



EDITORIAL COMMENT

How much does the choice of new oral anticoagulant matter for reducing the burden of stroke in atrial fibrillation?☆



Quanto importa a escolha do anticoagulante oral direto para a redução da carga de acidente vascular cerebral na fibrilhação auricular?

Carlos Aguiar

Serviço de Cardiologia, Hospital Santa Cruz, Centro Hospitalar de Lisboa Ocidental, Carnaxide, Portugal

Available online 28 February 2016

Atrial fibrillation (AF) is the most prevalent chronic arrhythmia. It can cause significant hemodynamic alterations, but its prognosis is mainly affected by associated thromboembolic phenomena, which can have serious consequences in terms of morbidity and mortality. Non-valvular AF increases the risk of ischemic stroke four- to five-fold in all age-groups.¹ Stroke is the leading cause of cardiovascular mortality and disability in Portugal, hence the importance of preventive measures, including prevention of thromboembolism in AF.

The pathogenesis of AF is complex, involving various factors such as atrial blood stasis, endothelial injury and dysfunction, inflammation and systemic or local hypercoagulability. Oral anticoagulation (OAC) with vitamin K antagonists (VKAs) is effective for stroke prevention in patients with non-valvular AF: a meta-analysis of six studies showed a risk reduction of 64% compared to placebo, the number needed to treat in one year to prevent one stroke being 37 patients in primary prevention or 12 patients in

secondary prevention.² OAC is also associated with a significant reduction (26%) in overall mortality compared to placebo. These findings support the recommendation in the European Society of Cardiology's guidelines that all patients with AF should be prescribed OAC therapy, except those with low thromboembolic risk or isolated AF.³

For a variety of reasons, many patients with non-valvular AF who are eligible for OAC are not anticoagulated. One of the main limitations of VKAs is the increased risk of intracranial hemorrhage (ICH), which is responsible for 90% of deaths from bleeding in AF patients treated with VKAs.⁴ The brain is a vital organ, highly vascularized and vulnerable to mechanical injury, but the cerebral microcirculation has a series of structural and functional properties that protect it against bleeding, including strong junctions between endothelial cells, low expression of antithrombotic molecules, and high expression of tissue factor (factor III), which triggers coagulation when it binds to circulating factor VIIa.⁵ The synthesis of factor VII requires vitamin K, which explains the increased risk for ICH in patients taking VKAs.

Many patients anticoagulated with VKAs are not adequately controlled. Observational studies have shown that the quality of control of the international normalized ratio (INR), as assessed by time in therapeutic range (TTR), is a strong predictor of mortality, embolic events and bleeding complications in AF patients taking VKAs.⁶ INR must be closely monitored in order to optimize the effectiveness of VKA therapy. With regard to safety, the risk of

DOI of original article: <http://dx.doi.org/10.1016/j.rpece.2015.09.013>

☆ Please cite this article as: Aguiar C. Quanto importa a escolha do anticoagulante oral direto para a redução da carga de acidente vascular cerebral na fibrilhação auricular?. Rev Port Cardiol. 2016;35:149–151.

E-mail address: ctaguiar@gmail.com

ICH is lower the greater the TTR, but it is always higher than in non-anticoagulated patients, even when INR is well controlled.⁷

The new oral anticoagulants (NOACs), direct factor Xa or thrombin inhibitors, were developed in order to overcome the limitations of VKAs, which are a challenge for both patients and their doctors. In large-scale controlled trials, dabigatran, rivaroxaban, apixaban and edoxaban were shown to be at least as effective as warfarin for prevention of stroke and systemic embolism in AF patients at moderate or high thromboembolic risk.^{8–11} The risk of ICH is significantly lower with any of the four NOACs compared to warfarin, independently of INR control as assessed by TTR. A meta-analysis of the RE-LY, ROCKET AF, ARISTOTLE and ENGAGE AF-TIMI trials, with a total of 71 683 patients, demonstrated that the NOACs reduce risk of stroke or systemic embolism by 19%, risk of ICH by 52%, risk of hemorrhagic stroke by 51%, and all-cause mortality by 10%.¹²

When choosing a NOAC for a particular patient, the physician cannot make an evidence-based decision, since there have been no trials directly comparing two or more NOACs. In the four published trials comparing individual NOACs with warfarin, there are considerable differences in study design and population characteristics, which affect thromboembolic event rates and bleeding complications, as well as variations in INR. There are also differences in definitions of endpoints, warfarin dose adjustment methods, and transition care. All these factors seriously compromise the results obtained in indirect comparisons. The European guidelines are accordingly clear as to the indications for preferring NOACs over VKAs, but say nothing about choosing between them.³

