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Selection of the Best of 2017 in Left Atrial Appendage Occlusion: Filling the Gap in Knowledge



Selección de lo mejor del año 2017 en cierre percutáneo de la orejuela izquierda: completando la evidencia científica

To the Editor,

It has been demonstrated that percutaneous closure of the left atrial appendage (LAA) is an alternative to oral anticoagulation (OAC) with coumarins in patients with nonvalvular atrial fibrillation (AF), especially in those with a contraindication. However, the latest European guidelines on AF¹ have not changed the previous grade of recommendation for LAA occlusion and they have retained a class IIb indication and level of evidence B for patients with a long-term contraindication for OAC due to untreatable bleeding problems. The justification for this decision lies in the high real-world complication rates, which are based on the analysis of insurance company databases, systematic reviews, and the lack of current data on LAA occluders compared with the new direct OACs for embolic prevention (sections 9.3.1 and 15.6 of the guidelines). In addition, the guidelines recognize other gaps in

the evidence, such as the role of LAA occlusion in managing patients who have already experienced bleeding or stroke (section 15.7) or after intracranial hemorrhage (section 9.4.3).

Several articles^{2–4} have been recently published that address these aspects and offer guidance on clinical decision making. Table 1 shows their main characteristics and results. Although these studies are observational single cohort studies or propensity score-matched control group studies, they provide valuable information in fields as complex as embolic prevention after bleeding (especially after intracranial hemorrhage) or very high risk of bleeding. In general, they demonstrate the efficacy and safety of LAA occlusion compared with the standard treatment of these patients (many of whom are without OAC due to their bleeding risk). Even the 2 matched control group studies (Nielsen-Kudsk et al.² and Gloekler et al. [NCT02787525]) demonstrate reductions in overall mortality. Another common finding is the wide variability in pharmacological treatment after LAA occlusion, reflecting the heterogeneity of patients with bleeding or at high risk of bleeding.

In all these studies, a common feature is the absence of procedure- or device-related deaths. Evidence in support of reductions in the incidence of complications has already been

Table

Recently Published Studies on Percutaneous Closure of the Left Atrial Appendage

	Nielsen-Kudsk et al. ²	Cruz-González et al. ³	Korsholm et al. ⁴	Gloekler et al. (NCT02787525)
Type of study	Propensity score-matched	Observational	Observational	Propensity score-matched
Indication for LAA occlusion	Intracranial hemorrhage	Intracranial hemorrhage	Previous bleeding or high bleeding risk	Not defined
Number of patients	151 + 151 pairs with SMT aspirin, 44%; without treatment, 31%	47	110	500 + 500 pairs treated with OAC(D)
CHA ₂ D ₂ S-VASc	3.9	5	4.4	4.3
HAS-BLED	4.2	4	4.1	3
Treatment after LAA occlusion	Aspirin only, 62%	Dual antiplatelet, 81%	Aspirin only, 85%	-
Follow-up, patient-y	150	108	265	2645
Mortality per 100 patient-y	1.7 vs 15.6; HR = 0.11*	-	7.5	8.3 vs 11.6; HR = 0.72*
Ischemic stroke per 100 patient-y	1.7 vs 8.1; HR = 0.21	2	2.3; RRR, 61%	2.0 vs 3.2; HR = 0.62
ICH per 100 patient-y	0.8 vs 9.5; HR = 0.10*	2	1.4	0.1 vs 0.5; HR = 0.20
Major bleeding per 100 patient-y	3.5 vs 9.5; HR = 0.28*	-	3.8; RRR, 57%	3.6 vs 4.6; HR = 0.80
Net benefit per 100 patient-y	5.3 vs 36.7; HR = 0.16*	-	-	8.1 vs 10.9; HR = 0.76*

ICH, intracranial hemorrhage; HR, hazard ratio; LAA, left atrial appendage; OAC(D), direct oral anticoagulants; RRR, relative risk reduction (relative to the predicted value according to the scales); SMT, standard medical treatment.

* $P < .05$.

