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EDITORIAL COMMENT

What is the future for left atrial appendage closure?☆

Qual o futuro do encerramento do apêndice auricular esquerdo?

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The left atrial appendage (LAA) is by far the most common origin of thrombi associated with non-valvular atrial fibrillation (AF).[1] This thrombogenicity is not solely due to the lack of atrial contractility, being influenced by a variety of local and systemic factors, but LAA thrombi rarely occur in patients in sinus rhythm. We may disagree with the current methods of LAA closure, or consider them limited, but theoretically it makes sense that closing this space could significantly reduce the thromboembolic risk associated with AF. It is thus certain that LAA closure will remain an option in the future; techniques and approaches will evolve in order to improve safety and efficacy, but the strategy will endure.

Current percutaneous techniques have the advantage of having been analyzed early in randomized clinical trials. PROTECT AF[2,3] was the first to demonstrate non-inferiority of percutaneous LAA closure compared to anticoagulation with warfarin in patients with non-valvular AF, with similar event reduction to non-inferiority trials of new oral anticoagulants (RE-LY[4], ARISTOTLE[5] and ROCKET AF[6]). However, complications associated with implantation of the closure device, which is an invasive procedure, raised doubts concerning the safety of an intervention which is after all intended to be preventive. The US Food and Drug Administration (FDA) accordingly commissioned an additional clinical trial (PREVAIL[7]), while the European Society of Cardiology (ESC) has issued recommendations on the use of LAA occlusion as an alternative to OAC for AF patients at high bleeding risk.[8] The recently published preliminary results of the PREVAIL study[7] show that the implant success rate for the Watchman was 95%, higher than the 91% in PROTECT AF,[2] even though centers without previous experience with the procedure were included. The primary safety endpoint – acute (7-day) death, ischemic stroke, systemic embolism and procedure- or device-related complications requiring surgical or endovascular intervention – occurred in 6 out of 269 patients (2.2%); the 95% upper confidence bound of 2.618% was lower than the pre-specified criterion of <2.67. A wider safety endpoint including cardiac perforation, pericardial effusion with tamponade, ischemic stroke, device embolization, and other vascular complications occurred in 4.4% of patients, significantly lower than in PROTECT AF.[2,3] Pericardial effusion requiring pericardiocentesis was observed in 1.5% of cases compared to 2.4% in PROTECT AF.[2,3] No procedure-related deaths were reported in any of the trials. Analysis of the primary efficacy endpoint of stroke, systemic embolism, and cardiovascular/unexplained death at 18 months was limited by the fact that follow-up is complete in only 58 patients in the intervention arm and 30 in the control arm out of a study population of 407 patients. The event rate for this endpoint was 0.064 (6.4 events per 100 patient/years) in both arms. In

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a pre-specified joint analysis including the PROTECT AF population, the upper 95% confidence bound of 1.88 was slightly higher than the success criterion of <1.75. A second, more limited efficacy endpoint of ischemic stroke or systemic embolism occurring >7 days post randomization, designed to exclude the acute effects of the intervention, met the non-inferiority criterion, although as for the first efficacy endpoint, 18-month follow-up was incomplete in most patients.

This trial therefore meets the safety requirements specified by the FDA; evaluation of the efficacy criteria must await the end of the defined follow-up period. The results will be crucial to the device gaining approval and may help identify those candidates with a better risk/benefit profile. Irrespective of the results of the PREVAIL trial and the history of this particular device, it seems certain that LAA closure will continue to undergo technical improvements and will be a valid alternative for reduction of thromboembolic risk in AF.

However, many would disagree. It is often argued that stroke is a systemic disease and cannot be reduced to a mechanical phenomenon in the LAA. Although this is undoubtedly true, it is equally true that the LAA is the origin of most thrombi in patients with non-valvular AF. LAA occlusion will not be a definitive solution, but it will play a part in risk reduction. Another argument is that new anticoagulants have precluded the need for alternative treatments, but all currently available anticoagulants are associated with at least some discontinuation due to intolerance, and cannot be used in patients with high bleeding risk[4–6]; they are thus not the solution for all patients. Another criticism is that in many countries the technique is being implemented only in patients with high bleeding risk, whereas the PROTECT AF[2] and PREVAIL[7] trials only included patients without contraindication to anticoagulation, which is inevitable given the need for such a randomized trial to have a control group taking warfarin to compare with the intervention group and thus provide proof of concept. LAA closure in patients with contraindication to anticoagulation was studied in the ASAP trial,[9] which showed that in terms of safety it was similar to the above trials and had excellent efficacy, showing a 77% lower incidence of ischemic stroke compared to that expected from the $CHADS_2$ score. Other interesting results from analyses of the PROTECT AF trial[2,3] and the CAP registry[10] include improved quality of life,[11] economic benefit[12] and net clinical benefit[13] soon after the procedure. The populations of these studies will be followed for up to five years, which will provide a large quantity of data on events and give a clearer idea of the long-term impact of this technique.

The analysis presented in this issue of the *Journal* is a good example of the responsible introduction of an invasive preventive technique. Patients were selected who could not take oral anticoagulants due to high bleeding risk but who also presented significant thromboembolic risk, on the assumption that the benefit would outweigh the potential risk, even considering the learning curve effect. Although the study population was significantly smaller than in the major trials and registries, it is fair to say that the safety profile in this series was excellent compared to previous studies. There are four centers in Portugal with considerable experience in LAA closure, having begun their programs before the technique was included in the ESC guidelines; all of them anticipated the trend and directed their programs towards patients with high bleeding risk and contraindication to oral anticoagulation. The responsible, rigorous and safety-conscious approach of these centers has contributed to the consistent growth in percutaneous LAA closure, increasing confidence in the technique in other centers and creating excellent prospects for the future.[14]

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