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EDITORIAL COMMENT

Vitamin K antagonists after all, or possibly not?☆

Antagonistas da vitamina K todavia, ou nem por isso?

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Atrial fibrillation (AF) is a major public health problem, with an estimated prevalence of 2.5% in the Portuguese population aged 40 and over according to the results of the FAMA study published in 2010.[1] Only 37.8% of patients in the study were taking vitamin K antagonists (VKAs).

One of the main limitations of chronic VKA therapy for the prevention of thromboembolism is the narrow therapeutic window for these drugs, international normalized ratio (INR) values often oscillating between reduced protection when below therapeutic levels and increased bleeding risk when above. The difficulty in maintaining patients within the therapeutic range (as reflected by percentage time in therapeutic range [TTR]) stems from the numerous interactions and complexity of warfarin metabolism. A TTR of >70% is considered ideal but this value is rarely achieved, even in patients with good control. In the large-scale clinical trials of the new oral anticoagulants (NOACs), TTR in the warfarin arm was 66% in RELY[2] (vs. dabigatran), 55% in ROCKET-AF[3] (vs. rivaroxaban), 62.2% in ARISTOTLE[4] (vs. apixaban) and 64.9% in ENGAGE[5] (vs. edoxaban).

A study of AF patients in the UK General Practice Research Database included 27 458 warfarin-treated patients and 10 449 patients not treated with antithrombotic therapy. The mean TTR of treated patients was 63%. However, risk reduction is clearly proportional to the effectiveness of anticoagulation control, the above study reporting a 79% reduced risk of stroke in patients who had TTR of ≥70% compared to those with TTR of ≤30%.[6]

Furthermore, bleeding risk is also proportional to the level of anticoagulation achieved, rising significantly with INR of >4, particularly in the first three months of therapy.[7,8]

In a study by Luís Cunha on admissions for ischemic stroke to the Neurology Department of Coimbra University Hospitals during the first trimester of 2011,[9] 37.3% were of cardioembolic etiology, of which 95% were in the context of AF. Of these, only 34.7% of patients were taking VKAs and only 11% had INR within the therapeutic range.

In an observational study published in 2015 of patients aged ≥30 years with a diagnosis of AF registered at eight family health units in Vila Nova de Gaia in northern Portugal,[10] the prevalence of AF was lower than reported in the FAMA study (1.29% vs. 2.5%) and only 56.8% of patients with indication for oral anticoagulation were receiving this therapy.

The study by Guedes and Rego published in this issue of the *Journal*[11] was of 26 healthcare units with oral anticoagulation programs (73% of the total) of the Espinho-Gaia and Gaia health center groups. It included 5883 INR records corresponding to 479 patients with non-valvular AF under chronic oral anticoagulation therapy with VKAs. Mean TTR was 67.4%, varying between 55.6% and 79.5% among the different units. The results were on a par with the best reported in the world. For example, in the control group of the ROCKET-AF clinical trial,[12] individual TTR (iTTR) was 66% in Western Europe and 65.8% in Canada and the US. Some units even had better values than the leading country

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in this field, Sweden, where mean TTR was 75% in this patient group.

These results clearly show that a motivated and dedicated group can make a difference in improving care. They demonstrate that a well-executed anticoagulation program can achieve high levels of effectiveness, even in Portugal. However, the situation in Gaia contrasts with the latest data for the country as a whole, particularly those of the SAFIRA study,[13] presented at the last Portuguese Congress of Cardiology. The study included 7500 patients aged ≥65 years, followed in primary care and in district and tertiary hospitals. Overall AF prevalence was 9%, and only 43.7% were treated with anticoagulants (two-thirds with VKAs and one third with NOACs). Mean TTR among patients taking VKAs was 41.7%. Experience with coordinating anticoagulation programs suggests that this is more in line with the real situation.

The criterion adopted by Guedes and Rego for inclusion in the study was a minimum of six visits for INR testing in 2014. This was a cross-sectional retrospective analytical study, with no longitudinal information, and so the start date or duration of anticoagulation therapy are not known. It would also be useful to know the level of patient adherence to the program over time, given the high rate of discontinuation of such therapy (20-25% in clinical trials of NOACs). Nevertheless, the results are impressive.

Many argue that when there is good control of VKA therapy (TTR >70), the NOACs lose their advantage in terms of clinical efficacy. This does not, however, appear to be the case. Although the best results with the NOACs are obtained in groups with lower TTR,[14] the treatment effect of various NOACs compared with warfarin for the prevention of cardiothromboembolism is maintained across different levels of TTR.[15,16]

It would be useful to compare the methodology of the Gaia group with that employed in other regions reporting worse results, with a view to improving their performance. Optimizing the organizational and logistical aspects of oral anticoagulation programs with VKAs would certainly have a favorable clinical impact. However, even compared to programs like that of the Gaia group with optimized VKA therapy, in my opinion the NOACs remain the best treatment option, even in clinically similar subgroups, due to their convenience, lower rate of intracranial hemorrhage and virtual absence of dietary interference, as well as a proven good cost-effectiveness ratio.[17] In addition, the issue of the lack of an antidote has already been resolved for one of the NOACs and is in the process of being resolved for the others.

Conflicts of interest

The author has no conflicts of interest to declare.

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