

Original article

Left atrial appendage occlusion for stroke despite oral anticoagulation (resistant stroke). Results from the Amplatzer Cardiac Plug registry



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ABSTRACT

Introduction and objectives: Despite the efficacy of oral anticoagulant (OAC) therapy, some patients continue to have a high residual risk and develop a stroke on OAC therapy (resistant stroke [RS]), and there is a lack of evidence on the management of these patients. The aim of this study was to analyze the safety and efficacy of left atrial appendage occlusion (LAAO) as secondary prevention in patients with nonvalvular atrial fibrillation who have experienced a stroke/transient ischemic attack despite OAC treatment.

Methods: We analyzed data from the Amplatzer Cardiac Plug multicenter registry on 1047 consecutive patients with nonvalvular atrial fibrillation undergoing LAAO. Patients with previous stroke on OAC therapy as indication for LAAO were identified and compared with patients with other indications.

Results: A total of 115 patients (11%) with RS were identified. The CHA₂DS₂-VASc and the HAS-BLED score were significantly higher in the RS group (respectively 5.5 ± 1.5 vs 4.3 ± 1.6; $P < .001$; 3.9 ± 1.3 vs 3.1 ± 1.2; $P < .001$). No significant differences were observed in periprocedural major safety events (7.8 vs 4.5%; $P = .1$). With a mean clinical follow-up of 16.2 ± 12.2 months, the observed annual stroke/transient ischemic attack rate for the RS group was 2.6% (65% risk reduction) and the observed annual major bleeding rate was 0% (100% risk reduction).

Conclusions: Patients with RS undergoing LAAO showed similar safety outcomes to patients without RS, with a significant reduction in stroke/transient ischemic attack and major bleeding events during follow-up. Adequately powered controlled trials are needed to further investigate the use of LAAO in RS patients.

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Cierre de la orejuela izquierda por ictus pese a la anticoagulación oral (ictus resistente): resultados del registro Amplatzer Cardiac Plug**RESUMEN****Palabras clave:**

Cierre percutáneo de la orejuela izquierda
Ictus isquémico
Anticoagulación oral crónica
Fibrilación auricular

Introducción y objetivos: A pesar de la eficacia de los anticoagulantes orales (ACO), algunos pacientes mantienen una alto riesgo residual y presentan ictus aun estando en tratamiento con ACO, y falta evidencia sobre el tratamiento de estos pacientes. El objetivo del estudio es analizar la seguridad y la eficacia del cierre percutáneo de la orejuela izquierda (OI) como prevención secundaria para pacientes con fibrilación auricular no valvular que han experimentado un ictus/accidente isquémico transitorio a pesar de los ACO (ictus resistente [IR]).

Métodos: Se estudió a 1.047 pacientes consecutivos con fibrilación auricular no valvular sometidos a cierre percutáneo de la OI incluidos en el registro multicéntrico Amplatzer Cardiac Plug. Se seleccionó a los pacientes con IR como indicación para el cierre de la OI, y se los comparó con pacientes con otras indicaciones.

Resultados: En un total de 115 pacientes (11%) se produjo un IR. Las escalas CHA₂DS₂-VASC y HAS-BLED eran significativamente más altas en el grupo de IR ($5,5 \pm 1,5$ frente a $4,3 \pm 1,6$; $p < 0,001$ y $3,9 \pm 1,3$ frente a $3,1 \pm 1,2$; $p < 0,001$). No hubo diferencias significativas en los eventos mayores de seguridad periprocedimiento (el 7,8 frente al 4,5%; $p = 0,1$). Tras $16,2 \pm 12,2$ meses de seguimiento medio, la tasa anual de ictus/accidente isquémico transitorio observada fue del 2,6% (el 65% de reducción del riesgo) y la tasa anual de hemorragia mayor observada fue del 0% (el 100% de reducción del riesgo) en los pacientes con IR.

Conclusiones: Los pacientes con IR sometidos a cierre percutáneo de la OI presentaron resultados de seguridad similares que los pacientes sin IR, con una reducción significativa de los eventos de ictus/accidente isquémico transitorio y hemorragia mayor durante el seguimiento.

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Abbreviations

LAAO: left atrial appendage occlusion
NOAC: nonvitamin K antagonist oral anticoagulants
OAC: oral anticoagulation
RS: resistant stroke
TIA: transient ischemic attack
VKA: vitamin K antagonist

INTRODUCTION

Percutaneous left atrial appendage occlusion (LAAO) is an alternative treatment for stroke prevention in patients with nonvalvular atrial fibrillation.^{1–3} The annual rate of ischemic stroke is approximately 5% in untreated patients with nonvalvular atrial fibrillation.⁴ This risk is significantly reduced by vitamin K antagonists (VKA), up to 64% compared with placebo,⁵ and high-dose nonvitamin K antagonist oral anticoagulants (NOAC) treatment is associated with lower risk of stroke and systemic embolism (19%), relative to VKA.⁶ Despite the efficacy of oral anticoagulation (OAC) therapy, some patients continue to have a high residual risk and experience a stroke on OAC therapy (henceforth, “resistant stroke” [RS]). In patients with RS despite adequate VKA, after exclusion of another potential cause, current guidelines propose either increasing the target international normalized ratio (INR) to 2.5 to 3.5 in patients taking VKA or switching from VKA to NOAC.² However, there is insufficient evidence to decide the management of patients who have experienced a stroke under treatment with NOAC. Thus, patients with stroke while on treatment with VKA and with INR 2.5 to 3.5, patients with a contraindication to switching to NOAC (for example, due to advanced renal failure) or when stroke occurs despite treatment with NOAC could be candidates for percutaneous LAAO. However, LAAO in this specific group of patients has not been analyzed before.

