STATE-OF-THE-ART

New Anticoagulants in the Treatment of Atrial Fibrillation in 2011

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In the last 60 years antivitamin K antagonists (AVK) represented the only effective medication for long-term treatment of venous thromboembolism (VTE) and stroke prevention in valvular and non-valvular atrial fibrillation (AF). Although effective, the anticoagulant effect of AVK is non- predictable, with narrow therapeutic window (INR between 2 and 3 in non-valvular AF) and has multiple interactions with drugs and food requiring repeated laboratory monitoring of the coagulation parameters (INR). In addition, resistance to AVK is registered in about 10% of cases. Extensive research over the last 5-10 years on the processes of thrombosis, both arterial and venous, focused on two major factors of the anticoagulation cascade: factor X and activated factor II (FII and FXa). They have become therapeutic targets. At present, three new molecules (dabigatran, rivaroxaban, apixaban) have extensive research programs and are in various moments of approval by the FDA (Food and Drug Administration) and EMA (European Medicine Agency, the new name of EMEA).

Currently, the indication for antithrombotic treatment in AF is determined in relation with the risk for stroke (risk stratification) by using CHA2DS2 or CHADS2-VASc risk scores. The risks of bleeding is determined by HAS-BLED bleeding score; recently it has been shown that embolic risk scores (CHADS2 and CHA2DS2-VASc) are useful also for determining the risk of hemorrhage (approx. 2%/year for major bleeding in patients treated with AVK). Recommendations for thromboprophylaxis in AF have been recently updated in the recent Atrial Fibrillation Management Guide (ESC 2010) (1).

F II inhibitors in the treatment of AF

Oral dabigatran etexilate is the pro-drug of dabigatran, a small molecule that acts as direct thrombin inhibitor, while blocking specifically and reversible the activity of free thrombin during thrombus formation. Unlike the anticoagulant effects of AVK by means of coagulation factors (II, VII, IX and X, proteins C and S), dabigatran acts as an anticoagulant through a direct effect on thrombin. On the other hand,

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selectively inhibiting thrombin, dabigatran preserves other hemostatic mechanisms from the coagulation cascade.

RE-LY (Randomized Evaluation of Long-term anticoagulant therapy), a Phase III clinical trial, brings convincing evidence of efficacy and safety of dabigatran compared to warfarin in patients with non-valvular AF (2). The multicenter randomized trial enrolled 18,113 patients with AF (900 centers, 44 countries, including Romania). Patients were randomized to receive either dabigatran etexilate, two doses, 110 mg bid or 150 mg bid, or warfarin (dose adjusted to maintain an INR between 2.0 and 3.0). The average duration of follow-up was 2 years. The primary endpoint was time to first embolic event (stroke or systemic embolism).

The study results can be summarized as follows:

1. Reduction of risk of stroke and systemic embolism: 1.53% / year for dabigatran 110 mg x 2, 1.11% for dabigatran 150 mg x 2 and 1.69% for warfarin. Both doses of dabigatran were non inferior to warfarin (p <0.001), while the dose of dabigatran 150 mg x 2 was superior to warfarin, with a 34% reduction in embolic events (p <0.001).
2. The rate of major bleeding was 3.96% / year for warfarin, 2.71% / year for dabigatran 110 mg bid and 3.11% / year for dabigatran 150 mg bid. Major bleeding was significantly less frequent in the low dose dabigatran group (-20%) (p = 0.003).
3. Incidence of hemorrhagic stroke compared to warfarin was lower for the low dose of dabigatran (-69%) and even lower (-74%) for the high dose of dabigatran (p <0.001);
4. Total mortality in the high-dose dabigatran (150 mg bid) was reduced by 12% (p = 0.051) and vascular mortality by 15% (p = 0.04).

In summary, the RE-LY study concluded that dabigatran, administered at a dose of 150 mg x 2/zi compared with warfarin was associated with a lower rate of stroke and systemic embolism, at a similar rate of major bleeding. A slight increase in gastrointestinal bleeding (only high dose of dabigatran), with a significant reduction in intracranial bleeding was also observed.

