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REVIEW ARTICLE

Phase III studies on novel oral anticoagulants for stroke prevention in atrial fibrillation: a look beyond the excellent results

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Summary. In this overview we address the three phase III studies that compared new oral anticoagulants (dabigatran, rivaroxaban and apixaban) with warfarin in the setting of stroke prevention in atrial fibrillation. Strengths and weaknesses of the studies were examined in detail through indirect comparison. We analyze and comment the inclusion and exclusion criteria, the characteristics of randomized patients, the primary efficacy and safety end points and side effects. All new oral anticoagulants resulted in being non-inferior to vitamin K antagonists in reducing stroke or systemic embolism in patients with atrial fibrillation. Dabigatran 150 mg and apixaban were superior to vitamin K antagonists. Importantly, new oral anticoagulants significantly reduced hemorrhagic stroke in all three studies. Major differences among new oral anticoagulants include the way they are eliminated and side effects. Both dabigatran and apixaban were tested in low- to moderate-risk patients (mean CHADS2 [Congestive heart failure, Hypertension, Age, Diabetes, Stroke] score = 2.1–2.2) whereas rivaroxaban was tested in high-risk patients (mean CHADS2 score = 3.48) and at variance with dabigatran and apixaban was administered once daily. Apixaban significantly reduced mortality from any cause. The choice of a new oral anticoagulant should take into account these and other differences between the new drugs.

Keywords: anticoagulants, apixaban, atrial, dabigatran, fibrillation, rivaroxaban.

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Introduction

Three novel oral anticoagulants (NOA), dabigatran, rivaroxaban and apixaban, have been tested vs. vitamin K antagonists (VKA) for stroke prevention in non-valvular atrial fibrillation (AF) [1–3]. NOA have potential advantages as compared with VKA [4]: (i) a rapid onset of action without the need for bridging therapy; (ii) a predictable anticoagulant effect without the need for dose-adjustment laboratory testing; and (iii) low food–drug interactions without the need for restrictions. Table 1 illustrates the characteristics of dabigatran, rivaroxaban and apixaban. Dabigatran etexilate is a prodrug that is rapidly converted into the active compound dabigatran by esterases. Dabigatran reversibly inhibits the active site of thrombin (IIa). Rivaroxaban and apixaban are direct factor (F)Xa inhibitors. The time to a maximal drug concentration in plasma after oral administration of each of the three NOA is short (1–3 h) and the pharmacokinetics is linear except for rivaroxaban. Dabigatran possesses a lower bioavailability (7%) and protein binding (35%) compared with the other NOA. The plasma half-lives are similar for the three drugs ranging from 8 to 15 h. Dabigatran is excreted unchanged by the kidneys (80%) and likewise rivaroxaban and apixaban are a

Table 1 Characteristics of novel oral anticoagulants (4,5 modified)

	Dabigatran	Rivaroxaban	Apixaban
Target	IIa	Xa	Xa
Prodrug	Yes	No	No
Hours to C_{max}	2	2–4	1–3
Linear pharmacokinetics	Yes	No	Yes
Bioavailability	7%	80%	66%
Protein binding	35%	> 90%	87%
Half-life (h)	12–14	9–13	8–15
CYP metabolism	No	Yes (CYP3A4/A5, CYP2J2)	Yes (CYP3A4, CYP1A2, CYP2J2)
Efflux transporter P-gp	Yes	Yes	Yes
Renal elimination	80%	66% (33% cleared unchanged)	25%
Dosing	Twice a day	Once a day	Twice a day

substrate of the P-glycoprotein (P-gp) transporter. One-third of rivaroxaban is cleared unchanged via the kidneys and the remaining two-thirds are metabolized by the liver via CYP3A4/CYP3A5 and CYP2J2-dependent or independent pathways (one-third each, respectively). Apixaban which has predominant non-renal clearance is eliminated via the CYP3A4, CYP1A2 and CYP2J2-dependent pathways and intestinal excretion. Recommended dosage is twice daily for dabigatran and apixaban and once daily for rivaroxaban.