The objective of the present study was to investigate the procedural safety and long-term outcomes of patients with nonvalvular atrial fibrillation who underwent percutaneous LAAO with the indication of stroke despite OAC therapy.

METHODS

This is a retrospective study that included 1047 consecutive patients with nonvalvular atrial fibrillation who underwent LAAO using the Amplatzer Cardiac Plug (ACP, Abbott, Plymouth, Minnesota, United States) in 22 centers between December 2008 and November 2013 and were included in the multicenter Amplatzer Cardiac Plug registry.¹ For the purpose of this study, patients with previous stroke on OAC treatment as indication for LAAO were identified and compared with patients with other indications. Procedural success was defined as successful implantation of the Amplatzer Cardiac Plug in the left atrial appendage. Periprocedural adverse events (occurring 0–7 days after the procedure or before hospital discharge, whichever occurred last) was based on the VARC criteria⁷ and included death, myocardial infarction, stroke, transient ischemic attack (TIA), systemic embolization, air embolization, device embolization, cardiac tamponade, and major bleeding. Adverse events during follow-up (excluding periprocedural events) included death (cardiovascular or noncardiovascular), stroke, TIA, systemic embolism, and major bleeding. Antithrombotic medication was recorded on the date of admission and at the last follow-up visit. The choice and the duration of antithrombotic therapy were individualized depending on the patient history, indication for LAAO, and physician preference. Device efficacy to prevent stroke, TIA, and systemic embolism was tested by comparing the actual event rate at follow-up with the predicted event rate by the CHA₂DS₂-VASC score.^{8,9} Similarly, bleeding reduction was assessed by comparing the actual major bleeding events to the rate predicted by the HAS-BLED score.¹⁰

Statistical analysis

Continuous variables are presented as means $\pm$ standard deviation and categorical variables are listed as frequencies and percentages. Continuous variables were tested using the independent samples *t* test and categorical variables using the chi-square test. A 2-sided *P* value $< .05$ was considered statistically significant. All statistical analyses were performed with SPSS 22.0 software (SPSS Inc, Chicago, Illinois, United States).

RESULTS

A total of 115 patients (11%) with stroke on OAC therapy were identified (RS group). The baseline patient and procedural characteristics are shown in Table 1 and Table 2. Patients with RS had no statistically significant differences in the baseline or procedure characteristics compared with the other indications group.

The mean CHA₂DS₂-VASc score was significantly higher in patients with RS (5.5 ± 1.5 vs 4.3 ± 1.6 , $P < .001$), the mean HAS-BLED score was also higher in the RS group (3.9 ± 1.3 vs 3.1 ± 1.2 , $P < .001$). The predicted annual risk of thromboembolism according to the CHA₂DS₂-VASc score was higher in the RS group (7.4 ± 2.6 vs 5.4 ± 2.7 , $P < .001$) and the annual major bleeding risk according to the HAS-BLED score was also higher in patients with RS (7.3 ± 2.0 vs 6.0 ± 2.2 , $P < .001$) (Table 3).

Procedural success was achieved in 1019 patients (97.3%) of the total cohort, without significant differences between both groups (Table 4). No significant differences were observed in periprocedural major safety events among 2 groups (7.8 vs 4.5% , $P = .1$). There were nonsignificant differences in the antithrombotic medication at baseline and at the last follow-up between the both groups (Table 5).

The mean clinical follow-up was 16.2 ± 12.2 months, resulting in a total of 1349 patient years, and was complete in 1001 of 1019 of successfully implanted patients (98.2%). In all, 561 patients completed at least 1 year of follow-up. The observed annual stroke or TIA rate at follow-up for the RS group was 2.6% (65% relative reduction of thromboembolism according to the CHA₂DS₂-VASc score) and 1.2% for patients without RS (78% relative risk reduction according to the CHA₂DS₂-VASc score) (Figure 1). The observed annual major bleeding rate at follow-up for the RS group was 0% (100% relative reduction

according to the HAS-BLED score) and 1.2% for those without RS (79% relative reduction) (Figure 2). A transesophageal echocardiogram at follow-up was available in 632 of 1001 (63%) of successfully implanted patients (RS group 78 of 111 patients [70%] and control group 554 of 890 [62%], $P = .099$) and was performed at a median of 7 (interquartile range, 3–11) months after LAAO. The rate of device thrombosis and peridevice leaks did not vary significantly between groups (device thrombosis in RS patients vs others: 5.2 vs 4.4%; $P = .754$; and peridevice leaks in RS patients vs others: 12.8% vs 11.4%; $P = .708$).

