Editorial

Factors in Deciding between Novel and Traditional Oral Anticoagulants to Prevent Embolism in Atrial Fibrillation Patients

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Atrial fibrillation (AF) is the sustained arrhythmia most frequently found in clinical practice. Its prevalence is expected to increase in the coming decades. Its occurrence implies a reduction in the quality of life and an increase in mortality, mainly due to stroke and systemic thromboembolism (TE). The stroke originating from AF carries a higher risk of severe complications, such as permanent disability and prolonged hospitalization, as compared to that of other etiologies.[1-3]

Since the discovery of vitamin K (VitK) antagonists more than 50 years ago, they have become the most effective treatment to prevent stroke and TE in patients with AF. However, because of the risk of hemorrhagic complications they pose, only patients with persistent AF considered of very high risk, previous embolic accidents, mechanical valvular prostheses, and those undergoing electrical cardioversion used to receive that treatment in an initial phase. Between the 1980 and 1990 decades, major clinical controlled studies determining the importance of stroke prevention in non-valvular AF were carried out, providing scientific support to the current clinical use of VitK antagonists. The greater benefit of the VitK antagonists as compared to placebo (a mean 64% reduction in relative risk) has been undoubtedly demonstrated, as has been the modest or even absent role of acetylsalicylic acid in stroke prevention in that population.[4]

Despite that evidence, the clinical use of VitK antagonists remained very limited over the following years, because of their complex pharmacokinetics and pharmacodynamics. Undesirable drug interactions and their narrow therapeutic window (borderline between efficacy in embolism prevention and risk of bleeding) are the major limitations of their use and the reason for the need to monitor often the anticoagulation level.[5-7]

On the other hand, the advances in knowing the risk factors for the formation of AF-related atrial thrombus and embolism and the risk of bleeding due to VitK antagonists have motivated the development of new strategies based on the risk-benefit ratio of using anticoagulants to prevent stroke.[8-11] The major risk scores currently used are CHA_2DS_2VASc for embolism, and HASBLED for bleeding. The balance between those two scores has made the use of anticoagulants easier. Nevertheless, VitK antagonists have been underused in clinical practice. Real world studies have shown that only 50% of the patients with indication for their use received medical recommendation, and only 50% of them (specially in Brazil) had proper INR control.[12-14]

Aiming at a better safety profile, with fewer drug and food interactions, non-VitK antagonist oral anticoagulants, the "novel oral anticoagulants" (NOACs), have been developed. Dabigatran, a direct thrombin inhibitor, was the first NOAC registered and approved by the major drug regulatory agencies around the world, based on the results of the RE-LY study in 2009.[15] Subsequently, NOACs belonging to the family of activated factor X inhibitors were developed, being approved for clinical use by the major drug regulatory agencies around the world after the publication of the following studies: ROCKET-AF (rivaroxaban);[16] ARISTOTLE (apixaban);[17] and, more recently, ENGAGE (edoxaban).[18]

Considering the high efficacy of warfarin as compared to placebo and acetylsalicylic acid to prevent TE phenomena, those four studies were designed for the non-inferiority hypothesis. The results obtained with a large number of patients (70,000) have shown that NOACs are at least non-inferior to warfarin regarding efficacy. On the other hand, an unequivocal comparison could not be established between the different NOACs, because the studies are not identical. On indirect analysis, dabigatran at the dose of 150 mg, twice a day, and apixaban at the dose of 5 mg, twice a day, stood out, showing superiority over warfarin in reducing total stroke. Regarding safety, all NOACs were superior to warfarin in reducing hemorrhagic stroke and potentially fatal hemorrhages. Rivaroxaban and edoxaban stood out because of their convenient administration, with just one daily intake. Based on those clinical studies, the European Guideline of Cardiology recommends any NOAC (dabigatran, apixaban, rivaroxaban) as an alternative to VitK antagonists in patients with non-valvular AF.[19] The American guideline for the management of patients with AF recommends VitK antagonists as class IA and the NOACs (apixaban, dabigatran and rivaroxaban) as class IB for patients with non-valvular AF and risk factors for stroke and systemic embolism.[20]

Real world observations have reproduced the initial clinical studies, confirming that NOACs are an effective alternative for stroke/TE prevention in patients with AF,[21] being also recommended by the Brazilian Society of Cardiology guideline on anticoagulation.[22] This wider range of choice, however, generates natural questioning about the current role of VitK antagonists. Two aspects have guided the selection of anticoagulants in this transition phase, in which

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clinicians acquire experience with the new drugs, comparing them with those traditionally used: 1) technical questions, related to drug efficacy and safety; and 2) the possibility that the patients pay for their treatment or have it paid for by health care services.