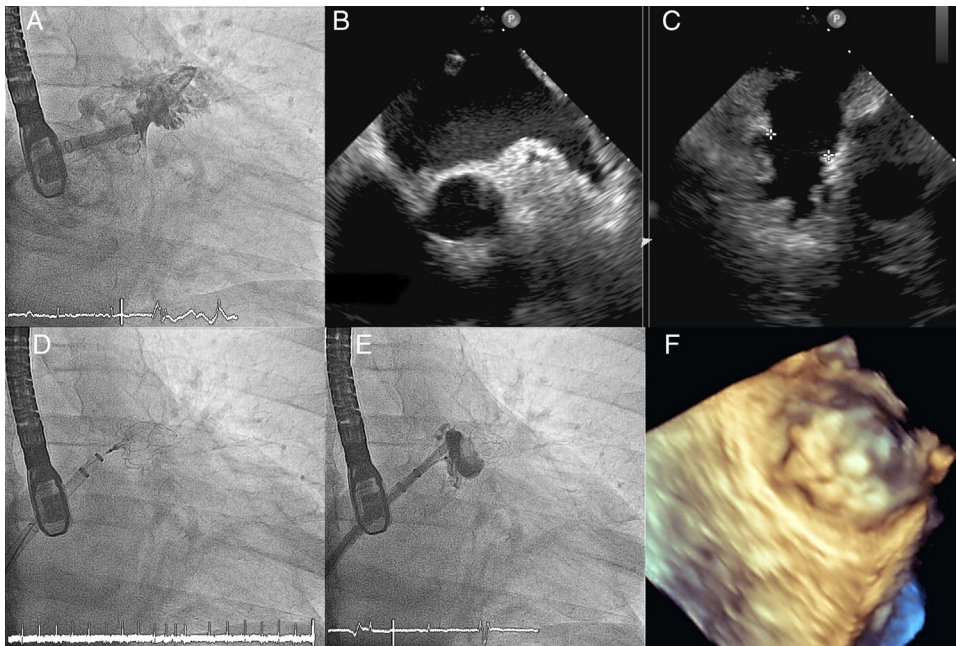


Figure. Left atrial appendage: angiography (A, LAA 30°- caudal 20°) and transesophageal echocardiogram (B, 45° view; C, 135° view). Placement of Watchman device (D), which occludes the appendage (E, angiography; F, 3D transesophageal echocardiogram).

shown in device-use registries, such as EWOLUTION⁵, which reported implantation success rates of more than 98% and major complications related to the procedure or device of less than 3%. Even in groups with less experience, there are very acceptable complication rates, which are probably due to widespread dissemination of knowledge of the technique and shorter learning periods. It seems then that one of the justifications for retaining the IIb indication in the guidelines is weakening. The program developed by the Spanish Health Ministry to monitor the results of this technique should help clarify doubts on this issue (Figure 1).

In the very near future, more information will be provided by studies comparing percutaneous LAA occlusion with the new direct OACs. These studies include: Evaluation of WATCHMAN Left Atrial Appendage Occlusion Device in Patients With Atrial Fibrillation Versus Rivaroxaban (NCT02549963); PRAGUE-17: Left Atrial Appendage Closure vs. Novel Anticoagulation Agents in Atrial Fibrillation (NCT02426944); A Pilot Study of Edoxaban in Patients With Non-Valvular Atrial Fibrillation and Left Atrial Appendage Closure (NCT03088072); Safety and Efficacy of Left Atrial Appendage Closure Versus Anti-thrombotic Therapy in Patients With Atrial Fibrillation Undergoing Drug-Eluting Stent Implantation Due to Complex Coronary Artery Disease (NCT02606552); and Prevention of Stroke by Left Atrial Appendage Closure in Atrial Fibrillation Patients After Intracerebral Hemorrhage (NCT02830152).

These studies will also increase knowledge in another area in which LAA occlusion has been shown to be superior to OAC therapy: that is, cost-effectiveness analysis. Previous studies⁶ have shown that LAA occlusion is superior (ie, the most effective and least costly) to direct OAC therapy at 5 years and warfarin therapy at 10 years.

In conclusion, percutaneous LAA occlusion is a well-established therapy for highly complex patients (previous bleeding, intracranial hemorrhage) in whom it is difficult to apply OAC therapy. We look forward to the results of comparisons between this technique and the new direct OACs. These results should fill in knowledge gaps and encourage the grade of recommendation of this therapy to be upgraded in the next update of the AF guidelines.

CONFLICTS OF INTEREST

A Pérez de Prado is a proctor in LAA occlusion procedures for Boston Scientific. M Pan has been a scientific speaker for Abbott Vascular.