A predefined sub-study from RE-LY analyzed the effect of association of antiplatelet medication to the anticoagulation therapy. Adding a dose of Aspirin has generated a significant increase in bleeding in all 3 randomized groups (x 1.6, p <0.05). Unfortunately only 10% of the total number of patients enrolled in the main study was included in this sub-study providing a low statistical power.

From PETRO (3) and RE-LY studies we learned some elements of safety and side effects:

1. In the RE-LY study approx. 20% of patients discontinued dabigatran due to poor tolerance.
2. Dyspepsia was the main cause of discontinuation, likely due tartaric acid found in the tablet.
3. In patients with renal dysfunction (CrCl ≤ 50 ml/min) the dose of dabigatran should be reduced, given the rate of excretion via kidneys of 80%. FDA approved for safety reasons (probably excessive), the dose of 75 mg bid in patients with renal dysfunction, although in RE-LY dabigatran demonstrated efficacy and safety for doses of 110 mg bid.
4. Liver functions were not affected by dabigatran, tranaminase level not exceeding three times the upper normal values.
5. Dabigatran does not interact with cytochrome P450 (or with drugs metabolized through this pathway), however, P-glycoprotein inhibitors such as amiodarone, verapamil, or quinidine, may increase plasma concentrations of dabigatran, with possible increased hemorrhagic risk.

FXa inhibitors in atrial fibrillation

Using inhibitors of factor Xa (FXa) is one of the options to stop clotting mechanism, given its role in the thrombogenesis. FXa initiates clotting common pathway by converting inactive plasma prothrombin in thrombin. FXa inhibitors prevent activation of prothrombin, blocking both fractions of protrombinase, the free one and the clustered on Fxa fraction. They act in an early stage of coagulation cascade before thrombin being implicated.

Rivaroxaban and apixaban are the two oral inhibitors of FXa recently used in clinical Phase II and III trials.

Rivaroxaban, a selective inhibitor of FXa, showed in Phase III ROCKET-AF trial to be an alternative to warfarin in patients with AF and moderate to high embolic risk. It is given in a single dose tablet of 20 mg / day (4). It has a bioavailability of 80% and a rapid and predictable onset of action. The peak plasma levels are reached in 3-4 hours and the drug has a

half-life of 11-13 hours. Main route of elimination is via the kidneys. Body weight and sex do not have significant influence on pharmacodynamics and pharmacokinetics, suggesting that the drug can be given in fixed doses in any patient. Co-administration of rivaroxaban with food increases its plasma minimum. Experimental studies showed minimal drug interactions. It has dual pathway of excretion: liver (one third) and renal (two thirds).

Numerous clinical trials investigating rivaroxaban led to the use of rivaroxaban in the prevention and treatment of venous thromboembolism, with good efficiency and safety.

The phase III clinical trial ROCKET-AF investigated 14 264 patients with non-valvular AF. Patients were followed for stroke prevention and systemic embolic events. They were randomized for treatment with rivaroxaban 20 mg/day (n = 7131) or warfarin dose adjusted to an INR between 2 and 3 (n = 7133). The median treatment duration was 19 months. The average age of the entire group was 73 years. Approximately 50% of patients had had previous stroke or TIA.

In the primary analysis, the patients in the rivaroxaban arm had fewer stroke or systemic embolic events compared to patients receiving warfarin. 1.71 events per 100 patients / year for rivaroxaban, compared to 2.16 for warfarin, proving noninferiority (p <0.001) were reported. Hemorrhagic stroke was the less frequent in the rivaroxaban arm (0.26 per 100 patients / year) versus warfarin arm (0.44 per 100 patients / year. The rate of major bleeding was similar for the two treatment groups (3.60% vs 3.35%), as well as major bleeding and clinically relevant non-major bleeding. The discontinuation rate for adverse events was similar between the two groups (approx. 25%).

ROCKET-AF has shown some advantages of rivaroxaban over dabigatran in AF:
1. administration of a single daily dose, a condition that may increase adherence to treatment;
2. prolonged anti-thrombotic efficacy (24 hours).

2950 patients (20.7%) showed moderate renal dysfunction, with a creatinine clearance CrCl = 30-49ml/min. In these patients a lower rivaroxaban dose of 15 mg OD was used. Those patients had an excess in hemorrhagic risk (18.3% vs. 13.7% for VKA), and a higher risk of thromboembolic events (2.77% vs. 2.0% for VKA).

