 trial investigating the efficacy and safety of idarucizumab in patients with life-threatening bleeding and/or patients require urgent surgery or intervention.³³ In this prospective cohort study, anticoagulation reversal capacity of 5 mg of idarucizumab is evaluated by measuring diluted thrombin time (dTT) and ecarin clotting time (ECT) before and 4 h after administration of idarucizumab. According to the pre-analysis results of the study, in patients with an increased coagulation profile (elevated dTT in 68; elevated ECT in 81 patients) median maximum reversal rate was 100%.³⁴

Factor Xa inhibitors and andexanet alfa

Andexanet alfa (PRT064445, r-Antidote; Portola Pharmaceuticals) is an enzymatically inactive modified recombinant human factor Xa decoy protein which has an increased affinity to factor Xa inhibitors (rivaroxaban, apixaban and edoxaban) and antagonises the anticoagulant effects.³⁵ Andexanet Alfa, a Novel Antidote to the Anticoagulation Effects of FXA Inhibitors Apixaban (ANNEXA-A) and Rivaroxaban (ANNEXA-R) trials are designed to evaluate the efficacy and safety of andexanet alfa, which is used to antagonise the anticoagulant effects of apixaban and rivaroxaban in healthy volunteers. In this randomised, placebo controlled, double-blind trial 101 participants between ages 50–75 years (48 patients in apixaban and 53 patients in rivaroxaban arm) were randomised to either andexanet alfa or placebo. In andexanet alfa arm, following the administration of the antidote, the activity of anti-factor Xa decreased rapidly and significantly within minutes (2–5 min) compared to placebo (andexanet alfa vs. placebo, decreasing of anti-factor Xa for apixaban [mean ± SD] 94 ± 2% vs. 21 ± 9%; p < 0.001, for rivaroxaban için 92 ± 11% vs 18 ± 15%; p < 0.001).³⁶

Real-world data of NOACs

Current guidelines recommend NOAC drugs for prevention of stroke in non-valvular AF patients. Recommendations and level of evidences of the guidelines are based on randomised trials of NOACs. Nevertheless, as some patient groups which are common in routine daily practice are not included in those trials, real-world data investigating the safety and efficacy of NOACs is needed. Designed for that purpose, XANTUS trial is an international, large-scaled, prospective, observational study collecting the real-world data of rivaroxaban which is used in stroke prevention in non-valvular AF patients. A total of 6784 patients (mean age: 71.5 years, 59% male) who were treated with rivaroxaban for non-valvular AF were included in the study and were followed up for one year independent of the risk of stroke. Mean CHADS₂ score was 2.0. Mild to severe renal insufficiency (CrCl < 50 mL/min) was seen in 9.4% of patients. In safety results of the trial, fatal bleeding (0.2 events per 100 p/y) in 0.2% of patients and major bleeding (n = 128, 2.1 events per 100 p/y) in 1.9% of patients occurred. Symptomatic thromboembolism (stroke, transient ischaemic attack, systemic embolism, MI) was seen in 1.6% of patients (n:108). In comparison with ROCKET-AF trial, mean CHADS₂ score (3.5 for ROCKET-AF and 2.0 for XANTUS), all-cause mortality rates, major bleeding, stroke and MI rates were lower in XANTUS trial.³⁷

United States Department of Defence Post-marketing Safety Surveillance (PMSS) trial is a retrospective, observational study designed to identify the major bleeding incidence associated with rivaroxaban. A total of 39,052 patients who were treated with rivaroxaban for total hip/knee surgery or non-valvular AF were included in the study.

Rivaroxaban associated major bleeding incidence was 2.89 events per 100 person-years ($n = 970$). Most of the major bleedings were gastrointestinal bleedings (846 patients, 87.2%). Fatal bleeding incidence was 0.1% ($n = 35$). Intracranial haemorrhages were responsible for 74.3% of fatal bleeding.³⁸ Results of the study were consistent with ROCKET-AF trial. The results of XANTUS and PMSS trials analysing the real-world data confirmed the results of ROCKET-AF trial.³⁹

Effectiveness and Safety of Dabigatran and Warfarin in Real-world US Patients With Non-Valvular Atrial Fibrillation: A Retrospective Cohort Study is a retrospective, observational study, conducted between 2010 and 2012, including patients with non-valvular AF on vitamin K antagonists or dabigatran therapy. A total of 64,935 patients were included in the study of whom 32.5% were on dabigatran therapy. Compared to warfarin, dabigatran was associated with lower risks of ischaemic stroke or systemic embolism (composite adjusted HR: 0.86, 95% CI: 0.79 to 0.93), haemorrhagic stroke (HR: 0.51, 95% CI: 0.40 to 0.65) and MI (HR: 0.88, 95% CI: 0.77 to 0.99). Conversely dabigatran was associated with increased risk of GI bleeding (HR: 1.11, 95% CI: 1.02 to 1.22).⁴⁰ Supportively, Graham et al. conducted a study with real-world data to find that 150 mg dabigatran was associated with lesser death, ischaemic stroke, intracranial haemorrhage risks and therefore increased GI bleeding risk.⁴¹ On the contrary, in a trial by Hernandez et al. Dabigatran was associated with increased risks of bleeding (HR: 1.30, 95% CI: 1.20–1.41), major bleeding (HR: 1.58, 95% CI: 1.36–1.83) and GI bleeding (HR: 1.85, 95% CI: 1.64–2.07). Intracranial haemorrhage was significantly lesser in dabigatran arm, similar to RE-LY trial. Investigators emphasize that bleeding risk was higher especially in patients with co-dominant comorbidities and that dabigatran should be used with caution in those patients.⁴² In a recent report published by FDA which was based on real-world data, dabigatran was associated with lower risks of stroke, death and intracranial haemorrhage.⁴³ In a trial which was conducted between 2007 and 2010 and was evaluating real-world data of non-valvular AF patients, NOACs were associated with lower rates of stroke compared to warfarin. It was emphasised that when excluding intracranial haemorrhages, apixaban was the only NOAC decreasing major bleeding rates. Numbers needed to treat (NNT) values for net clinical benefit (stroke plus major bleeding except intracranial haemorrhage) were 32 and 84 for apixaban and dabigatran respectively.⁴⁴

Conclusions

The novel oral anticoagulant drugs for prevention of stroke in non-valvular AF have been evolved and adding new options and advantages for patients and physicians such as fewer frequency of drug and food interactions, no need for monitoring, broad therapeutic index and tolerated better by patients.

Large-scale phase III trials are completed for dabigatran, rivaroxaban, apixaban, edoxaban and all these trials ended up with non-inferiority of these new anticoagulant drugs compared with warfarin for prevention of stroke for patients with non-valvular atrial fibrillation. Additionally, compared with VKA, dabigatran 150 mg and apixaban twice daily were superior and associated with significant reductions in the incidence of stroke. Intracranial haemorrhages and haemorrhagic stroke occurred significantly less with novel oral anticoagulants. Especially in patients with poorly controlled INR values in follow-up, the potential advantages of the NOACs are likely to be most manifest.

Conflict of interest

We have no commercial, financial, and other relationships in any way related to the subject of this article that might create any potential conflict of interest.

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