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Stroke prevention in patients with atrial fibrillation—anticoagulation strategy 2012

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ABSTRACT

Vitamin K antagonists have been recommended as the only available oral anticoagulants for stroke prevention in patients with atrial fibrillation for many years. Despite their proved effectiveness, there are several limitations and drawbacks of this therapy. Recently three major clinical trials of novel oral anticoagulants clinical trials have been published. Dabigatran, a direct thrombin inhibitor, as well as rivaroxaban and apixaban, direct Xa factor inhibitors, were found to have at least noninferior efficacy and safety in comparison to vitamin K antagonists for stroke prevention in patients with non-valvular fibrillation. These novel oral anticoagulants may constitute a valuable alternative to vitamin K antagonists.

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1. Introduction

Atrial fibrillation (AF) is the most common arrhythmia in clinical practice. AF increases almost five-fold the independent risk of ischemic stroke [1]. AF related strokes account for at least 20% of all strokes and are associated with worse survival [2]. For more

than 60 yr, vitamin K antagonists (VKAs) have been the reference standard treatment of AF with risk factors for stroke. Until recently VKAs were the only available oral anticoagulants for stroke and systemic embolism prevention in patients with AF [3]. Warfarin, the most commonly used VKA, reduces stroke risk by 64% compared with 22% reduction with any antiplatelet

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Table 1 – Main characteristics of novel oral anticoagulants.

	DABIGATRAN	RIVAROXABAN	APIXABAN
Point of action	Iia	Xa	Xa
t_{\max} (h)	0.5–2	2–4	1–4
$t_{1/2}$ (h)	12–17	5–13	8–15
Bioavailability (%)	6.5%	60–80%	50%
Active drug clearance	80% renal; 20% liver	33% renal; 66% liver	25% renal; 75% liver
CYP 450	no	3A4/2J2	3A4
Prodrug	Dabigatran etexilate	no	no
Dose	110 mg or 150 mg b.i.d.	20 mg o.d.	5 mg b.i.d.

treatment, and 19% risk reduction with aspirin alone in nonvalvular AF [4]. Despite VKAs effectiveness, there are several limitations and drawbacks of this anticoagulation therapy. The international normalized ratio (INR) therapeutic index 2.0–3.0 is the optimal value for stroke prevention. Below this narrow range stroke and systemic embolism prevention is ineffective, but higher values significantly increase the risk of hemorrhage [5]. Major bleeding occurs in about 2% of patients with AF on VKAs treatment per year [6]. Significantly increased risk of hemorrhage is the result of the long VKAs half-life, delayed action onset, high inertion after withdrawal and necessity of heparin bridging therapy during urgent surgical procedures. As it is known from clinical trials, patient presenting with AF are in the therapeutic INR range only during 60% of treatment time and data from everyday practice show that this time is even shorter [7,8]. Numerous food and drug interactions, wide variations in metabolism and individual response to drug doses explain the requirement for frequent laboratory monitoring and adequate VKAs dosage. To achieve therapeutic INR range appropriate patient education and strict compliance is necessary.

In the last decade, several novel oral anticoagulants (NOACs) were developed, but so far only three major randomized phase III clinical trials have been completed and published. Dabigatran, the oral direct thrombin inhibitor, as well as two oral factor Xa inhibitors – rivaroxaban and apixaban, were found to have at least noninferior efficacy and safety in comparison to VKAs. No need for routine laboratory monitoring because of predictable anticoagulant effect, fixed dosage, as well as very few drug- and no food interactions are the major advantages of NOACs. The summary of the main pharmacokinetic properties of NOACs is presented in Table 1.

