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Editorial

Defining the Role of Left Atrial Appendage Closure in Atrial Fibrillation

Definición del papel de la oclusión de la orejuela auricular izquierda en la fibrilación auricular

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Despite more than 10 years' clinical experience,[1] the role of percutaneous left atrial appendage (LAA) closure in patients with nonvalvular atrial fibrillation (NVAF) is still elusive. The reasons include the complexity of the procedure, the limited clinical information from controlled trials, and recent developments in the field of anticoagulation. A weak, grade IIb recommendation (ie, usefulness/efficacy less well established by evidence/opinion) was released by the 2012 European atrial fibrillation guidelines, reflecting uncertainty over LAA closure in patients with a high stroke risk and contraindications for long-term oral anticoagulation.[2] A valuable addition to our current knowledge of LAA closure in patients with NVAF is provided by the experience of López-Mínguez et al.[3] with the use of the Amplatzer occlusion device (Amplatzer Cardiac Plug [ACP]). Some practical questions and concerns relating to LAA closure in patients are discussed below, with the aim of helping readers shape an informed opinion about this transcatheter procedure.

RATIONALE OF CLOSING THE LEFT ATRIAL APPENDAGE IN ATRIAL FIBRILLATION

The purpose of this intervention is to exclude a major source of thromboembolism from the rest of the circulation in patients with dilated and poorly contracting atria, without the need for long-term antithrombotic therapy. The advantages would be twofold: prevention of ischaemic events caused by emboli originating from thrombi in the LAA and discontinuation of antithrombotic therapy within a few months of the procedure, avoiding the bleeding risk associated with the long-term use of antithrombotic drugs.

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TO WHAT EXTENT, HOWEVER, DO THROMBOEMBOLI IN ATRIAL FIBRILLATION COME FROM THE HEART AND, IN PARTICULAR, FROM THE LEFT ATRIAL APPENDAGE?

In a subgroup of approximately 800 patients with NVAF enrolled in the Stroke Prevention in Atrial Fibrillation III trial,[4] complex aortic plaques were detected by transesophageal echocardiography (TEE) in 25% and were independently correlated to thromboembolic events, with a risk not dissimilar from that associated with the presence of LAA thrombi, detected in 10% (relative risks: 2.1 vs 2.5). Thus, atherothrombotic embolism, in addition to cardioembolism, may contribute to ischaemic events in patients with NVAF. A recent overview of autopsy, surgical, or TEE studies found that, in patients with NVAF, approximately 10% of left atrial thrombi (27 of 254) were outside the LAA, and this proportion increased to approximately 20% among patients who were not properly anticoagulated, or had left ventricular dysfunction, or a prior stroke.[5] Interestingly, in patients with valvular atrial fibrillation, more than 50% of left atrial thrombi (334 of 592) were found outside the LAA, a finding which may explain the conflicting outcomes of surgical LAA exclusion.[2,5] Percutaneous LAA occlusion, therefore, represents a localized treatment for what, not uncommonly, appears to be a broader problem.

TO WHAT EXTENT ARE THE AVAILABLE CLOSURE DEVICES THROMBOGENIC AND WHAT ANTITHROMBOTIC REGIMENS HAVE BEEN USED?

There are 2 self-expanding occluders in current use: the Watchman device, a parachute-shaped filter with midperimeter fixation barbs; and the ACP, a 3-part system made of an anchoring lobe linked by a flexible waist to a proximal sealing disc.[1,6] The use of a third system, PLAATO (Percutaneous Left Atrial Appendage Transcatheter Occlusion), was discontinued for financial reasons.[7] Serial TEE has documented thrombus formation on the luminal side of the device with a variable frequency, ranging from 4%[8] to 10%[6] or even 14%[3] of cases. The rates of device thrombosis seem directly proportionate to the frequency of serial TEE[3] (stated differently, the harder you look the more you see) and inversely proportionate to the concomitant use of warfarin.[8] Thrombus detection is more frequent in the first few months of implantation[3]; thrombosis rates

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presumably decline along with complete endothelization of the foreign surfaces.

Various antithrombotic regimens have been used with LAA closure. In the Watchman left atrial appendage system for embolic protection in patients with atrial fibrillation trial (PROTECT-AF),[9] warfarin was given for 45 days and TEE was performed during this time; then dual antiplatelet therapy (DAT) with acetylsalicylic acid (ASA) and clopidogrel was given up to a 6-month TEE control, followed by ASA alone. However, in 14% of patients warfarin was continued beyond 45 days; and in 8% of patients warfarin was continued beyond 6 months, because of incomplete LAA closure (defined as a residual flow>5 mm) or because of device thrombus.[9] A more recent registry of 150 patients receiving the Watchman occluder suggests that DAT prescribed for 6 months followed by ASA alone may be an adequate antithrombotic regimen.[10] With the use of the ACP device, warfarin has been avoided and DAT has been prescribed for variable durations: either 1 month of DAT followed by ASA for 3 months to 4 months,[6] or 3 months of DAT followed by ASA for up to 6 months.[2] In case of device thrombus, DAT has been prolonged and subcutaneous heparin given for 2 weeks, followed by TEE.[2] Clearly, both the duration and the type of antithrombotic treatment prescribed after implantation are evolving and remain to be defined.

