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EDITORIAL COMMENT

Thromboembolic events in patients with atrial fibrillation under anticoagulation☆

Acidentes tromboembólicos em doentes com fibrilhação auricular sob anticoagulação

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The article by Fernandes et al. published in this issue of the *Journal*[1] addresses an important subject, particularly in view of the introduction of the new oral anticoagulants (NOACs): the occurrence of thromboembolic events in patients with atrial fibrillation (AF) under oral anticoagulation therapy.

It is known that patients medicated with vitamin K antagonists (VKAs) may still be at thromboembolic risk due to periods in which their international normalized ratio (INR) is outside the therapeutic range.[2] This may be due to various factors, including poor treatment adherence, inadequate clinical control of dosing, and drug-drug or drug-food interactions. The main measure for the appropriacy of VKA therapy is time in therapeutic range (TTR), the percentage of time in which the patient's INR is within the established limits.

Less well known is the occurrence of thromboembolic complications in patients medicated with NOACs. These may be due to the short duration of their therapeutic effect, which means that missing even one dose can be critical.[2]

The factors underlying the occurrence of stroke in patients with AF despite anticoagulant therapy may be patient-related, such as missing one or more doses or discontinuing treatment altogether. The physician, lacking the means to monitor treatment adherence, may be unaware of these events. In other cases, the fault may be clinical, such as dosing errors or inappropriate discontinuation, or inadequate knowledge of the risks of bleeding complications; it may also be due to suspending medication for too long before surgery or other interventions.[3]

Drug-drug or drug-food interactions may lead to thromboembolism if they reduce the drug's anticoagulant effect. This is an important problem with VKAs but not with NOACs, for which interactions with other drugs or foods are rare or non-existent.[3]

The limitations of VKA therapy have long been known, including their narrow therapeutic window, drug-drug and drug-food interactions, and need for frequent laboratory testing. Maintaining therapeutic levels of these drugs is thus a challenge and failure can have deleterious consequences, notably the occurrence of thromboembolic events.

An important aspect of prevention of thromboembolic events is to ensure that patients prescribed an anticoagulant are aware that they will need to continue the treatment indefinitely. However, persistence with VKAs is low; 21-50% of patients discontinue their medication by one year after inception.[4]

Most cases of stroke under VKA therapy are attributed to periods in which the patient's INR is below the therapeutic window (<2). The most frequently used measure of quality of anticoagulation is TTR, which is subject to various factors, some patient-related and others clinical.

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Using the AFFIRM trial population,[5] Apostolakis et al.[6] developed a score based on the clinical and demographic characteristics of patients with AF to assess the likelihood of poor INR control in VKA therapy. Using linear regression analysis, the authors identified female gender, age <60 years, ethnic minority status, smoking, more than two comorbidities, and medication with amiodarone as predictors of low TTR. In this score, which the authors designated as SAMe-TT_2R_2 (sex, age, medical history; treatment, tobacco, race), ethnic minority status and smoking score two points, while age <60 years, more than two comorbidities, female gender and amiodarone for rhythm control score one point. The score was tested in derivation and internal validation cohorts and the derived model was validated externally in a real-world population of AF patients. The authors concluded that, using a mean TTR cut-off of 0.65, a score of 0 or 1 predicted good INR control and scores $\geq$2 predicted poor control. This score may be useful before beginning VKA treatment by identifying patients in whom poor INR control is more likely, information that may be useful in identifying patients who will need more frequent follow-up and appropriate counseling.

Problems of adherence should be reduced with NOACs, with the convenience of fixed doses without need for INR monitoring, less interactions with other drugs, and lower bleeding risk. However, real-world experience shows that this is not always the case; the high price of the drugs, together with concerns about bleeding complications, lead some patients or their physicians to discontinue NOACs or to replace them with less effective remedies in high-risk situations.

At the same time, the fact that patients under NOACs do not need to be seen regularly to monitor INR leads to lower levels of clinical surveillance and thereby reduces the physician's ability to assess whether patients are adhering to their prescribed treatment.[7]

Tests to measure serum levels of NOACs can be performed in only a few specialized centers and, given the short half-life of these drugs, the information on adherence that they provide is limited to a short period before the test.[8]

Clinical trials on patients with AF under NOACs suggest that, each year, 1.0-2.0% may experience stroke, which causes major problems since effective anticoagulation is a contraindication for the standard approach of thrombolytic therapy in cases of stroke.[9]

Assessment of adherence to NOAC therapy has shown varying results.[10,11] In the few prospective studies carried out, levels of adherence have generally been high (70-98%). Factors associated with poor adherence include educational level, employment status, social isolation and cognitive problems. However, these results may have been influenced by selection bias and by the close clinical surveillance to which these patients are subjected, which may not reflect clinical practice.

Observational studies and small series, which are closer to real-world populations, reveal more variable adherence levels (57-96%), due in part to differences in definitions of adherence and in ways of determining it. Many of these studies were unable to identify factors determining adherence, or produced sharply differing results.

It is now considered that assessment of patients taking NOACs should take into consideration not only adherence (the percentage of doses of a drug taken as prescribed) but also persistence (the duration of treatment from initiation to discontinuation).[12] However, data on which to base a rigorous assessment are lacking, since few studies have been performed using objective measures such as electronic monitoring devices to count pills taken.

There have also been few studies comparing adherence to NOACs with adherence to VKAs and the results are conflicting; several have shown no significant differences between the two.[7,10,11,13] There are some data suggesting lower rates of discontinuation with NOACs compared to VKAs, although it is unclear whether adherence in these cases corresponds to correct intake of the medication.

In a study by Beyer-Westendorf[14] of 7265 patients with AF, persistence in a follow-up of at least 180 days was better with rivaroxaban and dabigatran than with a VKA, and in a follow-up of at least 360 days was better with rivaroxaban than with dabigatran.

The study by Fernandes et al.[1] comes to three main conclusions, not all of them in agreement with the literature:

- Among patients with ischemic stroke despite chronic oral anticoagulation, poor treatment adherence is more frequent in patients taking NOACs than in those taking VKAs;
- The majority of patients taking VKAs had a subtherapeutic INR at admission;
- In most patients suffering a cardioembolic stroke despite taking a NOAC, the event was associated with subtherapeutic dosage or poor treatment adherence.

One of the study's limitations is that it is observational, being based on patients with non-valvular AF admitted to a neurology department with a diagnosis of ischemic stroke. The authors acknowledge other limitations, including the small sample size, the subjectivity inevitable with the use of questionnaires and the acute clinical status of patients following stroke, which often prevents the patient from collaborating.

The most unexpected result was the high level of non-adherence in patients taking NOACs (almost 40%), significantly higher than in those taking VKAs, which suggests serious failings in physicians' counseling of patients taking these new drugs.

Conflicts of interest

The author has no conflicts of interest to declare.

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