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Review

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Non-valvular atrial fibrillation - a more and more visible menace

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Abstract

Taking into account the fact that the cardiovascular endemic pathology nowadays represents a menace more and more difficult to overcome, preventing the complications of arterial hypertension is a matter of great interest. Since non-valvular atrial fibrillation is one of the most common complications of uncontrolled hypertension, thus, the prevention of its embolic complications with oral anticoagulants is a very important measure in the management of this specific category of patients. This brief review is presenting some of the advantages of the novel oral anticoagulants, and especially Apixaban, in compare to antivitamin K oral anticoagulants.

Keywords: non-valvular atrial fibrillation, oral anticoagulants, thrombotic and hemorrhagic risk

In every public health registry, the cardiovascular endemic pathology nowadays represents a menace more and more difficult to overcome. The year 2016 registered the greatest cardiovascular related mortality, counting 42% for men and 49% for women, a percent significantly superior to other pathologies [1]. In Romania the situation was even more critical, with a 60% of cardiovascular mortality out of the total number.

The „iceberg" of this statistical numbers is still represented by arterial hypertension, a disease that is still lacking inadequate evaluation and control. One of the most common complications of uncontrolled hypertension is represented by non-valvular atrial fibrillation (NVAF). Actually, at the time of atrial fibrillation onset, most of the clinical and subclinical organ damage lesions are already installed, leading to complicated disease evolution and also to a rise of the thrombotic, as well as of the hemorrhagic risk.

Also, taking into account the constant rise of the medium life expectancy, NVAF has a constant growth of incidence and prevalence, for all its EHRA standardized manifest forms, as specified by the latest ESC Guideline of the management of atrial fibrillation [2]. For instance, for 2015 the estimated prevalence of atrial fibrillation was 2% of the European population, with an annual rise of 0.04%, that is almost 10 million atrial fibrillation patients. Beyond physic discomfort, arrhythmia perception consequences, myocardial damage risk, including systolic ventricular function, the thrombo-embolic systemic risk is the most consistent. A percent of 20% of ischemic stroke are due to thrombo-embolic

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events due to atrial fibrillation. The one year mortality following such an event is important- 50%, and so is the incidence of permanent disabilities. Therefore, cerebral embolic events in NVAF are an event even greater than atherosclerotic thrombosis of cerebral arteries.

Of course, during the last decade, progress was made concerning the evaluation of that risk, mainly by using more and more performant risk charts. Since CHADS2, a risk score that has been used in all the studies that have compared different anticoagulant agents - the only certain remedy against embolic stroke, more competent risk scores were being put in use- CHA2DS2-VASc, accepted by the actual EHRA guidelines and even more specific risk scores for populations that were under previous medical follow-up, - the ATRIA score (an initial Californian score, recently accepted in Sweden), a score that is setting a wide differentiation based on a pre-existent cerebral ischemic event, as well as on the evaluation of other functions, such as the renal one, function that was not taken into account by the previous scores.

All these progresses, mainly realized in countries with performant health and quality of anticoagulation registries (see the politics of Unique Competent Anticoagulation Center, as well as the one of districtual priorities guidelines, for each and every pathology – Sweden, again) led to obtaining a country TTR superior to 70%, by correctly using antivitamins K (AVK), as well as a cost-efficiency justification according to QUALY new oral anticoagulants prescription criteria (NOAC) - in fact direct oral anticoagulants, anti Xa or IIa factor, without intermediate metabolization or indirect component, such as vitamine K. This is how national and districtual guidelines were developed, with an universal accepted score, for the moment CHA2DS2-VASc – superior to 2 in men and superior to 3 in women, especially for the ones with bleeding risk score HAS-BLED under 3, that implies mandatory anticoagulation, and initiation for the NVAF new diagnosed case to benefit of NOAC, preferred to AVK, all this in acquaintance with the upper evidenced based cost-efficiency studies. Unfortunately, including double – blind controlled studies (randomized controlled trials - RCT) - TTR in different countries, as well the general TTR of the study, did not reach 70% for the AVK arm, with an obvious inferior value in the real life, mostly around 50%. It has been demonstrated that for medium TTR under 60-70% the efficacy /safety of AVK administration is far from the optimal expected value. The reality from RCT- studies that have compared anticoagulation with AVK versus NOAC (RE-LY [3], ARISTOTLE [4], ROCKET-AF [5] and ENGAGE AF-TIMI 48 [6]), was highly confronted with the reality from real life - post-marketing studies due to national and international health registries as well as marketing studies from health insurances societies.