WHAT ARE THE RELATIVE BLEEDING RISKS OF ACETYLSALICYLIC ACID, DUAL ANTIPLATELET THERAPY, WARFARIN, OR NEW ANTICOAGULANTS IN NONVALVULAR ATRIAL FIBRILLATION PATIENTS?

In the BAFTA (Birmingham Atrial Fibrillation Treatment of the Aged Study),[11] approximately 1000 patients with ≥75 years of age were randomized to ASA 75 mg per day or warfarin (target international normalized ratio, 2-3) and followed for 2.7 years; the annual major bleeding rates were 2.0% for ASA vs 1.9% for warfarin, and those of intracranial haemorrhage were 0.5% for ASA vs 0.6% for warfarin. In the ACTIVE W (Atrial Fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events),[12] approximately 6600 patients were randomized to ASA (75 mg to 100 mg per day) plus clopidogrel 75 mg per day (DAT), or warfarin (target international normalized ratio, 2-3) and followed for 1.3 years; the annual major bleeding rates were 2.4% with DAT vs 2.2% for warfarin, and those of haemorrhagic stroke were 0.12% with DAT vs 0.36% (*P*=.036) for warfarin. In the AVERROES study,[13] approximately 5600 patients with NVAF for whom warfarin was not suitable were randomized to ASA 81 mg to 324 mg per day (>90% took≤162 mg per day) or apixaban 5 mg twice daily, and followed for a mean of 1.1 years; the annual major bleeding rates were 1.2% for ASA vs 1.4% for apixaban, and those of haemorrhagic stroke were 0.3% for ASA vs 0.2% for apixaban. In the 3 trials mentioned above, efficacy and net clinical benefit were significantly greater with anticoagulation than with antiplatelet agents. Thus, the bleeding potential of ASA or DAT may not be inferior to that of warfarin or of new oral anticoagulants. Moreover, in patients with NVAF, the new oral anticoagulants dabigatran, rivaroxaban, and apixaban have resulted in lower rates of intracranial haemorrhage and fatal bleeds, with similar or superior efficacy, as compared to warfarin.[14]

IS LEFT ATRIAL APPENDAGE CLOSURE BETTER THAN WARFARIN FOR STROKE PREVENTION?

In the unblinded PROTECT-AF trial,[9] NVAF patients with a CHADS (congestive heart failure, hypertension, age ≥75, diabetes, and stroke) score>1 were randomized to LAA closure (n=463) or warfarin (n=244), for a mean of 18 months. Patients with contraindications to warfarin, LAA thrombus, patent foramen ovale, or mobile aortic atheroma were excluded from the trial.[9] After intervention, TEE was performed at 1.5 months, 6 months, and 12 months to assess device position and peridevice flow.[9] With intervention, as compared to warfarin, the hazard ratio for stroke, systemic embolism, and cardiovascular or unexplained death was 0.63 (credibility interval 0.33-1.17); ischaemic stroke was numerically more frequent (2.2% per year with intervention vs 1.6% per year with warfarin), while haemorrhagic stroke was definitely less frequent (0.1% per year with intervention vs 1.6% per year with warfarin) in the intervention group.[9] This trial suggests that the efficacy of LAA closure is noninferior to long-term warfarin, with lower rates of cerebral bleeds but similar overall stroke rates. To date, PROTECT-AF is the only randomized trial[9] performed on LAA closure; it is relatively underpowered (as indicated by the wide credibility interval) and, because it compares LAA closure to the use of long-term warfarin, the results cannot be directly applied to a warfarin-ineligible population. The potential risks and benefits of LAA closure as compared to warfarin in patients with NVAF are listed in the Table.

AT PRESENT, IS LEFT ATRIAL APPENDAGE CLOSURE RISKY?

There is an upfront concentration of adverse events and a clear learning curve for the LAA closure procedure. In the PROTECT-AF trial,[9] the annual safety event rates were 7.4% with intervention (more than half on the day of the procedure) vs 4.4% with long-term warfarin. Events included serious pericardial effusion requiring drainage and device embolization.[9] With operator experience, the 7-day periprocedural event rate declined from approximately 10% to approximately 5%.[8] Most strokes after LAA closure were caused by air embolism[9]; stroke-related disability or death was higher with intervention vs warfarin.[8] In some centers endocarditis prophylaxis was performed for a few months, followed by TEE control.[6]

HOW DOES THE SERIES BY LÓPEZ-MÍNGUEZ ET AL. ADD TO OUR CURRENT KNOWLEDGE?

