EDITORIAL

New oral anticoagulants in Brazil

*Marcos Arêas Marques**

For about five decades, vitamin K antagonists (VKA) were the only oral anticoagulants available for the treatment and prophylaxis of venous thromboembolism (VTE)[1]. The already known pharmacodynamic and pharmacokinetic limitations of this class of drugs fostered research into the development of new anticoagulant molecules, with similar effectiveness but presenting the following "theoretically ideal" characteristics: single daily dose oral administration; wide therapeutic window; rapid onset of action; no need for regular laboratory monitoring; predictable pharmacokinetics and pharmacodynamics; fast reversibility in case of bleeding (with antidote); limited food and drug interactions; and a low cost[2].

Following the frustrated experience with ximelagatran, which was withdrawn from both Brazilian and international markets in 2006 for causing severe liver injury,[3,4] new, promising perspectives emerged in Brazil with the release, by the Brazilian Health Surveillance Agency (ANVISA), of orally administered dabigatran etexilate (Pradaxa®, Boehringer Ingelheim), a direct thrombin inhibitor, for VTE prophylaxis, and rivaroxaban (Xarelto®, Bayer Healthcare), a direct inhibitor of activated factor X, for VTE prophylaxis and treatment. The RE-Novate, RE-Model, and RE-Mobilize dabigatran studies showed safety and effectiveness profiles that were not inferior to those obtained with subcutaneous enoxaparin in VTE prophylaxis during major hip and knee surgeries, using both the European regimen (40 mg/day) and the American regimen (30 mg every 12 hours)[1]. Similar safety and effectiveness standards were obtained with rivaroxaban in VTE prophylaxis during major hip and knee surgeries, also using both the American and the European regimens, in four large-scale studies collectively referred to as RECORD (see comment in Yoshida et al.[1]). Moreover, rivaroxaban showed effective results in the treatment of VTE in the EINSTEIN studies (compared with conventional treatment with enoxaparin and warfarin)[5]. In addition to those initiatives, some studies are currently under way investigating other new, promising oral anticoagulants, e.g., apixaban (Eliquis® - Bristol Myers Squibb-Pfizer), edoxaban (Lixiana® - Daiichi-Sankio), betrixaban (Portola), and otamixaban (Sanofi-Aventis)[1,6] – all of which will probably be introduced into the Brazilian market soon, increasing the number of therapeutic options available for the prophylaxis and treatment of VTE.

These two new drugs approved by ANVISA have some characteristics considered not only to be advantageous, but to come close to the ideal profile of an anticoagulant. The possibility of using oral anticoagulant monotherapy, with no drug or food interactions and no need for regular laboratory monitoring, for VTE prophylaxis and treatment, with therapeutic results that are similar to those obtained with other already established regimens, is undoubtedly attractive. However, one should not forget that these new drugs also have limitations, e.g., the impossibility of being used in pregnant and lactating women, some drug interactions, limited dosage in cases of renal failure, lack of a specific antidote, and a relatively high cost – features that prevent these new drugs from being widely used in VTE prophylaxis and treatment.

Regardless of the wide adoption of new oral antigoaculants (NOACS) in the daily clinical practice of angiologists and vascular surgeons, we have to understand that anticoagulant therapy has, for some time already, been undergoing progressive, irreversible evolution. This stated, I believe that we should avoid any radical, Manichean attitude towards these new drugs, as the NOACS have allowed the creation of interesting, effective, safe alternatives in VTE treatment and prophylaxis. Rather, we should remember that low-molecular-weight heparin was also heavily questioned as of the moment it was approved by government regulatory agencies, always in comparison with unfractioned herapin – until then the only option available for parenteral administration –, especially in terms of its cost and the absence of a specific antidote for cases of hemorrhage resulting from the use of these drugs.