2. Dabigatran

Administered orally as a prodrug, dabigatran etexilate is a direct inhibitor of thrombin that converts fibrinogen into fibrin and promotes thrombus formation. Dabigatran inactivates free and clot-bound thrombin, which prevents thrombus expansion. After intestinal acid sensitive absorption, blood esterases convert dabigatran etexilate into the active metabolite. To promote the process of absorption, dabigatran tablets contain a tartaric acid core which could be responsible for higher rates of dyspepsia. Proton pump inhibitors reduce dabigatran bioavailability by about 20%, but without clinical significance and necessity of dosage adjustment. Dabigatran is not metabolized by the P450 cytochrome, so only very few drugs (verapamil, amiodarone, quinidine, macrolides, tenophovir, rifampicin and St John's wort) can interact with it. The bioavailability and metabolism is also not influenced by food. The maximum

plasma concentration is reached within 0.5–2 h, and the half-life time is 12–17 h. In case of emergency (overdosage, urgent surgical procedure) dabigatran can be dialyzed because of its low plasma protein binding. It is eliminated unchanged mostly via renal excretion, and only 20% is excreted to bile, thus in patients with renal insufficiency dose adjustment and regular creatinine clearance monitoring is necessary [9–11].

RE-LY was a randomized, phase III trial comparing two doses of dabigatran etexilate (110 mg b.i.d. and 150 mg b.i.d.) with open-label, dose-adjusted warfarin to an INR of 2.0–3.0. The 150 mg b.i.d. of dabigatran dose was superior to warfarin for the primary efficacy end-point of stroke and systemic embolism, with no significant differences in the risk of major bleeding. Dabigatran at a dose of 110 mg was safer than warfarin with 20% less major bleeding and non-inferior to warfarin in the prevention of stroke and systemic embolism. There was a non-significant reduction in all-cause mortality, while the rates of hemorrhagic stroke and intracranial hemorrhage were lower with both doses of dabigatran [12,13]. A significant age interaction was also reported, with the beneficial effect better expressed in patients younger than 75 yr [14]. Benefits of dabigatran treatment over the VKA were independent of quality of INR control [15], prior stroke [16] or prior VKA usage [17]. In patients with AF who undergo cardioversion the rates of stroke and major bleeding within 30 days of cardioversion, on both doses of dabigatran were comparable to those on warfarin [18].

3. Rivaroxaban

Rivaroxaban is an oral direct inhibitor of factor Xa which is playing a critical role at the intersection of intrinsic and extrinsic pathways of the coagulation cascade and thrombin generation. Rivaroxaban, without the need of a cofactor, can inhibit not only free factor Xa but also the prothrombinase- and clot-bound factor Xa. Rivaroxaban has a good bioavailability and its absorption is increased by food, so it is recommended to take the drug with or shortly after meals. After absorption, rivaroxaban is metabolized by CYP 3A4 or 2J2, therefore there are several interactions with drugs like antimycotic azole or HIV protease inhibitors, with significant increases in plasma concentrations. The maximum blood level is reached within 2–4 h, and the half-life time is 5–13 h. Unlike dabigatran, rivaroxaban is insoluble in water and has high plasma protein binding, so may not be dialyzable. It is eliminated mostly via renal excretion (one third in the active, unchanged form and two thirds in the form of liver metabolites), and only about 25% with feces. Therefore, rivaroxaban is contraindicated in patients with severe hepatic or renal failure [19,20].