Regarding the technical question, the advantages of warfarin are as follows: 1) it is the one and only drug with proven efficacy in patients with mitral stenosis, patients with metal valve prostheses and renal failure; 2) greater experience over decades (50 years of use); 3) the physician follows the effectiveness or risk of the treatment by controlling INR; 4) easily maintained treatment because of the low cost of the medication; 5) possibility of effect attenuation by administrating vitK or blood derivative products; and 6) prolonged therapeutic effect, so that skipping one dose usually does not interfere with the therapeutic activity. Regarding the technical question, the advantages of the NOACs are as follows: 1) rapid onset and end of their anticoagulant effect; 2) they usually do not require transition with low-molecular-weight heparin; 3) low drug interaction; 4) no food interaction; 5) important reduction in the risk for hemorrhagic stroke; and 6) smaller necessity for periodical laboratory control (although anticoagulation control is not recommended, regular renal function monitoring is still required).

There are some gray areas in the use and indication of NOACs, such as the procedures of cardioversion and ablation and the context of acute coronary disease, and the interventions with bare-metal and drug-eluting stent implantation. Regarding the cardioversions for AF, the substudies RE-LY, ARISTOTLE and ROCKET-AF have shown similar effectiveness between NOACs and VitK inhibitors, an observation confirmed by the X-VeRT trial, which randomized rivaroxaban and VitK antagonists in patients with AF undergoing cardioversion.[23] Regarding AF ablation, isolated studies have shown that NOACs are usually effective and safe, depending on the type of protocol used. There are new ongoing studies to define the best strategy for patients in that condition.

Regarding patients with AF in the context of acute coronary disease, recently or during hemodynamic interventions, prospective studies on NOACs are awaited. The subanalyses of previous multicenter studies have not authorized the unrestricted use of NOACs in those patients, warfarin being the most often studied drug, in double or triple combination with antiplatelet agents. However, there are "recommendations" for the early use of NOACs at their lowest dose studied (rivaroxaban 15 mg, once a day; dabigatran 110 mg, twice a day; or apixaban 2.5 mg, twice a day) in association with an antiplatelet agent, preferably clopidogrel.[19] The future results of the studies conducted with that purpose will or will not support the current orientation.

A very important aspect for the incorporation of NOACs is their cost, much higher than that of VitK antagonists. This has relevant clinical implications, because their suspension, even if transient, places the patient at risk for embolic events due to the rapid loss of their anticoagulant effects and the possibility of paradoxical hypercoagulability. In the social context, most patients treated at public hospitals receive VitK antagonists. The incorporation of new anticoagulants should promote a significant impact on the budget of those hospitals.[24,25] Therefore, Brazilian studies assessing the local needs and the clinical and financial impact of the introduction of those new therapeutic strategies in patients with AF are required. In addition, it is worth noting that, while that cost/effectiveness ratio has not been clarified, the prevention of embolism in AF by using VitK antagonists is well established, and the maintenance of INR within the therapeutic range promotes efficacy levels equivalent to those of NOACs.

In conclusion, the knowledge acquired with the management of VitK antagonists over the years allows us to glimpse a horizon of opportunities to use NOACs to perfect the prevention of TE phenomena in patients with AF. The comfort provided by NOACs, by not requiring anticoagulation level monitoring, however, should not be interpreted as no need for drug surveillance and for periodical care of the patient as a whole. Further clinical studies conducted in Brazil are required to allow the identification of patients' profiles more favorable to each of those new drugs, considering a good cost/effectiveness ratio.

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