This is a single-center study of 35 consecutive patients with NVAF deemed unsuitable for long-term anticoagulation, undergoing LAA closure with the ACP.[3] The authors admirably describe the technical aspects of the procedure, the patients' natural history up to 1 year, and the implanted devices monitored by TEE after 24 hours, 1 month, 3 months, 6 months, and 12 months. Two caveats, however, should be considered: the lack of a contemporary control group (reference to historical controls should be discouraged) and the undersized sample with limited power to assess clinical safety and efficacy.

WHO, AT PRESENT, IN THE AUTHORS' VIEW, MIGHT BE ELIGIBLE FOR LEFT ATRIAL APPENDAGE CLOSURE?

NVAF patients with a life-expectancy of at least 1 year, a high thromboembolic risk (CHADS score≥2), and either a very high bleeding risk (HAS-BLED [hypertension, abnormal liver function, abnormal kidney function, stroke history, bleeding history, labile international normalized ratio, elderly age ≥65 years, concomitant alcohol intake, or concomitant drug therapy] score>3) or an absolute contraindication to long-term anticoagulation, might be eligible for LAA closure. Absolute contraindications to warfarin

Table
Potential Risks and Benefits of Left Atrial Appendage Closure vs Warfarin in Patients With Nonvalvular Atrial Fibrillation.

	LAA Closure	Warfarin
Pros	• Exclusion of a major source of thromboembolism • Long-term antithrombotic treatment not required • In PROTECT-AF, lower haemorrhagic stroke rates vs warfarin • In patients ineligible for anticoagulation, potentially lower rates of ischaemic and haemorrhagic strokes vs antiplatelet agents or vs placebo (to be tested)	• Effective stroke prevention vs placebo, acetylsalicylic acid, or dual antiplatelet therapy in NVAF • Systemic treatment for a potentially broad source of thromboembolism • INR: good measure of effective anticoagulation • In PROTECT-AF, noninferior rates of strokes, systemic embolism, and cardiovascular death vs LAA closure • Noninvasive. Simple. Little or no training required • Established track record • Cheap
Cons	• Local treatment against a potentially broader source of thromboembolism • Single randomized trial in a relatively small, warfarin-eligible population • Thrombogenic foreign surface for the first few months until endothelization occurs • Suboptimal procedure in up to 30% patients: up to 10% failed implants, approximately 10% periprocedural complications, and approximately 10% extended antithrombotic regimen • Learning curve and specialized training to be considered. Procedure usually performed under TEE or intracardiac echocardiography guidance. Serial TEE advisable during the first few months • Invasive. Adverse contrast medium effects, eg, on kidney function • Upfront costs • Long-term safety unknown	• Frequent monitoring • Drug-drug and drug-food interactions • ≥30% of treated patients not in therapeutic range • Compliance suboptimal and declining over time • Underuse in the elderly where stroke prevention is most needed • Annual rate of major bleeding is approximately 2% to 3%, including intracranial haemorrhage (approximately 0.5% per year)

INR, international normalized ratio; LAA, left atrial appendage; NVAF, nonvalvular atrial fibrillation; PROTECT-AF, Watchman Left Atrial Appendage System for Embolic Protection in Patients With Atrial Fibrillation; TEE, transesophageal echocardiography.

may include active or recent major bleeding not provoked by invasive procedures[3]; a history of intracranial haemorrhage, either spontaneous or during warfarin; chronic haematological bleeding disorders (eg, thrombocytopenia and myeloproliferative diseases); lack of compliance or poor international normalized ratio control; and severe liver disease. Patients with life-expectancy<1 year, with TEE evidence of LAA thrombus (thromboembolic risk of procedure too high), or with low thromboembolic or low bleeding risk (risk of procedure surpasses potential benefits) in our view, should not be considered for this procedure.

CONCLUDING REMARKS AND PERSPECTIVE

Percutaneous LAA closure in NVAF patients appears noninferior to warfarin for the prevention of all types of stroke, systemic embolism, and cardiovascular death, but is a risky procedure; moreover, evidence from randomized trials is limited. Extreme caution in performing the implantations and in interpreting the available clinical data is recommended. Future controlled trials should try to address 2 main questions: *a)* in anticoagulation-ineligible patients, what are the ischaemic stroke rates associated with LAA closure as compared to long-term antiplatelet treatment or no antithrombotic treatment?, and *b)* (addressed in the PROTECT-AF trial),[9] in anticoagulation eligible patients, what are the overall (particularly haemorrhagic) stroke rates associated with LAA closure as compared to warfarin or a new oral anticoagulant?[15] The latter strategy is currently being explored in the PREVAIL (a prospective trial using the Watchman device) and ACP randomized controlled trials.[1]

CONFLICTS OF INTEREST

None declared.

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