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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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.5,6 Percutaneous LAA occlusion, therefore, represents a localized treatment for what, not uncommonly, appears to be a broader problem.

RATIONALITY 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.
presumably decline along with complete endothelialization 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), warfarin was given for 5 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. 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. 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, or 3 months of DAT followed by ASA for up to 6 months. In case of device thrombus, DAT has been prolonged and subcutaneous heparin given for 2 weeks, followed by TEE. 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 ANTI COAGULANTS IN NONVALVULAR ATRIAL FIBRILLATION PATIENTS?

In the BAFTA (Birmingham Atrial Fibrillation Treatment of the Aged Study), 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), 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=0.36) for warfarin. In the AVERROES study, 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.

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, the annual safety event rates were 7.4% with intervention (more than half of the day on the procedure) vs 4.4% with long-term warfarin. Events included serious pericardial effusion requiring drainage and device embolization. With operator experience, the 7-day perioperative event rate declined from approximately 10% to approximately 5%. Most strokes after LAA closure were caused by air embolism; stroke-related disability or death was higher with intervention vs warfarin. In some centers endocarditis prophylaxis was performed for a few months, followed by TEE control.

HOW DOES THE SERIES BY LÓPEZ-MÍNUEZ 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. 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
may include active or recent major bleeding not provoked by invasive procedures\(^1\); 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 normalised 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 antiocoagulation-ineligible patients, what are the ischaemic stroke rates associated with LAA closure as compared to long-term antplatelet treatment or no antithrombotic treatment?, and b) (addressed in the PROTECT-AF trial),\(^9\) in antiocoagulation 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.\(^1\)

**REFERENCES**

10. Without warfarin, Watchman still prevents strokes, says registry [accessed, 2012 Sep 15]. Available at: www.theheart.org/article/13980695

**Table**

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

<table>
<thead>
<tr>
<th>LAA Closure</th>
<th>Warfarin</th>
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<tbody>
<tr>
<td>Pros</td>
<td>Cons</td>
</tr>
<tr>
<td>• Exclusion of a major source of thromboembolism</td>
<td>• Local treatment against a potentially broader source of thromboembolism</td>
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<tr>
<td>• Long-term antithrombotic treatment not required</td>
<td>• Single randomized trial in a relatively small, warfarin-eligible population</td>
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<tr>
<td>• In PROTECT-AF, lower haemorrhagic stroke rates vs warfarin</td>
<td>• Thrombogenic foreign surface for the first few months until endothelialization occurs</td>
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<td>• In patients ineligible for anticoagulation, potentially lower rates of ischaemic and haemorrhagic strokes vs antiplatelet agents or vs placebo (to be tested)</td>
<td>• Suboptimal procedure in up to 30% patients: up to 10% failed implants, approximately 10% periprocedural complications, and approximately 10% extended antithrombotic regimen</td>
</tr>
<tr>
<td><strong>Confs</strong></td>
<td><strong>Cons</strong></td>
</tr>
<tr>
<td>• Effective stroke prevention vs placebo, acetylsalicylic acid, or dual antiplatelet therapy in NVAF</td>
<td>• Frequent monitoring</td>
</tr>
<tr>
<td>• Systemic treatment for a potentially broad source of thromboembolism</td>
<td>• Drug-drug and drug-food interactions</td>
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<td>• INR: good measure of effective anticoagulation</td>
<td>• &gt;30% of treated patients not in therapeutic range</td>
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<tr>
<td>• In PROTECT-AF, noninferior rates of strokes, systemic embolism, and cardiovascular death vs LAA closure</td>
<td>• Compliance suboptimal and declining over time</td>
</tr>
<tr>
<td>• Noninvasive. Simple. Little or no training required</td>
<td>• Underuse in the elderly where stroke prevention is most needed</td>
</tr>
<tr>
<td>• Established track record</td>
<td>• Annual rate of major bleeding is approximately 2% to 3%, including intracranial haemorrhage (approximately 0.5% per year)</td>
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