The cost-effectiveness of three NOACs (dabigatran, rivaroxaban and apixaban) compared to warfarin in patients with AF has been demonstrated in the Portuguese context.^{13–15} The results of an indirect comparison between two of these drugs, dabigatran and rivaroxaban, are published in this issue of the *Journal*.¹⁶ Besides the problems with such comparisons, as pointed out above, there are two important factors that limit the authors' analysis. Firstly, they do not present the proportion of patients taking 110 mg (the more common dose in Portugal) or 150 mg of dabigatran; this significantly affects the results obtained, since the two dosages have different safety and efficacy profiles. Secondly, a 15 mg dose of rivaroxaban is not considered, but this is frequently used in clinical practice and has a lower daily cost than either dosage of dabigatran. Since the cost of the drug is an essential component of the economic evaluation model, the inclusion of this dosage could change the conclusion that dabigatran is dominant.

A recent analysis of 100 913 patients in 21 controlled trials confirms that the clinical differences between the NOACs are modest and depend on the relative importance given to bleeding complications and ischemic events.¹⁷ This analysis also found no significant differences between the NOACs in terms of medical costs.

To summarize, there is still great potential for further health gains by preventing stroke in non-valvular AF. To achieve this, measures need to be taken to improve the diagnosis of AF and to increase the number of patients treated among those eligible for OAC. In general, the NOACs present

a favorable balance between efficacy and safety compared to warfarin, and so a greater proportion of eligible patients can undergo OAC therapy. In the absence of specific trials, no NOAC should be considered superior to another on the basis of indirect comparisons.

How much does the choice of new oral anticoagulant matter for reducing the burden of stroke in atrial fibrillation? We cannot be sure, but probably not very much.

Conflicts of interest

The author has received honoraria from the following companies: Bayer, Boehringer Ingelheim, Bristol-Myers Squibb/Pfizer, and Daiichi Sankyo.

References

1. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation: a major contributor to stroke in the elderly; the Framingham Heart Study. *Arch Intern Med.* 1987;147:1561–4.
2. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med.* 2007;146:857–67.
3. Camm AJ, Lip GY, De Caterina R, et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. *Eur Heart J.* 2012;33:2719–47.
4. Fang MC, Go AS, Chang Y, et al. Death and disability from warfarin-associated intracranial and extracranial hemorrhages. *Am J Med.* 2007;120:700–5.
5. Fisher MJ. Brain regulation of thrombosis and hemostasis: from theory to practice. *Stroke.* 2013;44:3275–85.
6. Mantovani M, Mueller I, Bassand JP, et al., for the GARFIELD Investigators. Outcomes and quality of anticoagulant control in patients newly diagnosed with non-valvular atrial fibrillation: insights from the worldwide GARFIELD Registry. *Circulation.* 2012;126:A18357.
7. Ho CW, Ho MH, Chan PH, et al. Ischemic stroke and intracranial hemorrhage with aspirin, dabigatran, and warfarin: impact of quality of anticoagulation control. *Stroke.* 2015;46:23–30.
8. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2009;361:1139–51.
9. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med.* 2011;365:883–91.
10. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2011;365:981–92.
11. Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2013;369:2093–104.
12. Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomized trials. *Lancet.* 2014;383:955–62.
13. Miguel LS, Rocha R, Ferreira J. Avaliação económica do dabigatran na prevenção de acidentes vasculares cerebrais isquémicos em doentes com fibrilhação auricular não valvular. *Rev Port Cardiol.* 2013;32:557–65.
14. Morais J, Aguiar C, McLeod E, et al. Estudo de custo-efectividade de rivaroxabano para prevenção de acidente vascular cerebral em doentes com fibrilhação auricular em Portugal. *Rev Port Cardiol.* 2014;33:535–44.

15. Costa J, Fiorentino F, Caldeira D, et al. Cost-effectiveness of non-vitamin K antagonist oral anticoagulants for atrial fibrillation in Portugal. *Rev Port Cardiol.* 2015;34: 723–37.
16. Miguel LS, Ferreira J. Consequências clínicas e económicas da utilização de dabigatrano e de rivaroxabano em doentes com fibrilhação auricular não valvular. *Rev Port Cardiol.* 2016;35:141–8.
17. Dogliotti A, Giugliano RP. A novel approach indirectly comparing benefit-risk balance across anti-thrombotic therapies in patients with atrial fibrillation. *Eur Heart J Cardiovasc Pharmacother.* 2015;1:15–28.