NOACS still have a long way to go before they can be widely and regularly used in VTE prophylaxis and treatment. Moreover, VTE is a multifactorial disease, with a range of very peculiar profiles and characteristics, many of which were not among the inclusion criteria of the aforementioned clinical studies. The effectiveness and safety of these drugs have to be further tested in VTE secondary to long-haul flights, in children, cancer patients, and

patients with different types of thrombophilia. Phase IV studies may shed some light on these clinical situations.

The emergence of NOACS may also help bring about some paradigm shifts in the prophylaxis and treatment of VTE. Furthermore, with the possibility of using these new drugs, some parameters, now considered immutable, may be rethought, especially regarding the exclusivity of the effectiveness-safety binomial in prophylactic or therapeutic prescriptions for VTE. The availability of a higher number of drugs will allow to add other variables to the existing binomial, e.g., costs involved, and will open new horizons for debate and for considering the opinions of patients regarding the advantages and disadvantages of each option.

In summary, these drugs have been expected for 50 years, and studies have shown that they are a safe and effective option in VTE prophylaxis and treatment[7]. Therefore, right now it seems cautious to adopt a flexible attitude towards the possibility to customize VTE prophylaxis and treatment to the characteristics of each patient, choosing either the well-established VKA, heparins, or the new NOACS. In this customization, the impacts of the use of each different drug in terms of cost, effectiveness, safety, and dosage should be considered. Furthermore, we should act critically and rationally when adopting any therapeutic or prophylactic anticoagulant regimen. And, most importantly, we should keep open the space for intense debate among specialists from our and other fields in relation to their experience with NOACS.

REFERENCES

1. Yoshida RA, Yoshida WB, Rollo HA. Novos anticoagulantes orais para a profilaxia e tratamento do tromboembolismo venoso em cirurgias ortopédicas de grande porte. J Vasc Bras. 2011;10(2):145-53.
2. Silvestre L, Ministro A, Evangelista A, Pedro LM. Novos anticoagulantes orais no tromboembolismo venoso e fibrilação auricular. Angiol Cir Vasc. 2012;8(1):6-11.
3. Infarmedia [site da internet]. Circular Informativa nº 023/CA de 2006. [citado 2013 ago. 26]. http://www.infarmed.pt/portal/page/portal/INFARMED/MAIS_ALERTAS/DETALHE_ALERTA?itemid=44936.
4. Yoshida WB, El Dib RP, Yoshida RA, Maffei FHA. Ximelagatran *versus* wafarin for prophylaxis of venous thromboembolism in major orthopedic surgery: systematic review. São Paulo Med J. 2006;124(6):355-61. PMid:17322960. http://dx.doi.org/10.1590/S1516-31802006000600012
5. Turpie AGG, Kreutz R, Llau J, Norrving B, Hass S. Management consensus guidance for the use of rivaroxaban – an oral, direct factor Xa inhibitor. Thromb Haemost. 2012;108(5):876-86. PMid:23014816. http://dx.doi.org/10.1160/TH12-03-0209
6. Yoshida RA, Yoshida WB, Maffei FHA, El Dib R, Nunes R, Rollo HA. Systematic review of randomized controlled trials of new anticoagulants for venous thromboembolism prophylaxis in major orthopedic surgeries, compared with enoxaparin. Ann Vasc Surg. 2012;27(3):355-69. PMid:23351997. http://dx.doi.org/10.1016/j.avsg.2012.06.010
7. Schulman S, Crowther MA. How I treat with anticoagulants in 2012: new and old anticoagulants, and when and how to switch. Blood. 2012;118(13):3016-23. PMid:22302737. http://dx.doi.org/10.1182/blood-2011-10-378950

Correspondence
Marcos Arêas Marques
Rua Sorocaba 464/308 – Botafogo
CEP 22271-110 – Rio de Janeiro (RJ) Brazil
E-mail: mareasmarques@gmail.com

Author's information
*MAM is a physician at the Angiology Teaching Unit, Universidade Estadual do Rio de Janeiro. He is also a member with the Scientific Council of SBACV.