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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 $CHADS_2$ 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 $CHADS_2$ 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.

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