Apixaban, another oral FXa inhibitor is a small molecule that selectively and reversibly inhibits the free and linked FXa protrombinase. After oral administration the peak plasma concentration is reached in about 3 hours and the half-life is approximately 12 hours. Like rivaroxaban, apixaban is predominantly metabolized in the liver. Food does not interfere with its absorption, conferring a predictable anticoagulant effect. There is low interaction with other medication. There are numerous clinical studies, completed or in progress, investigating the efficacy and safety of apixaban:
1. Prevention and treatment of venous thromboembolism (ADVANCE 1, 2, and 3, ADOPT, AMPLIFY, AMPLIFY-extension);
2. Acute coronary syndromes (APPRAISE2, concluded prematurely because of bleeding risk of dual antiplatelet therapy associated to apixaban)
3. AF (Aristotle and Averroes). For this article, we will focus on important studies of AF. Apixaban was used as 5 mg bid.

AVERROES study (Apixaban versus Acetylsalicylic Acid to Prevent Stroke) compared apixaban (n = 2809) with aspirin (n = 2791) in patients ineligible for AVK (5). The study was ended prematurely due to net superiority of apixaban. Stroke or systemic embolic events fell by 56% in the apixaban arm (1.6 per 100 patients/year) versus aspirin (3.6 per 100 patients/year). Total deaths were also lower in the apixaban group with (RR 0.79), while major bleeding was only slightly increased in the apixaban group (RR 1.14).

ARISTOTLE trial (Apixaban for the prevention of stroke in subjects with atrial fibrillation) compares apixaban with warfarin in patients with non-valvular AF and at least one additional risk factor (6). The study enrolled 18 206 patients followed for 1.8 years, the largest study of its kind in AF.

Briefly, the results are as follows:
1. Decrease in incidence of stroke and systemic embolism by 21% (1.6% vs. 1.27%, p <0.001 for noninferiority and p = 0.001 for superiority).
2. Decrease in total mortality by 11% p = 0.047.
3. 31% decrease in major bleeding (3.09% vs. 2.13% per year, p <0.001).
4. Therapeutic INR rate for the entire study was 66.6%, with better profile for apixaban regardless of the INR. Although the percent-

age of effective anticoagulation was lower than in other studies with anticoagulant medication (64% RE-LY, 55% ROCKET-AF) the use of apixaban proved efficiency both in patients with therapeutic INR and those without effective anticoagulation.

Prospects for new anticoagulants in AF

So far the three oral anticoagulant drugs, Dabigatran etexilate, Rivaroxaban and Apixaban were proven effective and safe in preventing stroke and systemic embolism in patients with non-valvular AF. All three show good and quick anticoagulation activity (hours) at fixed dose. The anticoagulation result was effective and predictable, with lower rates of embolic and hemorrhagic stroke compared to warfarin. Therefore, monitoring of the laboratory parameters is no longer necessary.

All these conditions allow a better adherence to anticoagulant treatment. The results of the phase III clinical trials already concluded (RE-LY, ROCKET-AF, ARISTOTLE) show good efficiency. They need good confirmation in "real life".

In addition there are clinical situations not yet evaluated in clinical trials studding these new oral anticoagulants:
1. Patients with valvular AF or mechanical heart valves.
2. Patients with moderate to high embolic risk.
3. Patients with large variations in INR under AVK therapy considered as having effective dosages (INR 2.0 to 3.0).
4. Elderly patients with AF.
5. Patients with recurrent embolic stroke during treatment with AVK, with optimal INR.

In this early phase of the new anticoagulation therapy there are still unanswered questions in important subgroups of patients:
1. It is possible to cardiovert under the new oral anticoagulants?
2. The possible association between the new anticoagulant and antiplatelet medication (aspirin, clopidogrel, prasugrel, ticagrelor); when association is required (acute coronary syndrome, stent implantation, etc)?
3. Therapeutic options in case of hemorrhagic event. The anticoagulant effect is visible at 24 hours after the last administration?
4. What is the protocol in case elective surgery or an emergency?

It is likely that the answers to these questions and others appear clear in the near future. The new anticoagulants represent an excellent alternative to VKA in preventing stroke and systemic embolism in a broad spectrum of patients with AF.

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