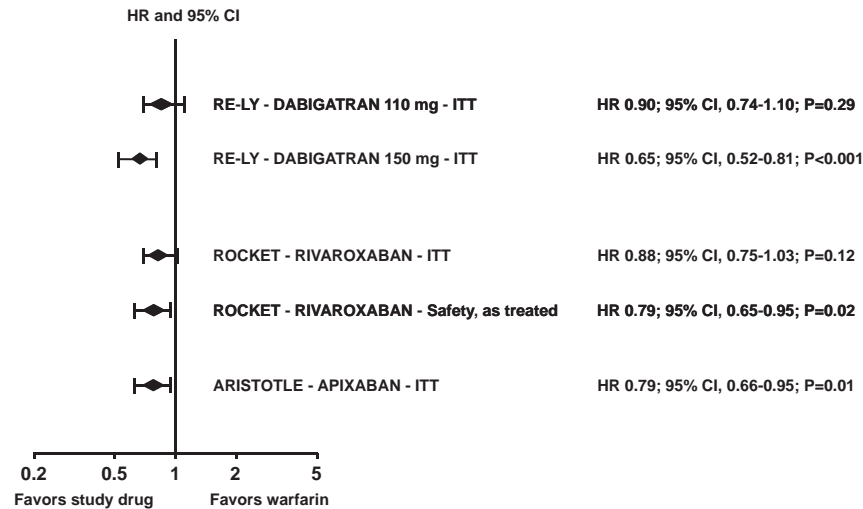


Fig. 1 – Primary efficacy end-point—NOACs trials (HR—hazard ratio; CI—confidence interval; ITT—intention to treat; *p*—level of significance for superiority). Adapted from [28].

Table 2 – Comparison of NOACs trials. Adapted from [28].

	RE-LY [12]	ROCKET AF [21]	ARISTOTLE [25]
Study drug	Dabigatran	Rivaroxaban	Apixaban
Comparator	warfarin (I N R 2–3)		
N	18,113	14,264	18,201
Study design	Open-label (warfarin) non-inferiority	Double-blind non-inferiority	Double-blind non-inferiority
Dose	110 mg b.i.d. or 150 mg b.i.d. (randomized to 2 separate arms)	20 mg o.d. 15 mg o.d. for moderate renal impairment (CrCl 30–49 ml/min)	5 mg b.i.d. 2.5 mg b.i.d. for patients with ≥ 2 at baseline: age ≥ 80 years; weight ≤ 60 kg; serum creatinine ≥ 1.5 mg/dl
Primary efficacy end-point	Stroke and systemic embolism		
Primary safety end-point	Major bleeding	Composite of major and non-major clinically relevant bleeding	Major bleeding
Inclusion criteria	Patients with ≥ 1 : <ul style="list-style-type: none"> • prior stroke, TIA or SE • CHF or LVEF $\leq 40\%$ • age ≥ 75 • age ≥ 65 and 1 of: -DM-HT-CAD 	Patients with prior stroke, TIA or SE or ≥ 2 : <ul style="list-style-type: none"> • CHF or LVEF $\leq 35\%$ • HT • age ≥ 75 • DM 	Patients with ≥ 1 : <ul style="list-style-type: none"> • prior stroke, TIA or SE • CHF or LVEF $\leq 40\%$ • age ≥ 75 • DM • HT
Major bleeding	Bleeding associated with: <ul style="list-style-type: none"> • \downarrow Hb ≥ 2 g/dl • transfusion of ≥ 2 U of blood • symptomatic bleeding in a critical area or organ 	Clinically overt bleeding associated with: <ul style="list-style-type: none"> • \downarrow Hb ≥ 2 g/dl • transfusion of ≥ 2 U of RBC/whole blood • fatal bleeding • critical anatomic site bleeding • permanent disability 	Clinically overt bleeding associated with: <ul style="list-style-type: none"> • \downarrow Hb ≥ 2 g/dl • transfusion of ≥ 2 U of RBC • fatal bleeding • critical site bleeding
Mean CHADS₂	2.1	3.5	2.1

NOACs—novel oral anticoagulants; TIA—transient ischemic attack; SE—systemic embolism; CHF—chronic heart failure; LVEF—left ventricle ejection fraction; DM—diabetes mellitus; HT—hypertension; CAD—coronary artery disease.

