EDITORIAL

# The Continuum of Stroke Prevention in Patients with Atrial Fibrillation in Clinical Practice: "Learning Curves", New Challenges and Unmet Needs Across the Globe

*Continuidad en la prevención del accidente cerebrovascular en pacientes con fibrilación auricular en la práctica clínica: "Curvas de aprendizaje", nuevos desafíos y necesidades insatisfechas a través del mundo*

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Stroke prevention is a cornerstone in the management of patients with atrial fibrillation (AF). Ever since historical trials showed the efficacy of vitamin K antagonists (VKAs) in reducing stroke and mortality compared with control (mostly aspirin or placebo) in patients with AF (1), the landscape of AF-related stroke prevention has been constantly changing.

The campaign promoting the importance of adequate prevention of cardioembolic ischaemic stroke using VKAs in patients with AF eventually resulted in a relatively high overall use of oral anticoagulation for stroke prevention in AF (2-4), but there were valuable lessons to be learned along the way. First, practitioners were to learn that using aspirin instead of oral anticoagulation was more harmful than helpful for AF patients, given broadly comparable rates of serious bleeding and the marginal effect of aspirin on stroke prevention and mortality. Then, the use of oral anticoagulation needed to be improved to include AF patients with one or more stroke risk factors, and not those at truly low risk of stroke who do not need stroke prevention therapy. While the decision on whether to use oral anticoagulant therapy should be based on individual patient stroke risk, the risk of bleeding needs to be assessed in order to address modifiable bleeding risk factors and schedule a more frequent clinical follow-up for patients with non-modifiable risk components (e.g., the elderly, those with a history of bleeding, etc.). Importantly, practitioners should not overlook the dynamic nature of individual stroke and bleeding risks, which change over time and need to be regularly re-assessed.

There are many well-known limitations of VKAs, posing a significant burden on their optimal long-term use. Non-vitamin K antagonist oral anticoagulants (NOACs) are at least as effective as VKAs, but safer (in terms of haemorrhagic stroke and intracranial bleeding) (5) and more convenient for long-term use (fixed dosing, predictable dose-related anticoagulant effect, less drug-drug and no food interactions). After the first NOAC approval (dabigatran, 2010), a number of large international registries have been set up to provide insight into the uptake of NOACs and their effectiveness and safety outside randomized trials, in the so-called 'real-world' setting (6, 7).

In this issue of Revista Argentina de Cardiología, Dubner et al. (8) reported findings from the Phase II Global Registry on Long-Term Oral Antithrombotic Treatment in patients with Atrial Fibrillation (GLORIA-AF). GLORIA-AF (9) was a multicentre, international, prospective registry assessing the long-term safety and effectiveness of dabigatran in adult patients with recently diagnosed non-valvular AF and at least one stroke risk factor. The GLORIA-AF registry has a three-phase design including Phase I, before dabigatran approval; Phase II, a cross-sectional study which commenced after dabigatran approval, with a 2-year follow up, and Phase III, which started after comparability between VKA and dabigatran had been achieved, with a 3-year follow-up (from 2014 to 2017).

In their report, including 15,308 patients from 44 countries, Dubner et al. (8) documented consistent improvements in the prescription of oral anticoagulant therapy in AF patients at high risk of stroke, especially among European centres, as well as the increasing uptake of NOACs, especially in Europe and North America (8). Compared with Phase I (10), the overall use of antiplatelet drugs for stroke prevention in AF patients was significantly lower in the GLORIA-AF Phase II registry, still being high in Asia (25.1%

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| | Patients with events | PY | Crude IR per 100 PY (95% CI) |
|---|---|---|---|
| All-cause mortality | 179 | 7.215 | 2.48 (2.13-2.87) |
| Stroke | 47 | 7.192 | 0.65 (0.48-0.87) |
| Acute myocardial infarction | 36 | 7.204 | 0.50 (0.35-0.69) |
| Major bleeding | 70 | 7.199 | 0.97 (0.46-0.84) |

CI = Confidence interval; IR = incidence rate; PY = patient-years.

**Table.** Crude incidence rates at 2 years of follow-up in patients treated with dabigatran.

of patients) and North America (14.1%). Inadequate thromboprophylaxis was more prominent in patients with a single stroke risk factor (antiplatelet therapy in 10.0% of patients, and no antithrombotic treatment in 6.8% of patients), compared with those with two or more stroke risk factors (19.3% and 14.1%, respectively). The high rate of aspirin prescription in North America may be explained by the local guidelines' recommendation at the time when the GLORIA-AF Phase II registry was conducted, whereas the high rates of aspirin use and low rates of oral anticoagulant prescription (55.2%) in Asia could have been influenced by the estimated high bleeding risk. Results from ongoing registries (9, 11) will show the most recent trends in stroke prevention in contemporary clinical practice.

The report of Dubner et al. (8) also tackled the important issue of long-term adherence to NOAC treatment. At 24 months, 30% of patients were not taking dabigatran (notwithstanding a significantly lower discontinuation rate in comparison to VKAs), and the problem of maintaining long-term persistence to NOAC therapy remains a challenge for clinicians. In the GLORIA-AF Phase II registry, most of dabigatran discontinuation occurred soon after the initiation of therapy. The most common reasons for discontinuation were not related to adverse events but were classified as ''other'' reason(s) without further explanation. A detailed analysis of the reasons for drug discontinuation would be very informative, potentially revealing areas of patient management that can be further improved.

Finally, the rates of adverse events observed in the study of Dubner et al. (8) (see Table) are broadly reflective of the effects of dabigatran in the pivotal randomized trial of dabigatran versus warfarin for stroke prevention in AF (12). In addition, the observations from the GLORIA-AF Phase II registry are concordant with other real-world reports highlighting the decreasing rates of stroke and acceptable rates of bleeding with increasing use of oral anticoagulant therapy (13). Nevertheless, as observed in many other datasets, all-cause mortality rates among patients with AF remain considerably high, suggesting that other elements such as cardiovascular risk factors and concomitant comorbidity should be timely identified and recognized as an equally important part of the integrated holistic management of AF patients (14).

## Conflicts of interest

None declared.

(See authors' conflicts of interest forms on the website/ Supplementary material)

## Ethical considerations

Not applicable.

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