Phase III studies

The Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) was a randomized trial designed to compare two fixed doses of dabigatran (110 mg per bid and 150 mg per bid), each administered in a blinded manner, with open-label use of VKA in patients who had AF and were at an increased risk for stroke. The Rivaroxaban Once Daily (20 mg) Oral Direct Factor Xa Inhibition Compared with VKA for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) and the Apixaban (5 mg per bid) for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) were multicenter, randomized, double-blind, double-dummy, event-driven trials. The three studies were designed as parallel group, non-inferiority trials. NOA were considered non-inferior to warfarin if they had at least half of the effect-size of warfarin as compared with placebo. Based on a previously published meta-analysis [6], a very similar non-inferiority margin (Δ) was chosen (1.46 in the RELY and ROCKET AF, 1.44 in the ARISTOTLE study). Primary analysis was pre-specified to be performed in the per-protocol population in the ROCKET trial. Results are encouraging enough to predict a major shift in the treatment of these patients. In this review, we give a comparison of these three trials in what we think would be a guide to a critical evaluation and a rational choice of NOA.

Inclusion criteria

All the studies included patients with EKG-documented non-valvular AF. Patients with an EKG-documented atrial flutter were also included in ARISTOTLE study. At least one of the risk factors for stroke among those comprised in CHADS2 score (congestive heart failure, hypertension, older than 75 years, diabetes, stroke/transient ischemic attack) was a prerequisite for enrolment in the RELY and ARISTOTLE trials. In contrast, ROCKET-AF enrolled only patients at a moderateto high risk of a stroke (i.e. a CHADS2 score of 2 or more).

Exclusion criteria

As shown in Table 2, there were numerous exclusion criteria for entry in the RE-LY, ROCKET-AF and ARISTOTLE studies. Among them, the Apixaban study excluded only patients with an ischemic stroke within the previous 7 days, whereas in both the Dabigatran and Rivaroxaban studies patients were excluded if they had a disabling stroke within the previous 6 months or any stroke within the previous 14 days. Fibrinolytic treatment was not an exclusion criterion if used within 2 to 10 days before randomization in the Dabigatran and Rivaroxaban studies, respectively. All the studies excluded patients with a history of intracranial, intraocular, spinal, retroperitoneal or traumatic intra-articular bleeding. Gastrointestinal bleeding in the previous year and major surgery in the previous month were exclusion criteria in the Dabigatran and Rivaroxaban studies. Recent malignancy or radiation therapy and ulcer disease in the previous 30 days were exclusion criteria in the Dabigatran trial. Patients with severe renal impairment and those with hemoglobin (Hb) < 10–9 g dL^{-1} or a platelet count of less than 100 or 90×10^9 L^{-1} were excluded from all three trials. Patients with planned cardioversion, major surgery or invasive procedures were excluded in the Rivaroxaban study; no information whatsoever was provided in the other two trials. However, some recent data on successful cardioversion on Dabigatran treatment do exist in literature [7]. The concomitant use of dual anti-platelet agents was not allowed in the Rivaroxaban and Apixaban studies; moreover, the concomitant use of other drugs was not allowed in the rivaroxaban study. Pregnancy and lactating patients were excluded in all the studies. Finally, patients with liver disease were excluded in the Dabigatran and Rivaroxaban studies.

Table 2 Exclusion criteria

Conditions	Dabigatran	Rivaroxaban	Apixaban
Heart valve disorders	Excluded	Excluded	Excluded
Disabling stroke within the previous 6 months or any stroke within the previous 14 days	Excluded	Excluded	Not Excluded*
Increased risk of bleeding			
Surgery within the previous month	Excluded	Excluded	NR
History of intracranial, intraocular, spinal retroperitoneal or a traumatic intra-articular bleeding	Excluded	Excluded	Excluded
Gastrointestinal hemorrhage within the past year	Excluded	Excluded	NR
Ulcer disease in the previous 30 days	Excluded	NR	NR
Recent malignancy or radiation therapy	Excluded	NR	NR
Severe renal impairment: creatinine clearance less than 30 mL min^{-1}	Excluded	Excluded	Excluded†
Anemia (Hb $<$ 10 g dL^{-1}) or thrombocytopenia ($<$ 100–90 $\times$ 10^9 L^{-1})	Excluded	Excluded	Excluded
Planned cardioversion	NR	Excluded	NR
Indication for anticoagulation other than AF	Excluded	Excluded	Excluded
Major surgery or invasive procedure planned	NR	Excluded	NR
Simultaneous treatment with both aspirin and a thienopyridine	NR	Excluded	Excluded
Fibrinolytic treatment within 2–10 days	Excluded	Excluded	NR
Liver disease	Excluded	Excluded	NR
Pregnant and lactating patients	Excluded	Excluded	Excluded
Concomitant therapies	NR	Excluded‡	NR

