Review Article

Novel Oral Anticoagulants in Atrial Fibrillation: Will the Benefit Outweigh the Cost?

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Over the last fifty years, the standard anticoagulant therapy for the prevention of stroke in patients with atrial fibrillation (AF) has been vitamin K antagonists. Warfarin, their main representative, is one of the most commonly prescribed drugs. In the USA around two million people start taking warfarin every year. The limitations of this treatment are well known: the narrow therapeutic window, the large variation in response, the interactions with other drugs and foods, and the need for regular blood monitoring and dose adjustments. The consequences of these limitations, in combination with the fear of haemorrhage, are its under-use (only two thirds of eligible patients receive therapy), inadequate control of the international normalised ratio (INR) (correctly controlled in less than half of the cases), and the frequent interruption of treatment.[1] Warfarin is the second most common pharmaceutical cause of a visit to the emergency department, and the most common reason for telephone contact with the treating physician. Thus, any prospect of more convenient, more effective, and safer therapies in this area is always welcome.[2]

Dabigatran, rivaroxaban and apixaban are three new oral anticoagulants with a different mode of action from that of warfarin. The first is a direct factor IIa (thrombin) inhibitor and the other two are direct factor Xa inhibitors. Substantial experience of these new substances—albeit short term—has been acquired from their perioperative use in orthopaedic surgery and from the treatment of acute thrombophlebitis.[3-5]

The value of these new drugs in AF was evaluated in three large, randomised clinical trials: Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY), Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF), and Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE).[6-8] After the approval of dabigatran for patients with non-valvular AF, physicians who were called upon to prescribe it became seriously concerned about the matter of cost. The purpose of this short review is to describe and comment on the results of the clinical trials in a way that will help the physician to relate their findings to daily clinical practice, also taking into account the cost, when it comes to the correct choice of anticoagulant drug in the patient with AF.

The standard warfarin treatment was compared in the RE-LY trial[6] with two dosing regimens of dabigatran (110 mg or 150 mg twice daily), in the ROCKET-AF trial[7] with rivaroxaban (20 mg once

daily), and in ARISTOTLE[8] with apixaban (5 mg twice daily). The comparison involved patients who had non-valvular AF of 6 months' duration and one or more risk factors for a thromboembolic episode. All three studies had the same endpoints: for effectiveness, stroke (ischaemic and haemorrhagic) and/or any systemic embolism; and for safety, haemorrhage. The clinical characteristics of the patients in the three studies were the same, apart from slight differences (Table 1), with the patients in the ROCKET-AF trial being at highest risk. Optimal control of INR (range 2.0-3.0) was achieved in 67% of patients in the RE-LY trial and in 57.8% in the ROCKET-AF trial.

Table 2 shows the annual rate of events (stroke and systemic embolism) and haemorrhages in the three trials.

Comments

Although dabigatran and apixaban significantly reduced the thromboembolic episodes (mainly haemorrhagic stroke), the reduction was not very great, while rivaroxaban was proved to be non-inferior to warfarin. All three drugs had a lower incidence of haemorrhage, especially intracranial, than warfarin, although in RE-LY and ROCKET-AF a greater incidence of gastrointestinal bleeding was observed (Table 2). An analysis of ARISTOTLE, which reported the most beneficial results from the new anticoagulant, showed that treating 1000 AF patients with apixaban for 1.8 years would prevent 6 strokes (4 haemorrhagic), 15 haemorrhages and 8 deaths. All three new drugs have the advantage that they do not require laboratory monitoring of coagulation parameters. A subgroup analysis of the RE-LY trial showed that dabigatran was neither superior nor inferior to warfarin in patients with a history of stroke ($CHADS_2$ Score ≥3).[9] The annual incidence of thromboembolic episodes in patients with a history of stroke was 2.32% and 2.07% in the groups taking 110 and 150 mg dabigatran (twice daily), respectively, and 2.78% in the warfarin group. As regards haemorrhagic complications, a significantly lower rate was observed in the dabigatran 110 mg group, while in the 150 mg group the rate was the same as for warfarin. Another subgroup analysis evaluated the endpoints of the RE-LY trial in relation to the mean time in the therapeutic range (TTR) of INR at all centres. The findings confirmed the initial findings of the superiority of the 150 mg dose and the non-inferiority of the 110 mg dose compared to warfarin, independently of the quality of the INR regulation.[10] For all vascular events, non-haemorrhagic events and mortality, the advantages of dabigatran were greater in centres with poor INR regulation than in those with good INR regulation. As far as age was concerned, in another subgroup analysis both the dabigatran dosage regimens had a lower risk of haemorrhage (intra- and extracranial) than warfarin in the 10,855 patients aged below 75 years.[11] In contrast, for the 7258 patients aged 75 years or over in-

Table 1. Clinical characteristics of patients with atrial fibrillation (AF) in three large randomised trials.

(% / year)	RE-LY (n:18,133)	ROCKET-AF (n:14,264)	ARISTOTLE (n:18,201)
Age (years)	71.5	73	70
Women (%)	37	40	35
>75 years (%)	40		31.2
Treatment duration (years)	2	1.9	1.8
Paroxysmal (%)	32.1	17.6	15.4
History of stroke (%)	20	55	19.5
$CHADS_2$ score	2.1 ± 1.1	3.48 ± 0.95	2.1 ± 1.1

Table 2. Annual rate of events and haemorrhages in the three trials.