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Selection of the Best of 2017 in Vascular Risk and Cardiac Rehabilitation



Selección de lo mejor del año 2017 en riesgo vascular y rehabilitación cardiaca

To the Editor,

2017 has been a prolific year for high-impact publications in this discipline. In the field of nutrition, the clinical practice guidelines recommend replacing the intake of fats, especially saturated fats, with unsaturated fats and carbohydrates to avoid increasing low-density lipoprotein cholesterol (LDL-C) and consequently the occurrence of cardiovascular (CV) events. Recent randomized clinical trials and meta-analyses of observational studies contradict these recommendations. One such study is the PURE¹ cohort study, with 135 335 individuals from 18 countries, in which it was observed that a high intake of carbohydrates (> 60%) increased the risk of total mortality, whereas intake of fats (including saturated fats) reduced this risk, with no association found between total fat intake and CV disease or CV mortality, and there was even an inversely proportional relationship between saturated fats and stroke. It is without doubt a study that raises new questions and will require, at least, revision of the current recommendations on the appropriate dietary proportion of the different macronutrients.

Regarding lipids, the Fourier² trial has been the real protagonist and has provided data on the CV benefits of treatment with evolocumab. In this trial, 27 567 patients with atherosclerotic disease (acute myocardial infarction, nonhemorrhagic stroke, or symptomatic peripheral arterial disease) and with LDL-C > 70 mg/dL (or non-high-density lipoprotein cholesterol > 100 mg/dL) were randomized to receive evolocumab 140 mg or placebo every 2 weeks. LDL-C decreased by 59% in the evolocumab group and reached a mean of 30 mg/dL. The reduction in relative risk for the primary outcome (CV death, acute myocardial infarct or stroke) in the evolocumab group was 15% at 36 months, with the greatest benefit occurring after the first 12 months. There were no significant differences regarding serious side effects. This study demonstrated that inhibition of proprotein convertase subtilisin-kexin type 9 (PCSK9) with evolocumab reduces LDL-C and translates to CV benefits.

For diabetes, the most noteworthy study was the CANVAS³ trial, in which 10 142 diabetic patients with high CV risk were randomized to receive canagliflozin or placebo. The canagliflozin group achieved a 14% reduction in the primary outcome (composite outcome of CV mortality, nonfatal myocardial infarction and nonfatal stroke), 26.9 vs 31.5 events/1000 patients/year (hazard ratio [HR] = 0.86; 95% confidence interval [95%CI], 0.75–0.97; *P* = .02 for superiority). There was an increase of almost double the number of amputations in the treated group (6.3 vs 3.4/1000 patients/year; HR = 1.97). This study provides evidence that the CV benefits of SGLT2 inhibitor oral antidiabetics are a class effect. It also supports

the focus of treatment of diabetes being based not only on lowering glucose levels, but also on more general effects in an aim to reduce CV events and improve prognosis, similar to what was seen last year with the GLP1 agonists liraglutide and semaglutide.

Another publication was the first study to demonstrate that a CV screening program can be associated with a reduction in mortality. The Viborg Vascular⁴ (VIVA) trial is a prospective randomized trial conducted in 50 156 Danish men aged between 65 and 74 years, assigned to triple screening for abdominal aortic aneurysm (AAA), peripheral vascular disease (PAD), and hypertension versus standard care. Those diagnosed with PAD or AAA received smoking cessation therapy, aspirin (75 mg/day), simvastatin (40 mg/day) and an antihypertensive, and those with AAA > 50 mm were referred to vascular surgery. More than 20% of participants received a diagnosis: 3% with AAA, 11% with PAD, and 11% with untreated hypertension. There was a 7% reduction in 5-year mortality, and 1 life was saved for every 169 participants assessed, making it more cost-effective than the European cancer screening programs. A substudy of the VIVA trial⁵ also showed an inverse association between AAA growth and glycated hemoglobin concentration in individuals with and without known diabetes.

The inflammatory hypothesis of atherothrombotic disease is based on inflammation playing a role in the formation, progression and rupture of the atheromatous plaque and in the generation of acute coronary events. Canakinumab is a monoclonal antibody against interleukin 1 β that produces an anti-inflammatory effect. The CANTOS trial⁶ compared subcutaneous 3-monthly administration of canakinumab vs placebo in patients with a history of acute myocardial infarction and high levels of C-reactive protein, with a combined primary outcome of CV death, nonfatal acute myocardial infarction, and nonfatal stroke at 48 months.

The main results were a significant reduction in the primary outcome in the treatment group due to a reduction in nonfatal acute myocardial infarction. There was also a reduction in C-reactive protein levels, no differences in LDL-C levels, and a lower risk of cancer in the canakinumab group vs placebo group, although this was at the expense of an increase in fatal infections. The most relevant result of this study was that it demonstrated the inflammation theory, paving the way in the search for promising new lines of treatment.

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