NR, not reported; Hb, haemoglobin.
*Excluded only in the case of a very recent ischemic stroke (within 7 days).
†Creatinine clearance less than 25 ml min^{-1}.
‡Anticipated need for chronic treatment with a non-steroidal anti-inflammatory drug; Current or planned treatment with a strong inhibitor of cytochrome P450 3A4, such as ketoconazole or protease inhibitors; Treatment with a strong inducer of cytochrome P450 3A4, such as rifampin/rifampicin.

Comments

Exclusions may leave future patients with similar characteristics susceptible to unintended harm from an inappropriate generalization of trial results. In the ARISTOTLE study there were less stringent exclusion criteria as compared with the other trials. Thus, it is possible that the Aristotle trial did not exclude patients who may be more likely to represent the population treated in clinical settings with a better relationship between efficacy and effectiveness.

Characteristics of randomized patients

The characteristics of randomized patients in the experimental drug arm are described in Table 3. In contrast to the RE-LY and ARISTOTLE studies, patients in the ROCKET-AF study were at a higher risk of a stroke (mean CHADS2 score 3.48), were older and with a previous stroke or systemic embolism in more than 50% of cases. Moreover, diabetes and hypertension were more frequent among the enrolled patients in the ROCKET-AF study.

Comments

Interestingly, the mean body weight was high in all three trials and this is in line with the hypothesis that obesity is a risk factor for AF [8].

Primary end point

The primary efficacy outcome was a stroke (ischemic or hemorrhagic) or systemic embolism. The median duration of

Table 3 Characteristics of randomized patients in tested groups*

Risk factors	Dabigatran 110 mg N = 6015	Dabigatran 150 mg N = 6076	Rivaroxaban 20 mg N = 7131	Apixaban 5 mg N = 9120
Age (years)	71.4 ± 8.6	71.5 ± 8.8	73 (65–78)†	70 (63–76)†
Female gender (%)	35.7	35.8	39.7	35.5
Weight (Kg)	82.9 ± 19.9	82.5 ± 19.4	–	82 (70–96)†
BMI, median (IQR)			28.3 (25.2–32.1)	
Prior stroke or embolism (%)	19.9	20.3	54.9	19.2
Heart failure (%)	32.2	31.8	62.6	35.5
Diabetes (%)	23.1	23.4	40.4	25.0
Hypertension (%)	78.8	78.9	91.3	87.3
CHADS2 score (mean)	2.1 ± 1.1	2.2 ± 1.2	3.48 ± 0.94	2.1 ± 1.1

BMI, body mass index.
*Plus-minus values are means ± SD.
†Values are expressed as median (IQR).

the follow-up period was 2.0 years in the RELY study, 1.9 years in the ROCKET-AF study and 1.8 years in the ARISTOTLE study. Results for intention-to-treat population are shown in Table 4. Overall, all NOA resulted in being non-inferior to VKA in reducing stroke or systemic embolism in patients with AF. Dabigatran 150 mg and apixaban were superior to VKA. Among the patients in the VKA groups, the mean percentage of time spent in the therapeutic range (TTR) was 64% in RELY, 55% in ROCKET-AF and 62.2% in the ARISTOTLE study.