Patients with non-valvular AF were randomized in the ROCKET AF phase III trial in double-blind, double-dummy fashion to either active treatment (20 mg o.d. or 15 mg o.d. in patients with creatinine clearance 30–49 ml/min) or dose-adjusted warfarin. Rivaroxaban was non-inferior to warfarin in preventing stroke or systemic embolism in the intention-to-treat population and even superior in the safety as-treated population analysis. There were no differences in the composite primary safety end-point composed of major and non-major clinically relevant bleeding. Rivaroxaban significantly reduced intracranial hemorrhages and hemorrhagic strokes, while transfusions and major gastrointestinal bleedings occurred more frequently [21]. The efficacy and safety of rivaroxaban was similar in the subgroups of patients with and without previous stroke or TIA. This subgroup analysis showed that rivaroxaban provides effective anticoagulation in primary as well as in secondary stroke prevention [22].

4. Apixaban

Apixaban is another NOAC recommended in patients with non-valvular AF. It is a direct, reversible, oral factor Xa inhibitor with absorption independent from food administration. Apixaban inhibits both free and prothrombinase- and clot-bound factor Xa. About one third of the drug is metabolized by hepatic

cytochrome CYP 3A4 and apixaban is eliminated mostly via bile excretion, thus in patients presenting with renal failure is the safest of all NOACs [23,24].

ARISTOTLE was a randomized, double-blind, double-dummy, phase III trial of stroke or systemic embolism prevention comparing apixaban at dose 5 mg b.i.d. (2.5 mg b.i.d. in patients ≥ 80 yr, weight ≤ 60 kg or serum creatinine ≥ 1.5 mg/dl) and dose-adjusted warfarin to an INR of 2.0–3.0. In the intention-to-treat population analysis apixaban was superior to warfarin in the primary efficacy end-point (stroke or systemic embolism). Apixaban significantly reduced intracranial hemorrhage, major and non-major clinically relevant bleeding and any bleeding, but most importantly also reduced all-cause mortality [25]. Secondary analysis of the ARISTOTLE trial shows that there was no difference in reduction of stroke or systemic embolism across all score categories (CHADS₂, CHA₂DS₂VASc, HAS-BLED). Also the rates of major bleeding were similar regardless of stroke or bleeding risk [26]. Reduction in rates of stroke or death compared to warfarin was irrespective of renal function. Benefits of apixaban treatment in patients presenting with renal failure (creatinine clearance ≤ 50 ml/min) are due to a greater relative risk reduction in major bleeding (HR 0.50; 95% CI 0.38–0.66; $p=0.005$) [27].

The main goal in RE-LY, ROCKET AF and ARISTOTLE trials was to demonstrate non-inferiority to VKAs for the primary efficacy and safety end-point in patients with non-valvular AF. These

Table 3 – Recommendations for prevention of thromboembolism in non-valvular AF adapted from [29].

Antithrombotic therapy is recommended for patients with AF besides those who are at low risk or with contraindications.	Class I. Level A.
According to the absolute risk of thromboembolism or bleeding and the benefit for a given patient the adequate therapy should be chosen.	Class I. Level A.
In patients with non-valvular AF with a CHA ₂ DS ₂ VASc score ≥ 2 oral anticoagulation therapy is recommended with dose-adjusted VKAs to a target INR of 2.0 to 3.0 or dabigatran, rivaroxaban, apixaban if there are no contraindications.	Class I. Level A.
In patients with a CHA ₂ DS ₂ VASc score of 1 oral anticoagulation therapy with dose-adjusted VKAs (2.0 to 3.0) or dabigatran, rivaroxaban, apixaban should be considered if there are no contraindications.	Class IIa. Level A.
In patients who are at low risk, with none of the risk factors (CHA ₂ DS ₂ VASc score of 0) no antithrombotic therapy is recommended.	Class I. Level B.
In female patients who are at low risk (age < 65 years with lone AF and CHA ₂ DS ₂ VASc score of 1 because of their gender) no antithrombotic therapy should be considered.	Class IIa. Level B.
In patients with AF where oral anticoagulation is required one of the NOACs is recommended when there are side effects of VKAs likewise difficulties in keeping therapeutic range or regular monitoring of INR.	Class I. Level B.
For most patients with non-valvular AF one of the NOACs should be considered rather than dose-adjusted VKAs.	Class IIa. Level A.
Dabigatran at 150 mg b.i.d. should be preferred in most patients to 110 mg b.i.d., but 110 mg b.i.d. is recommended in elderly patients (age > 80 yr), high bleeding risk (HAS-BLED score ≥ 3), moderate renal failure (creatinine clearance 30–49 ml/min) and interacting drugs treatment.	Class IIa. Level B.
Rivaroxaban at 20 mg o.d. should be preferred in most patients to 15 mg o.d., but 15 mg o.d. is recommended in high bleeding risk (HAS-BLED score ≥ 3) and moderate renal failure (creatinine clearance 30–49 ml/min).	Class IIa. Level C.
In patients treated with one of the NOACs baseline and then regular renal function (creatinine clearance) assessment should be done annually and in patients with moderate renal impairment 2 to 3 times per year.	Class IIa. Level B.
In patients with severe renal failure (creatinine clearance < 30 ml/min) dabigatran, rivaroxaban and apixaban are not recommended.	Class III. Level A.
VKA therapy or dabigatran is recommended for patients with AF of 48 h duration or when the duration of AF is unknown for at least 3 weeks prior to and for at least 4 week after cardioversion.	Class I. Level B.
Dose-adjusted VKAs or dabigatran, rivaroxaban, apixaban should be continued lifelong regardless of sinus rhythm following cardioversion in patients with stroke risk factors or recurrent AF.	Class I. Level B.

