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Editorial

Evidence and Indications for Percutaneous Closure of the Left Atrial Appendage

Evidencia e indicaciones del cierre percutáneo de la orejuela izquierda

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In patients with atrial fibrillation (AF), the standard therapy for the prevention of thromboembolic events is oral anticoagulation (OAC). However, OAC is associated with a risk for major and minor bleedings, which in some patients may be deemed more important than the prevention of thromboembolic complications. An alternative strategy for stroke prevention in AF patients is percutaneous closure of the left atrial appendage (LAA). Its rationale is that most clots form in the LAA, and therefore its obliteration will prevent clot formation. The most commonly used devices for percutaneous LAA closure (LAAC, or occlusion, LAAO) are the Watchman (Boston Scientific) and Amulet (Abbott) devices. However, current evidence on short- and long-term outcomes with these devices is still incomplete, making treatment choices difficult.

Only 2 randomized controlled trials have compared percutaneous LAAC with OAC. In both PROTECT AF[1] and PREVAIL,[2] implantation of the Watchman device was compared with vitamin K antagonists (VKA; warfarin). All included AF patients had to be eligible for VKA therapy.[3] Many analyses of these trials have been reported in the literature over the years. Recently, a 5-year follow-up and meta-analysis of the 2 trials combined was published.[4] While the PREVAIL trial did not reach its noninferiority objective, the composite endpoint of stroke, systemic embolism, and cardiovascular death was similar between the Watchman and VKA groups for both trials combined (hazard ratio [HR], 0.82; P = .27). In addition, the rates for all strokes and systemic embolisms were similar (HR, 0.96; P = .87). Importantly, the rate of ischemic stroke and systemic embolism was higher with Watchman, but this difference did not reach statistical significance in this 5-year analysis (HR, 1.71; P = .08) as it was performed after a 2.7-year follow-up (HR, 1.95, P = .05).[5] Therefore, the original hypothesis, that occluding the LAA is sufficient to prevent ischemic stroke, seems flawed. The reasons are that a significant proportion of clots may form in the body of the left atrium, and that clots may be the result of a more systemic vascular and procoagulant state, both leading to atrial clots and to primary thrombotic occlusion of cerebral vessels. In contrast, LAAC was shown in PROTECT AF and PREVAIL to be associated with decreases of 80% in hemorrhagic stroke, 59% in disabling stroke, 52% in postprocedure bleeding, 41% in cardiovascular death, and 27% in all-cause death.[3,4] The reduction in disabling strokes with Watchman is based on the fact that hemorrhagic strokes tend to have a higher functional impact than ischemic strokes. This led to a new focus for LAAC: that its potential bleeding benefit makes it especially attractive in AF patients at high risk of bleeding and/or with other contraindications for OAC therapy, resulting in a net clinical benefit compared with VKA.

PROTECT AF and PREVAIL were designed and conducted at a time when VKA were still the treatment of choice for patients with AF. In recent years, however, it has been proven in many randomized controlled trials that nonvitamin K oral anticoagulants (NOACs) have a clear net clinical benefit compared with warfarin.[6,7] This has resulted in a clear preference of the 2016 ESC Guidelines for NOACs over VKA in eligible AF patients. Compared with VKA, NOACs result in significantly lower bleeding rates without an increase in ischemic stroke and systemic embolism,[7] in contrast to observations in trials comparing LAAC with warfarin. Moreover, real-world data with NOACs confirm their net clinical benefit compared with warfarin also in higher risk groups, such as the elderly or other patients at increased bleeding risk.[8,9] On the other hand, the combined dual antiplatelet plus anticoagulant regimen, which was part of the original LAAC protocol, has in the real-world been replaced by shorter and less aggressive combined regimens. Therefore, the largest unanswered question is currently whether there is a net clinical benefit of LAAC compared with NOACs. It is clear that with moving targets at both ends of the spectrum, it becomes very unclear how both would compare. The overall result is that there are no firm data on which to base the choice between LAAC or NOAC.

A sizable number of real-world registries are currently ongoing in patients after LAAC. Although registries provide less information than randomized controlled trials regarding indications and net clinical benefit, they do provide valuable information on complication rates and longer-term outcomes.[10] Procedural success and complication rates are important because they might counterbalance any lifetime beneficial outcomes of LAAC compared with VKA. Data on all patients undergoing Watchman implantations in the US (US postapproval cohort) have recently