Comments

Rivaroxaban fared better when investigators analyzed only patients treated with the drug in an on-treatment superiority comparison ($P = 0.02$); however, in an intention-to-treat superiority analysis, rivaroxaban was not shown to be superior to warfarin owing to events occurring when switching to VKA at the end of the study. This might be related to the low half-life of rivaroxaban, that when suspended left patients unprotected against a stroke until VKA fully reached antithrombotic levels. On the other hand, most patients assigned to the VKA arm, had probably a therapeutic INR at the end of the study. We can argue that, like dabigatran and apixaban, rivaroxaban also did significantly better than warfarin in intention-to-treat analysis in the absence of this inconvenience. Notably, this poses a warning when there is the need to switch rivaroxaban to warfarin in clinical practice. Patients in the VKA arm of the ROCKET study had their INR in a therapeutic interval in a lower percentage of time: older high-risk patients were enrolled in this study with the vast majority affected by heart failure, a condition '*per se*' predisposing to a high INR variability.

The primary safety outcome

The primary safety outcome in the RE-LY and Aristotle studies was major bleeding defined according to the definition proposed by the International Society on Thrombosis and Haemostasis (ISTH) [9]. A composite of major and non-major clinically relevant bleedings was considered as a primary outcome in the ROCKET AF study [2]. A subcategory of major bleeding termed as 'life-threatening' bleeding was also set in the RE-LY trial [1]. The rate of major bleedings in the groups treated with VKA was rather consistent across the studies, ranging from 3.09% per year to 3.4% per year. In the Dabigatran vs. VKA study, major bleeding was significantly reduced (RR = 20%, $P = 0.003$) in the lower Dabigatran dose group and life-threatening bleedings was less frequent with both Dabigatran doses.

An important reduction of intracranial hemorrhages was recorded with both Dabigatran doses, with a risk reduction of 60% or more. In contrast, a significant increase in gastrointestinal bleeding was observed with the higher Dabigatran dose vs. VKA ($P < 0.001$) (Table 5). In the ROCKET-AF study no difference was detected for major and non-major clinically relevant bleedings (primary safety outcome) between the Rivaroxaban- and VKA-treated group; however, a significant increase in gastrointestinal bleeding and a significant lower rate of intracranial hemorrhages was recorded in the Rivaroxaban group. A significant reduction ($P < 0.001$) in both primary and secondary safety outcomes was documented in Apixaban- vs. VKA-treated subjects in the ARISTOTLE study. Particularly important was the reduction in intracranial hemorrhages (risk reduction > 50%).

Comments

Sub-analyzes focusing on specific aspects of the trial results have recently been published. As far as age is concerned, the risk of all major bleedings was lower with both doses of Dabigatran vs. VKA in patients aged < 75 years; in those aged ≥ 75 years both doses of Dabigatran fared better when the risk of intracranial bleeding was considered, but extracranial bleeding was similar or higher. [10]. The annual rates of major and intracranial bleeding increased significantly ($P < 0.001$) among all participants in association with increasing CHADS2 scores (from 0 to 1, 2, or 3 to 6); this significant increase was present for both experimental drug doses for major bleeding and only for the higher dose for intracranial bleeding [11].

Lower rates of total bleeding were reported from participating centers that had lower TTR levels of the VKA-treated group; these results are attributed by the investigators to a possible underdosing or poor compliance at sites with lower TTR or more meticulous recording of bleedings at sites with better TTR [12]. It is evident that more elderly patients were present in the ROCKET-AF study and especially that this study included more severe patients, as shown by the high number of those with a $CHADS_2 \geq 3$, with a previous stroke or transient ischemic attack and with concomitant aspirin use. The importance of increasing age (especially ≥ 75 years) and a

Table 4 Primary outcome (intention-to-treat population)

	No./100 patient-year	Relative risk (95% CI)	Noninferiority (*P*)	Superiority (*P*)
Dabigatran 110	1.53	0.91 (0.74–1.11)	< 0.001	0.34
Dabigatran 150	1.11	0.66 (0.53–0.82)	< 0.001	< 0.001
Warfarin	1.69			
Rivaroxaban	2.1	0.88 (0.75–1.03)	< 0.001	0.12
Warfarin	2.4			
Apixaban	1.27	0.79 (0.66–0.95)	< 0.001	0.01
Warfarin	1.60			