three trials proved the efficacy of the novel anticoagulants at the same level as VKAs. Apixaban, dabigatran at 150 mg b.i.d., and rivaroxaban (in safety as treated analysis), were even superior to VKAs in stroke or systemic embolism prevention [Fig. 1].

All of the NOACs confirmed non-inferiority to VKAs in primary safety end-point. Apixaban and dabigatran at 110 mg b.i.d. significantly reduced the rates of major bleeding and, what is noteworthy; every tested NOAC decreased the number of intracranial hemorrhages and hemorrhagic strokes. There are several differences in trials design and outcomes. Trials comparison is presented in Table 2.

Due to such favorable results of the NOACs phase III clinical trials, the European Society of Cardiology updated the ESC guidelines for the management of AF for stroke or systemic embolism prevention. Recommendations for prevention of thromboembolism in non-valvular AF are presented in Table 3 [29].

Although data from NOACs trials are encouraging, there are several practical aspects that still should be elucidated. Safety of long-term treatment and all drug or food interactions are not completely known. Relatively short half-life requires strict patient compliance to assure appropriate anticoagulation levels. Missing more than one dose may result in losing anticoagulant protection. No need of laboratory monitoring is the advantage of NOACs, but in some urgent cases it could be also a disadvantage. Several immediate surgical procedures require certainty of correct coagulation status, which cannot be precisely measured in currently available laboratory tests. Prior to elective procedures NOAC treatment should be interrupted. The time of dabigatran cessation depends on creatinine clearance. In patients with creatinine clearance more than 80 ml/min treatment should be stopped for 24 h, respectively 50–80 ml/min for 1–2 days and 30–50 ml/min for 2–3 days before a surgical procedure, coronary angiography or cardiac pacemaker implantation. In patients treated with rivaroxaban at least 24 h interval is obligatory before any invasive procedures [30]. Moreover, the lack of specific antidote that can be used prior to urgent procedures or in case of overdosage is also a disadvantage and needs additional exploration. There are some data from healthy volunteers showing the effectiveness of prothrombin complex concentrate or low-dose FEIBA (factor eight inhibitor bypassing agent) in anticoagulation effect of rivaroxaban or dabigatran reversal [31,32]. There are preliminary data showing the cost-effectiveness of NOAC treatment in every-day clinical practice, but this needs further precise investigation.

Dabigatran, rivaroxaban and apixaban constitute a valuable alternative to VKAs in patients with non-valvular AF, firmly establish their role in the anticoagulation therapy.

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