(% / year)	RE-LY			ROCKET-AF		ARISTOTLE	
	D 110	D 150	W	R	W	A	W
Stroke or embolic event	1.53	1.11	1.69	2.12	2.42	1.27	1.60
Major haemorrhages	2.71	3.11	3.36	3.4	3.6	2.13	3.09
Intracranial haemorrhages	0.23	0.30	0.74	0.49	0.74	0.33	0.80
Gastric haemorrhages	1.12	1.50	0.9	3.2	2.2	0.76	0.86

D – dabigatran; R – rivaroxaban; A – apixaban; W – warfarin.

tracranial haemorrhages were fewer but extracranial haemorrhages were the same or more, for both dabigatran dosage regimens in comparison with warfarin.[11]

The main side effect of dabigatran is dyspepsia. The dropout rates for dabigatran and warfarin in the RE-LY trial were 21% and 17%, respectively.

One disadvantage of all three drugs is the lack of an antidote in the case of haemorrhage. However, the short half-life (8-12 hours) makes them useful in cases of haemorrhage or urgent surgical procedures, since their action wears off at 24 hours. Dabigatran can also be an alternative to warfarin in the case of conversion of AF to sinus rhythm. Although dabigatran has not been studied in a prospective randomized trial to assess the drug's safety and efficacy related to cardioversion procedures, cardioversion on the study drug was permitted during the RE-LY trial. From an analysis of this trial we have data regarding 1983 cardioversions (1657 electrical) in 1270 patients.[12] The incidence of stroke and large haemorrhages at 30 days after cardioversion was low compared to that of warfarin, independently of the use or not of transoesophageal echocardiography. More specifically, for the two dabigatran dosage regimens, 110 mg and 150 mg, and warfarin, the incidence of stroke was 0.8%, 0.3% and 0.6%, and of haemorrhages 1.7%, 0.6% and 0.6%, respectively.

The RE-LY study excluded patients if their creatinine clearance (CrCl) was less than 30 mL/min. Although the FDA approved a dose of 75 mg twice a day for patients with CrCl in the 15-30 mL/min range, they made no recommendations if the CrCl was less than 15 mL/min or if the patient was getting dialysis. Many clinicians are reluctant to use warfarin in patients with renal failure because of concerns about bleeding and the risk of valvular calcification. Since dabigatran is eliminated mainly by the kidneys, dose adjustment is necessary in patients who have renal dysfunction. In patients with CrCl <30 mL/min the recommended dose is 75 mg twice per day. For rivaroxaban, two thirds are metabolised in the liver via cytochrome CYP3A4, without the creation of active metabolites, and the remaining one third is eliminated unchanged by the kidneys. Apixaban is partly metabolised by CYP3A4; 75% of the drug is excreted in stools and 25% in the urine. All three trials excluded patients with CrCl <30 mL/min, whereas in the ROCKET AF study the daily dose of rivaroxaban was reduced from 20 to 15 mg in patients with a CrCl of 30-49 mL/min.

The results from a substudy of ROCKET-AF in subjects with moderate renal impairment have been reported.[13] Compared with patients with CrCl <50 mL/min (mean age 73 years), the 2950 (20.7%) patients with CrCl 30-49 mL/ min were older (79 years) and had higher event rates irrespective of study treatment. Among those with CrCl 30-49 mL/min, the primary endpoint of stroke or systemic embolism occurred in 2.32 per 100 patient-years with rivaroxaban 15 mg/day vs. 2.77 per 100 patient-years with warfarin. Intention-to-treat analysis yielded similar results to the per-protocol results. Rates of the principal safety endpoint (major and clinically relevant nonmajor bleeding: 17.82 vs. 18.28 per 100 patient-years; p=0.76) and intracranial bleeding (0.71 vs. 0.88 per 100 patient-years; p=0.54) were similar with rivaroxaban or warfarin. Fatal bleeding (0.28 vs. 0.74% per 100 patient-years; p=0.047) occurred less often with rivaroxaban.

The aim of a subgroup analysis from the RE-LY study was to evaluate the prognostic importance of $CHADS_2$ risk score in patients with AF who received oral anticoagulants.[14] Higher $CHADS_2$ scores were associated with increased risks for stroke or systemic embolism, bleeding, and death in these patients. In patients with different baseline risks for stroke as defined by using the $CHADS_2$ score, dabigatran, 150 mg twice daily, was consistently and significantly associated with lower annual rates of stroke or systemic embolism and of intracranial haemorrhage than warfarin. The net benefit of dabigatran (in terms of the sum of the lower rates of stroke, systemic embolism, and intracranial haemorrhage) increased from 0.77% per year in persons with $CHADS_2$ scores of 0 or 1 to 1.4% per year in those with $CHADS_2$ scores of 3 or higher.

Although the subgroup population analyses should be interpreted with care and caution, they are nevertheless useful for identifying groups that might benefit or be harmed by one or the other therapy.