Table 5 Bleeding complications recorded in the phase III clinical trials

Trial	Safety outcomes (bleeding) % (years)				Hazard ratio; *P*-value		
RE-LY		D 110	D150	W	D 110 vs. W	D 150 vs. W	D 150 vs. D 100
	Major	2.71	3.11	3.36	0.80; 0.003	0.93; ns	1.16; 0.052
	Life threatening	1.22	1.45	1.80	0.68; < 0.001	0.81; 0.04	1.19;ns
	Intracranial	0.23	0.30	0.74	0.31; < 0.001	0.40; < 0.001	1.32;ns
	Gastrointestinal	1.12	1.51	1.02	1.10; ns	1.50; < 0.001	1.36; 0.007
	Minor	13.16	14.84	16	0.79; < 0.001	0.61; 0.005	1.16;< 0.001
ROCKET			R	W	R vs. W		
AF	Primary safety outcome		14.9	14.5	1.03; ns		
	Major		3.6	3.4	1.04; ns		
	Intracranial		0.5	0.7	0.67; 0.02		
	Gastrointestinal		3.1	2.2	1.46;< 0.001		
	Non-major clinically relevant		11.8	11.4	1.04; ns		
ARISTOTLE			A	W	Hazard ratio; *P*-value A vs. W		
	Primary (major)		2.13	3.09	0.69; < 0.001		
	Intracranial		0.33	0.80	0.42; < 0.001		
	Secondary (major and non-major clinically relevant)		4.07	6.01	0.68; < 0.001		

vs., versus; D, dabigatran; R, rivaroxaban; A, apixaban; W, warfarin; Asp, aspirin; Cr, creatinine; CrCl, creatinine clearance; *p*-values are reported for underlined results.

high $CHADS_2$ score (especially ≥ 3) on the risk of either thrombotic or hemorrhagic complications in this patient setting was recently confirmed by two subgroup analyzes of the RE-LY trial [10,11]. From a clinical point of view it would be better to avoid dabigatran and rivaroxaban in patients with a history of gastrointestinal disorders or patients taking antiplatelet drugs or the chronic use of non-steroid anti-inflammatory drugs. Apixaban can be used in these patients while a preference for rivaroxaban should be given in patients without gastrointestinal disorders and a high CHADS2 score as they were specifically tested in the ROCKET-AF trial.

Death from any cause

A reduction in mortality from any cause (Table 6) is noticeable in all the three studies and it is significant in the ARISTOTLE trial. However, an absolute risk reduction is similar in all the trials (0.38%; 0.49; 0.4; 0.42 for Dab 110, Dab 150, Rivaroxaban and Apixaban, respectively) with around one death avoided every 250 treated patients.

Side effects

No significant alterations in liver enzymes (aspartate transaminase/alanine transaminase) were observed across different studies. Dabigatran, but not Rivaroxaban or Apixaban, is associated with a significant increase in gastrointestinal disorders. Dyspepsia, nausea, upper abdominal pain and diarrhoea were the most common side effects reported during the 2 years follow-up in the RE-LY trial, with both 150 mg and 110 mg twice daily dosages as compared with VKA (11.8%, 11.3% and 5.8%, respectively); this brought a higher rate of drug discontinuation (2.2%, 2.1% and 0.6%, respectively; $P < 0.001$) [1]. The presence of dyspepsia may depend on the increased acidity as a result of tartaric acid in the Dabigatran capsules. In the RE-LY trial, a clinical myocardial infarction (MI) was significantly more frequent in Dabigatran 150 mg twice daily compared with VKA (0.74% vs. 0.53%; $P = 0.048$), showing a trend towards significance in Dabigatran 110 mg (0.72% vs. 0.53%; $P = 0.07$) [1]. A subsequent analysis including four previously unreported clinical MI and 28 silent MI concluded that there was a non-significant increase in MI with Dabigatran 150 mg per bid compared with VKA [13]. Recently, a meta-analysis of the seven trials comparing Dabigatran with VKA, enoxaparin and placebo in different clinical settings showed an increased relative risk (27–33%) of MI among all Dabigatran-treated patients [14]. No statistical differences in side effects as compared with VKA were demonstrated in the ROCKET-AF and ARISTOTLE trials (published as supplementary appendix of the original investigations).