Of course, we can widely comment the differences due to applying criteria more or less subjective for the actual therapeutic options, but, the superior quality of anticoagulation using NOAC is more and more evident, from the point of view of a more facile treatment, without monthly minimal INR control, without very large interferences, both with medications as well as with food, the variable bioavailability of all AVK available formulas, versus the much more safe stability and predictability of NOAC treatments. Moreover, if there still are doubts regarding the superior antithrombotic efficacy of NOAC versus AVK (using a TTR superior to 70 %...), concerning safety – hemorrhagic risk, very high related to life threatening or intracerebral bleeding, the efficacy of some of the NOAC is already proven. We will make references, based on the personal experience as well as based on data from literature, on the efficacy and safety of the treatment with Apixaban, a NOAC with excellent evidences, especially in what concerns safety.

Why is this specific characteristic our matter of interest? Also from registries and studies we know that the fear of bleeding is responsible for the fact that, despite the universally accepted risk scores, medical practice in NVAF in many countries is just about 50% out of the need for anticoagulation (PINACLE-USA registry) [7]. And not just for nothing: in a recent Canadian registry, counting more than 125.000 patients, the incidence of major bleeding while using AVK was of 3,8% patients/year, mostly in the first 30 days after treatment initiation, and also, in a monitoring of 5 years of 10840 patients – 8,7% presented in the hospital for significant bleeding, with a number of deaths of 18,1% [8]! This is why, the safety of long term oral anticoagulants is of great importance. Of course, we cannot compare and extrapolate from the studies NOAC versus VKA the efficacy and safety of every NOAC molecule, only from head to head studies. However, in the registries ordered by national profile authorities or by

medical health insurances, as well as in the follow-up of health and treatment registries, visible differences emerged, despite the different option criteria for one anticoagulant or another, lacking the relative ideal selection of double blind randomized studies. A recently published Danish registry revealed that molecules such as Apixaban and Dabigatran were detached by a superior safety in compare to Warfarin and Rivaroxaban [9]. The same conclusion, plus some evidences in favor of cost-efficiency were observed in an English follow-up registry, presented during an European profile congress, the most efficient molecule, also safe (QUALY) and cost-efficient was proven to be represented by Apixaban, mostly in a doses of 5 mg BID [10]. A post marketing study of the Medicare and Truven Marketscan Data Base, USA, also favors Apixaban, twice safer (in major hemorrhagic risk) then warfarin, an advantage, it is true, a bit lower for Dabigatran and no advantage, but even an slightly increased hemorrhagic risk for Rivaroxaban [11]. Of course, these data are from post-marketing studies, but they are also involving molecules features and metabolization and excretion of the active substance, which is, regarding Apixaban, mostly on liver level (73%) and not renal. On the other hand, in a recently published study, the renal function is a powerful determinant of vital risk, and, much more than that, of the evolution towards renal endothelial dysfunction and chronic kidney disease patients with comorbidities, most obvious in the case of NVAF patients that require mandatory anticoagulation [12]. Once more, the comfort due to this specific feature makes this NOAC a drug with compliance particularities and lower risk in long term administration.

Beyond this, related to acute coronary syndrome, another possible outcome of endothelial dysfunction generated by arterial hypertension, a condition requiring the association, on short term, from 1 to 6 months, of two antiplatelet agents (Clopidogrel and Aspirin) to an oral chronic anticoagulant, leading to an increase of the bleeding risk. The question is about acute coronary syndromes that are requiring interventional revascularization – PCI with stent implantation- using bare metal stents (the preferable option in this type of patient, aiming the shortest triple antithrombotic therapy period) or drug eluting stents (preferably from the latest generations, also aiming a short double antiplatelet therapy period). Beyond one, respectively 6 months, a double association between oral anticoagulant and a single antiplatelet is required, and after twelve months, just oral anticoagulation, for an unlimited period of time.

