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EDITORIAL COMMENT

My patient cannot or will not comply with oral anticoagulation. Do I cross my fingers or cross the septum?☆

O meu doente não pode, não quer ou não cumpre a anti-coagulação oral. Cruzo os dedos ou cruzo o septo?

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Atrial fibrillation (AF) is a prevalent disease that affects up to 3% of the population and accounts for 1–3% of health care costs due to stroke, sudden death, heart failure, unplanned hospitalizations and other complications.[1–3]

Once non-valvular AF is diagnosed, a multidisciplinary and multifaceted approach is required, including acute management, treatment of underlying and concomitant conditions, rate and rhythm control, and prevention of the most feared complication, stroke. The tendency for blood pooling in the left atrium and left atrial appendage (LAA) due to AF was first reported in 1996, and although oral anticoagulation with vitamin K antagonists and direct oral anticoagulants (DOACs) has significantly reduced stroke risk, up to 40% of patients with AF are untreated, due to intolerance, bleeding, or other contraindications.[1,4,5]

Left atrial appendage occlusion (LAAO) aims to perform complete mechanical blockage of the LAA, which is the anatomical origin of around 90% of the thrombi that cause stroke. The two main trials comparing LAAO with warfarin, PROTECT AF and PREVAIL, demonstrated that closure is non-inferior for the prevention of ischemic stroke and is superior for the prevention of cardiovascular and all-cause mortality.[2,5,6] However, the randomized clinical trials were restricted to a single device and did not include patients who were intolerant to anticoagulation. Percutaneous LAAO, like AF ablation, has not been properly assessed in randomized trials with the standard current comparator, DOACs, in terms of major cardiovascular events. There have, of course, been large observational studies that suggest a reduction in stroke risk compared with risk estimates such as the CHA_2DS_2-VASc score. These studies often included patients who were only prescribed antiplatelet agents or took no antiplatelet or anticoagulant agents at all following the implantation procedure.[6] Furthermore, there is no evidence that the presence of peri-device leak is associated with subsequent thromboembolic events, although these

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studies had short follow-up periods and varying antithrombotic regimens (antiplatelet, anticoagulant or both). In the largest randomized trial, PROTECT AF (455 participants), and in 339 patients from the multicenter Amplatzer Cardiac Plug study, the number of ischemic events was low (16 and seven, respectively).[5,7]

The study by Paiva et al. published in this issue of the *Journal*[8] is highly relevant to this question. They set out to determine whether the risk-benefit ratio of LAAO for cerebrovascular prevention is superior to that of DOACs over a mean follow-up of 17 months. This prospective observational study assessed 302 patients (62 of whom were excluded) with non-valvular AF at high risk for stroke admitted to a single reference center between 2015 and 2017. The authors concluded that LAAO (n = 91) was not inferior to long-term treatment with NOAC (n = 149) for preventing the composite endpoint of death, stroke and major bleeding. This result differs from those of previous large observational studies, in which the reduction in stroke risk was similar in patients who received only antiplatelets, or neither antiplatelets nor anticoagulants, after the procedure.

The study has several merits. It provides a clear picture of the skill and expertise of a highly-regarded Portuguese group with extensive experience in this procedure, whose success rate is 96.3%, and who make use of guidance by intracardiac echocardiography (ICE) and transesophageal echocardiography.[9] It is unusual in bringing together two different high stroke risk case mixes: primary and secondary prevention by LAAO and secondary prevention with DOACs in the Neurology AF registry. This naturally reflects the different profiles of these two patient groups but does not consistently favor the LAAO group. Three devices used in real-world practice, selected by individual operators, are analyzed: the AMPLATZER Cardiac Plug™ or Amulet™ (St. Jude Medical) and the WATCHMAN™ (Boston Scientific). The study portrays real-world contemporary anticoagulant and antiplatelet regimens following LAAO, including the fact that a fifth of these patients stopped antiplatelet treatment six months after device implantation, and observes that mortality in the DOACs group was initially higher, while in the LAAO group it was distributed more evenly over the follow-up period. Finally, it reports a very real risk of fatal bleeding, with two deaths due to severe bleeding.

The authors point out certain methodological limitations. Besides the biases inherent to the study design, its statistical power (approximate and not always consensual) was estimated at 51%, indicating a 49% probability of not finding a statistically significant difference and a 5% probability of finding a difference that does not exist (type 1 error). However, this does not invalidate the conclusions.

It is important to bear in mind that despite progress, stroke prevention, by LAAO and generally in the context of non-valvular AF, still faces several challenges. The CHA_2DS_2-VASc and HAS-BLED risk scores, which are recommended in the guidelines, are useful tools but have their limitations. Even in the best circumstances, they are not particularly robust for predicting individual stroke and bleeding risk.[3]

Individuals who stand to derive greater benefit from LAAO – those who are intolerant of chronic anticoagulation – are excluded from studies of the procedure, despite its growing use in these cases. For example, a recent meta-analysis of 12 observational studies (seven retrospective and five prospective) in patients with a history of intracranial bleeding concluded that LAAO can potentially be an effective and relatively safe treatment option after shared decision-making with individual patients.[5,6]

The presence on screening exams of thrombi in the LAA that do not respond to anticoagulation is another exclusion criterion in the major studies, due to concerns that they increase the risk of complications. The impact of embolic protection devices in such cases is not known, but there have been reports of successful implantation using appropriate techniques and selected devices.[10]

The LAA's considerable anatomical variability in shape, volume, length and width requires a variety of devices to be available. In addition, fibrosis of this structure may have prognostic impact.[5]

Increasing access to three-dimensional ICE may help to widen the use of LAAO.[5,11]

In conclusion, the study by Paiva et al. is original and has the merit of describing the profile of a real-world population of Portuguese patients with non-valvular AF at high stroke risk. It indicates that percutaneous LAAO is safe and effective compared to DOAC therapy in the medium term. The use of LAAO is supported by the pressing need for therapeutic alternatives to chronic OAC, but assessment of the prognostic value of the procedure requires further validation in randomized trials, led by individual researchers or by medical societies. That is our present challenge.

Conflicts of interest

The author has no conflicts of interest to declare.

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