Table 6 Death from any cause across the studies

			% per year			
Clinical Events	Study	Drugs	NOA	W	Relative risk (95% CI)	*P*-value
Death from any cause	RE-LY	Dabigatran 110	3.75	4.13	0.91 (0.80–1.03)	0.13
		Dabigatran 150	3.64	4.13	0.88 (0.77–1.00)	0.051
	ROCKET-AF	Rivaroxaban	4.5	4.9	0.92 (0.82–1.03)	0.15
	ARISTOTELE	Apixaban	3.52	3.94	0.89 (0.80–0.99)	0.047

Comments

Before prescribing NOA, it might be appropriate to take into account both specific drug side-effects and individual patient characteristics. A clinical follow-up of patients taking dabigatran is mandatory to avoid drug discontinuation in relation to gastrointestinal side-effects. As VKA are effective in the secondary prevention of MI, they may be considered together with the novel anti-Xa oral anticoagulants as a first choice in patients with a previous MI or known coronary artery disease [14]. Post marketing monitoring will shed light over this issue.

Quality of the studies

Table 7 reports the study design, number of subjects lost to follow-up and withdrawals in the published phase III studies comparing NOA with VKA. All studies had adequate randomization, provided by a computerized voice response system. Contrary to the double-blind, double-dummy ARISTOTLE and ROCKET trials, RE-LY had an open-label design in which both patients and physicians were aware of the investigational drug. This latter study is therefore slightly more prone to observer bias, which may artificially increase the efficacy of a new treatment up to 17% higher [15,16].

All studies had a very limited and negligible number of subjects lost to follow-up (0.11–0.48% of all enrolled subjects). In all studies and in all treatment arms, there were significant numbers of subjects not completing the scheduled study observation time. Across all studies, the mean proportion of patients leaving the investigational treatment was 23.0% and 22.8% in patients on VKA ($P = 0.63$); however, the odds of leaving treatment were significantly different within each treatment arm in each individual study. Only the RE-LY trial fully reported the reasons for patient drop-out.

One of the clinically more relevant issues is subgroup analysis, that is, however, prone to both type I and II errors. First, all subgroup analyzes should be pre-specified to control for multiple comparisons ('fishing' effect). Second, subgroup analysis should be done only for the adequate sub-sample size, accounting for the expected low rate of events. For instance, given an incidence of major endpoints around 1–2% per year, a subgroup of less than a thousand individuals is expected to have around 15 events, resulting in very imprecise estimates. Both the ARISTOTLE and ROCKET trials, but not the RE-LY, did pre-specify some subgroup analysis in the study protocol. The ROCKET trial reported more subgroups analyzes than those specified in the study protocol, sometimes with an inadequate subgroup size.

Comments

The quality of evidence from the published phase III studies is indisputably high, with a low number of withdrawals and follow-up losses. However, the RE-LY trial had a lower Jadad score because of its open-label design [17], and a possible (although small) overestimate of a drug effect could not be excluded for dabigatran.

Specific issues

Renal function

Renal impairment can influence the balance between the safety and efficacy of NOA. They have different renal elimination (see Table 1) and this issue may affect the choice of a specific agent. Dabigatran is almost exclusively eliminated by the kidney and its pharmacokinetic properties are clearly affected by renal failure. After oral administration of a single dose of 150 mg, the areas under the plasma concentration-time curve (AUC) were 3.2- and 6.3-fold higher in subjects with moderate (creatinine clearance 30–50 mL min^{-1}) and severe renal impairment (creatinine clearance < 30 mL min^{-1}), as compared with the values in healthy subjects [18]. In subjects with severe renal impairment, the mean terminal elimination half-life was doubled (28 vs. 14 h for control) [18]. Thus, exposure to Dabigatran is increased by renal impairment and correlates with the severity of renal dysfunction. As a consequence, the drug requires dose adjustment in patients with moderate renal impairment and is contraindicated in those with severe renal insufficiency [19,20]. These last patients were not included in the phase III RE-LY study [1]. In spite of a dose reduction, drug accumulation and overdose were reported in elderly patients with a low body weight and moderate renal insufficiency leading to severe and fatal bleeding complications [21]. For patients with stage 4 Chronic Kidney Disease (creatinine clearance < 30 mL min^{-1}), dose adjustment to 75 mg twice daily is recommended by the Food and Drug Administration on the basis of pharmacokinetic and pharmacodynamic considerations more than safety or efficacy data [22]. However, other regulatory boards, including the European Medicine Agency, issued a recommendation on the 110 mg twice-daily dose for use on an individual basis and at the physician's