The efficacy and comfort given by the safe administration of these drugs leads to, from the personal experience of the authors, a rationale option for Apixaban, for a larger category of patients, with the permanent respect of the comparison between thrombotic risk above 2 (3) - CHA2DS2-VASc, and the hemorrhagic HAS-BLED, preferably under 3.

In reality, nothing is easy in that matter, since the risk scores are always variable in time, and, most often, rising. Data from Aristotle study, that started with non-inferiority-superiority criteria in thrombotic prevention (a reduction of 21%, $p=0.01$) and an even more superior rate regarding major bleeding risk (31%, $p<0.001$) and, in fact, all types of bleeding, led to an increased confidence in this type of therapeutic option [4].

However, the temptation to avoid this apparently aggressive anticoagulation measure in this type of „fragile" patients remains important. But safety also means understanding pharmacodynamics and pharmacokinetics of drugs, while aging, taking into account major renal dysfunction, liver and metabolic ones, thus leading to supplementary difficulties.

Mechanistic and pharmacodynamics Studies have led to particular doses indications, for instance, in the USA, the authorized doses for Dabigatran is 75 mg BID, instead of 110 mg BID as in Europe, in the presence of 2 out of the following significant criteria: age over 75-80 years, glomerular filtration rate <30-40 ml/minute, and, most importantly, underweight. A recently published study has demonstrated that this last criterion, underweight, even alone, must be followed by the administration of the minimal anticoagulant 2.5 mg BID dosis [13].

The fear of bleeding may also be attenuated, by the preliminary results of ANNEXA-4 study, that is the administration of Andexanet in patients treated with antiX-a factor, Apixaban, with the rapid annihilation of antiXa factor and efficient hemostasis in 79% of the tested subjects [14]. Until now, we were only familiar with the effect of Idarucizumab, in order to counteraction the effect of Dabigatran, in case of bleeding and urgent surgery.

On the other hand, the attitude regarding arrhythmia must be kept in mind. Beginning with the premise-the control of rhythm and cardiac rate, we are in

favor today of a more aggressive therapy in order to restore sinus rhythm, for as long as possible, not just by pathogenic medical therapy of the disease, but also by antiarrhythmic chemistry and more invasive measures - radiofrequency ablation, surgical antiarrhythmic techniques, in countries that have acquired a high procedure standard and that have modified the incidence of embolic events, of course, not leaving apart anticoagulant medication because of the presumptive lack of new onset of the arrhythmia, an attitude that we consider incorrect. Moreover, also with percutaneous approach, the left atrial appendage closure was followed by a more important decrease in thrombo-embolic risk. All these new standards, found in the guidelines as recommendation levels and evidence classes, also determine a decrease of the morbi-fatal risk.

Very interesting studies, recently published, have demonstrated that, in fact, there is a very specific connection between the onset and long term atrial fibrillation and the inflammation, left atrial fibrosis and hypercoagulability status, in the case of these patients.

Unfortunately, AVK, cannot stop this tendency mediated through PAR 1 and/or PAR 2. Even more, the long term administration of AVK determines a tendency to form arterial wall calcifications (also on coronary level), endothelial dysfunction factor and independent risk event, as well as a tendency to hyper platelet adhesion. NOAC, instead, are blocking this mechanism, the X-a factor stimulated by thrombinic intermediate status being easily blocked by thrombinic intermediation by anti X-a factors, with inflammatory effect and effective anticoagulant one, with the decrease of progressive atrial fibrosis and onset of permanent atrial multifocal fibrillation [15].

Beyond life comfort and QUALY superior parameters, including in what concerns cost-efficiency, the administration of Apixaban versus AVK demonstrated a significant decrease in general as well as in cardio-vascular mortality (11%, $p< 0.047$), also in randomized controlled trials as well as in health registries, the comparison being, of course, with less expertise.

All these data, along with a personal modest yet concrete experience, represent arguments for a valid therapeutic option, and, last but not least, not just effective and safe, but also cost-efficient, despite the apparent disproportion of price between anticoagulant drugs (NOAC versus AVK) on the current medical market.

Conflict of interest

The authors have received speaker fee from Pfizer and BMS, Boehringer Ingelheimer, Bayer.

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