Before the era of the new anticoagulants, information about the cost of AF was available from the EuroHeart Survey, which was carried out during 2003-2004.[15] In Greece, the costs of admission and/or one-year follow up were calculated as €1363 and €1507, respectively. In the European Union it is estimated that AF costs €6.2 billion per year, which is equivalent to €1500-3200 per patient per year. Table 3 shows the annual and total cost from five EU countries.[15]

A recent systematic analysis of the financial burden of AF that was carried out for the time period 1990-2009 showed that hospitalisations were responsible for the largest part of the cost.[16] The costs and the hospitalisations because of AF have shown an in-

Table 3. Annual and total cost of treating atrial fibrillation in five countries of the European Union.

	Annual cost (€/patient)	Total cost (€ million)
Greece	1507	272
Italy	3225	3286
Poland	1010	526
Spain	2315	1545
Netherlands	2328	554

creasing trend during the last decades and are expected to increase in the future because of the ageing of the population.

We observe that AF is costly; hence the main obstacle to the use of the new anticoagulants will be an exacerbation of the cost. The annual cost of dabigatran therapy in Greece is estimated at €1680 ($3000 in the USA, $4000 in Canada), while the cost of Coumadin is €50-150 per annum (€12 for the drug and the rest depending on where the INR measurements are made).

Cost-effectiveness analyses in the USA using a Markov model, where the cost of treatment, all events, and hospitalisations are taken into account, have shown that dabigatran can be superior to warfarin in certain cases. An analysis of patients aged over 65 years with AF of non-valvular aetiology who were at high risk of stroke ($CHADS_2$ Score ≥1) showed that dabigatran may be more cost-effective than warfarin, depending on the daily cost of dabigatran.[17] Another similar analysis showed that, in patients at high risk of haemorrhage or stroke ($CHADS_2$ Score ≥3), dabigatran in a dosage of 150 mg twice daily had a greater benefit than warfarin in patients whose INR control was not ideal (TTR>76%). In contrast, warfarin was superior in moderate risk patients with AF when the INR control was assumed to be inadequate (TTR<57.1%).[18]

In another cost-effectiveness study in the UK, Pink and colleagues assessed the incremental costs and benefits of dabigatran versus warfarin in patients with non-valvular AF.[19] On the basis of their data, if all British patients with AF took dabigatran, expenditures related to stroke and warfarin monitoring would diminish. These and other studies[20] have found that dabigatran was likely to be cost effective for patients at high risk of stroke ($CHADS_2$ score of 3 or more) unless INR control was excellent. For example, at a $CHADS_2$ score of 3, Pink and colleagues calculated a cost of GBP 15,895 per quality adjusted life year (QUALY) for centres with average INR control. In contrast, all studies found that the cost per QUALY gained was high in patients at low risk of stroke.

To calculate the cost in Greece some peculiarities must be taken into consideration. The cost of the drug is set by the insurance funds (with 25% patient contribution), but in the case of INR control the patient bears the cost of travel (usually accompanied), since there is no free public transportation (such as ambulance service). The amount the patient has to pay depends on the distance from the follow-up centre, the type of centre (hospital, private clinic), and the means of transport (private, public transport, taxi). If the patient is 50 km from the examination centre a taxi costs €50-100 (depending on the waiting time). Few hospitals have outpatient departments for monitoring anticoagulant therapy and few health care centres have the capability of measuring INR. Usually, the patients do not get the results the same day and must call their doctor for the dose adjustment (it is not unusual for it to take three working days). This discourages the patient from monitoring INR regularly (once per month), resulting in poor regulation. It should be noted that even in clinical trials with close monitoring of INR, the rate of good regulation does not exceed 60%.[6,7] Measuring INR at home could be an alternative solution.

Dabigatran and rivaroxaban have received FDA approval and the European guidelines for AF already recommend dabigatran as an alternative treatment. The recommended dosage is 150 mg × 2 for patients at low risk of haemorrhage and 110 mg × 2 for patients at high risk (HAS BLED score >2).

Atrial fibrillation is responsible for 15% of total strokes and the number of thromboembolic episodes in the USA has been estimated at about 75,000 annually. The corresponding number for Greece should be about 2500-3000. Two thirds of these episodes could be prevented by the administration of anticoagulant medication. Therefore, the first concern of treating physicians should be to prescribe anticoagulant drugs, since they are responsible for non-administration. Clinical decision making about the kind of anticoagulant medication is guided by the expected benefit, the risks, the cost, and the patient's preferences. The newer drugs represent great progress in anticoagulation medication. Presently, however, in a period when health care provision is undergoing a crisis and economic prospects are uncertain, their high cost is the factor that inhibits their widespread use. Thus, we are waiting for a reduction in their price and the accumulation of greater clinical experience that can be

gleaned from their use outside clinical trials. This will surely lead to more generalised use. If, however, we would like to use them more selectively at the present time, the new drugs are ideal for patients in whom correct INR regulation has proved difficult, or for patients who do not have access to regular laboratory tests. Patients who are already on coumarins and have good INR control will gain a smaller benefit from a change to the new generation of anticoagulant drugs.

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