Table 7 Study design, number of subjects lost to follow-up and withdrawals

	Study design	Lost to follow-up *N* (%)	Discontinuation % before end of study			Jadad scale
			NOA	VKA	*P*	
Dabigatran 110 mg vs. warfarin	Open-label	20 (0.11)	20.7	16.6	< 0.0001	3
Dabigatran 150 mg vs. warfarin	Open-label	20 (0.11)	21.1	16.6	< 0.0001	3
Rivaroxaban vs. warfarin	Double-blind	32 (0.22)	23.7	22.2	0.03	4
Apixaban vs. warfarin	Double-blind	69 (0.48)	25.3	27.5	0.001	4

discretion in patients with low thromboembolic and high bleeding risks [23].

Rivaroxaban and Apixaban excretion is only partly dependent on renal function (Table 1) and the risk of drug accumulation in patients with renal insufficiency is lower than that observed with Dabigatran. Both drugs can be administered at fixed doses in patients with moderate renal impairment [24,25]. Importantly, severe renal disease was an exclusion criterion from the trials comparing these drugs with VKA in patients with AF [2,3].

Comments The following practical recommendations can be given: (i) renal function should be evaluated in all patients before choosing one of the NOA [19,20,25]; (ii) in patients with moderate renal impairment (creatinine clearance 30–50 mL min^{-1}) Dabigatran should be given at a reduced dose (110 mg per bid) and renal function monitored during treatment every 6 months; Rivaroxaban, Apixaban or VKA are probably safer options, particularly in elderly patients with a low body weight [21]; (iii) in patients with severe renal impairment (creatinine clearance < 30 mL min^{-1}) NOA should not be given.

Elderly patients

Patients aged ≥ 75 years were 40.1%, 43.1% and 31.2% in RELY, ROCKET AF and ARISTOTLE, respectively. Data analysis in age subgroups of the above-mentioned trials are limited (Table 8). Data of the RE-LY trial were examined in detail in relation to age; a highly significant interaction between age and major bleeding was found (see above) [10]. In the ROCKET-AF study, the efficacy and safety of rivaroxaban appears to be consistent across ages, although, to our knowledge, no detailed analysis on elderly people has emerged so far. Apixaban was shown to be superior to VKA in the ARISTOTLE trial and no interaction with age was reported for the efficacy outcome and major bleeding.

Comments The mean age of patients enrolled in the published trials is lower than that reported in observational studies performed in routine practice [26,27]. Renal function declines with age and a creatinine clearance reduction of about 1 mL min^{-1} per year after the age of 40 years is estimated. It is known that a large proportion of elderly AF patients have severe or moderate renal impairment [28]. It was estimated that a 97-year-old patient taking Dabigatran etexilate has an approximately 11.5% increase in the plasma concentration-time curve at the steady state as compared with a 72-years-old patient [29]. Since the duration of anticoagulant treatment in patients with AF is life long, the progressive decline in renal function needs to be considered. Moreover, elderly patients are more frequently prone to acute episodes of intercurrent diseases, such as infections or heart failure, that are commonly associated with a rapid worsening of the renal function. This issue should be carefully evaluated in patients treated with NOA, particularly Dabigatran that is mainly cleared via the kidneys. The European Medicines Agency and the Canadian Health Authority approved Dabigatran for the prevention of stroke and systemic embolism in patients with AF at the dose of 150 mg bid and at the dose of 110 mg bid for elderly patients aged > 80 years and for patients at a higher risk for bleeding.