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been published, with the caveat that this is a sponsor-organized and maintained registry.[11] Among 3822 consecutive cases, implantation was successful in 95.6%. Procedural complication rates included 1.02% pericardial tamponades, 0.24% device embolizations, 0.078% procedure-related strokes, and 0.078% procedure-related deaths. Overall, complication rates were lower in this postapproval cohort than in the PROTECT AF and PREVAIL trials, although 71% of the operators were new and were not involved in the clinical trials.[11] The EWOLUTION trial is an EU-based registry including 1025 patients. It is smaller than the US postapproval cohort, but has published data that cover both the peri-implant period and a follow-up period of 1 year.[12] The most interesting finding of this registry is a stroke rate of 1.1%, representing an 84% relative risk reduction (compared with no anticoagulation) from what could be expected based on the $CHADS_2$ score (7.2% stroke rate).[12] Most patients in EWOLUTION did not receive VKA/NOAC after implantation but only antiplatelet therapy or even no therapy, which apparently did not affect the occurrence of stroke or other thromboembolic events.[12] In the recently published Belgian registry of LAAC in 457 consecutive patients,[13] implantation was successful in 97.1%. Procedural complication rates included 1.9% pericardial tamponades, 0.4% device embolizations, and 0.6% procedure-related deaths. The annual stroke rate was 1.2%, similar to the EWOLUTION registry.

Safety and efficacy with non-Watchman devices have not been established in randomized controlled trials. Differences in device design, implant outcomes, residual device leak, and device-associated thrombosis might influence net clinical benefit. Direct head-to-head comparisons between different devices are missing, but in the Belgian registry no differences were observed between the Watchman device or AMPLATZER cardiac plug/Amulet devices.[13] Furthermore, several noninferiority trials of new devices compared with Watchman are ongoing or planned. For instance, the AMPLATZER Amulet LAA Occluder Trial (NCT02879448) started recruiting patients in 2016 and is a randomized controlled trial comparing the Amulet device with the Watchman device in 1600 patients; trial completion is expected in 2023.

An important question for clinicians is which patients can be selected for LAAC and which factors should be taken into consideration? The first treatment choice for prevention of thromboembolic events in patients with AF remains OAC, preferably by NOACs unless these are contraindicated.[14] Based on the randomized trials discussed,[3,4] efficacy for prevention of ischemic stroke and systemic embolism is lower for LAAC compared with OAC and it can be assumed that this would be even more so in the case of NOACs. Anticoagulation has the additional benefit of preventing strokes based on thrombi formed outside the LAA. Therefore, LAAC is not presented as a substitute for OAC therapy in AF patients in the ESC Guidelines.[6] On the other hand, although bleeding risk is lower with NOACs compared with VKA, a number of patients still develop life-threatening bleedings. Given the long-term bleeding benefit of LAAC over VKA, especially for nonprocedure-related bleeding, a net clinical benefit of LAAC could be anticipated in patients at high bleeding risk. Therefore, the ESC Guidelines indicate that LAAC may be considered for stroke prevention in patients with AF and contraindications for long-term anticoagulant treatment (class IIb, level of evidence B), while recognizing that there has been no formal prospective trial that has tested LAAC vs (N)OAC in such AF patients.[6] Aspirin monotherapy is no alternative: while stroke prevention is at best 30%, LAAC registries indicate a much higher decrease in stroke rate, at least when compared with historical controls.[12] The selection of such patients requires discussion within an AF Heart Team, since many patients deemed unsuitable for OAC therapy might be candidates for NOAC therapy (ie, after correcting modifiable bleeding risks).[6,14]

Many questions remain unanswered. As mentioned, a direct comparison of LAAC with NOACs is needed. An academic study randomizing 400 patients to either NOAC or LAAC has been initiated by the Charles University in the Czech Republic (PRAGUE-17: Left Atrial Appendage Closure vs Novel Anticoagulation Agents in Atrial Fibrillation; NCT02426944). Another ongoing study is STROKECLOSE (Prevention of Stroke by Left Atrial Appendage Closure in Atrial Fibrillation Patients After Intracerebral Hemorrhage; NCT02830152) in which LAAC with the Amulet device is compared with anticoagulant therapy (including VKA and NOACs). A second question is how other devices perform, including Amulet (Abbott) and WaveCrest (Coherex). A number of noninferiority trials comparing these devices with the Watchman device will inform us in the future. All LAAC studies will require long-term follow-up to correctly evaluate the efficacy and safety of these different devices, in different patient groups. Finally, trials are needed to prospectively evaluate less stringent postimplant antiplatelet + anticoagulant regimens, which are often used in daily practice. Many registries in different countries are ongoing and will provide additional long-term data on mortality, stroke rates, and bleeding rates, although their scientific value is clearly weaker.

In conclusion, randomized trials indicate that LAAC is less effective in reducing ischemic stroke than VKA (and likely than NOAC). However, they may have a long-term bleeding benefit, which may translate into a net clinical benefit, although this needs confirmation against NOACs and less stringent postimplant regimens. As per the guidelines, NOACs remain the mainstay of stroke preventive therapy in AF, since LAAC is not a proven substitute. However, in patients with contraindications for OAC therapy, a balanced judgment in light of the available evidence may lead to consideration of LAAC. Ideally, all these patients should be implanted in the context of a clinical trial or prospective registry, since our patients deserve more definitive answers.

CONFLICTS OF INTEREST

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