Conclusion

The large Phase III clinical trials of NOAs in the prevention of stroke and peripheral embolism in patients with AF showed that they are not inferior to warfarin and even superior (dabigatran 150 mg bid and apixaban 5 mg bid). This does not mean that all NOAs are equivalent as the choice of the new drug depends on many other considerations. In Table 9 we list the strengths and weakness of NOAs that could help in choosing a specific drug. For instance, in a 66 years of age hypertensive patient with normal renal function and a low risk of bleeding, dabigatran 150 mg bid or apixaban may be chosen as in phase III trials both significantly reduced the primary efficacy end point as compared with warfarin. In a similar patient with moderate renal insufficiency (creatinine clearance 30–50 mL min^{-1}) or an increased risk of bleeding dabigatran 110 mg bid or apixaban 5 mg bid could be the choice. In high-risk elderly patients with a previous stroke or congestive heart failure or recent acute coronary syndrome, rivaroxaban might be preferred as it was used in this clinical setting and it was recently shown to reduce major cardiovascular events in the ATLAS ACS 2- TIMI 51 study [30]. Moreover, rivaroxaban may be considered in patients with expected poor compliance as it is administered once daily. On the other hand, in

Table 8 Efficacy and safety outcome (expressed as rate % per years) in patients aged ≥ 75 years in the trials with the new oral anticoagulants compared with warfarin

	Tested drug	Efficacy outcome (% per year) Tested drug	Efficacy outcome (% per year) warfarin	Safety outcome (% per year) Tested drug	Safety outcome (% per year) warfarin
RE-LY	Dabigatran 110 mg bid	1.89	2.14	4.43	4.37
	Dabigatran 150 mg bid	1.43	2.14	5.10	4.37
ROCKET AF	Rivaroxaban	2.67	4.03	25.78*	23.43*
ARISTOTLE	Apixaban	1.6	2.2	3.3	5.2

*Major and clinically relevant non major bleeding.

Table 9 Strengths and weaknesses of novel oral anticoagulants (NOA) for stroke prevention in atrial fibrillation (AF)

	Strengths	Weaknesses
Dabigatran 150	Less stroke/systemic embolism Less life-threatening bleeding Less intracranial bleeding Less drug interaction (no cytochrome metabolism) Less protein binding (dialyzable)	No antidote More bleeding in elderly > 75 years of age and at increasing CHADS2 score GI bleeding GI side effects Possible (although small) increase in myocardial infarction Predominant renal excretion Tested in low risk population
Dabigatran 110	Less major bleeding Less life-threatening bleeding Less intracranial bleeding Probably few drug interaction (no cytochrome metabolism) Less protein binding (dialyzable)	No antidote GI side effects Tested in low risk population
RIvaroxaban	Robust design of phase III study Once daily (better compliance) Predominant non renal excretion Effective in elderly and high risk patients Less intracranial bleeding	No antidote Possible reversal by prothrombin complex concentrates [31] GI bleeding Possible drug interaction (via cytochrome metabolism)
Apixaban	Robust design of phase III study Less stringent exclusion criteria Less stroke/systemic embolism Predominant non renal excretion Less intracranial bleeding Reduction in total mortality	No antidote Tested in low risk population Possible drug interaction (via cytochrome metabolism)

patients on multiple medications, dabigatran might be considered in light of its less drug interactions (no cytochrome metabolism). In patients with previous gastrointestinal bleeding or dyspepsia, apixaban should be considered as the first choice. In very elderly patients with declining renal function either apixaban or rivaroxaban may be preferred or warfarin in case of severe renal insufficiency. These are just examples; however, further research to enhance our knowledge on the new drugs is mandatory. In this respect, the extension of the RE-LY study (RELY-ABLE trial [32]) will give us more information on the long-term safety of this new agent.

Addendum

All authors gave a substantial contribution to concept and design of this review.

Disclosure of Conflict of Interest

The authors state that they have no conflict of interest.

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