One-year all-cause mortality was 4.3% for the total population (Figure 3). A total of 63 deaths were reported at follow-up, 8 (7.2%) in the RS group and 55 (6.2%) in the non-RS group ($P = .67$). There were 8 periprocedural deaths (1 in the RS group [0.9%] and 7 [0.8%] the non-RS group; $P = .89$) and none was reported as being related to the device. There were 18 strokes or TIA at follow-up, 4 (3.6%) in the RS group and 14 (1.6%) in the non-RS group ($P = .12$). Kaplan-Meier curves of cumulative survival free of stroke or TIA after LAAO are shown in Figure 4.

DISCUSSION

The present study evaluated the role of LAAO in patients with nonvalvular atrial fibrillation who had a stroke despite being treated with OAC. The most important findings of the study can be summarized as follows: a) the percutaneous LAAO success rate was high, above 97%, and LAAO was safely performed in patients with RS. The rate of complications was similar to that reported in other studies and to that in the non-RS group; b) percutaneous LAAO was effective for stroke reduction in both groups of patients (RS and non-RS); c) although patients with RS also had a higher risk for bleeding, there were no significant bleeding events at follow-up, which is remarkable for this patient cohort, and d) overall survival and stroke-free survival were similar in the 2 groups: RS and non-RS.

VKA have important limitations regarding their use in clinical practice.¹¹ Regular follow-up visits are needed to keep the INR within the narrow therapeutic range which is, nonetheless, only achieved in 60% to 70% of cases according to previous studies,¹² leaving a large number of patients in subtherapeutic levels and therefore at an increased risk of stroke.¹³ In addition, VKA may cause a number of complications, mainly bleeding. In this regard, NOAC offer some

Table 1
Baseline patient characteristics

Number of patients	Total (N = 1047)	RS (n = 115)	Others (n = 932)	P
Age, y	74.9 $\pm$ 8.4	73.8 $\pm$ 10.2	75.1 $\pm$ 8.2	NS
Male	648 (62.0)	75 (65.2)	573 (61.5)	NS
Atrial fibrillation				
Permanent	594 (56.7)	63 (54.8)	531 (57.0)	NS
Paroxysmal or persistent	453 (43.3)	52 (45.2)	401 (43.0)	NS
Body mass index	27.2 $\pm$ 4.8	27.0 $\pm$ 4.4	27.2 $\pm$ 4.9	NS
Arterial hypertension	868 (82.9)	93 (80.9)	775 (83.2)	NS
Dyslipidemia	326 (47.7)	28 (46.7)	298 (47.8)	NS
Diabetes mellitus	306 (29.3)	34 (29.6)	272 (29.2)	NS
Smoking	116 (16.2)	8 (13.3)	108 (16.5)	NS
Coronary artery disease	367 (35.6)	35 (31.0)	332 (36.2)	NS
Myocardial infarction	164 (15.9)	13 (11.5)	151 (16.4)	NS
PCI	228 (22.2)	24 (21.2)	204 (22.3)	NS
CABG	166 (20.0)	19 (26.8)	147 (19.4)	NS
Carotid disease	87 (8.4)	11 (9.7)	76 (8.3)	NS
Chronic kidney disease	281 (27.3)	23 (20.4)	258 (28.1)	.08

CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; RS, resistant stroke. Variables are expressed as mean $\pm$ standard deviation or No. (%).

Table 2

Procedural characteristics

Number of patients		Total (n = 1047)	RS (n = 115)	Others (n = 932)	P
Success		1010 (97.3)	112 (97.4)	907 (97.3)	NS
ACP size, mm	16	32 (3.1)	3 (2.7)	29 (3.2)	NS
	18	51 (4.9)	8 (7.2)	43 (4.8)	NS
	20	106 (10.1)	8 (7.2)	98 (10.8)	NS
	22	208 (19.9)	13 (11.7)	195 (21.5)	NS
	24	204 (19.5)	25 (22.5)	179 (19.8)	NS
	26	172 (16.4)	25 (22.5)	147 (16.2)	NS
	28	103 (9.8)	14 (12.6)	89 (9.8)	NS
	30	140 (13.4)	15 (13.5)	125 (13.8)	NS
No success or unknown		31 (3.0)	4 (3.5)	27 (2.9)	NS

ACP, Amplatzer Cardiac Plug; RS, resistant stroke.

Variables are presented as No. (%).

Table 3

Risk scores and predicted annual risk of thromboembolism and major bleeding

Number of patients	Total (n = 1047)	RS (n = 115)	Others (n = 932)	P
CHADS ₂ score	2.8 ± 1.3	3.9 ± 1.0	2.6 ± 1.3	< .001
CHA ₂ DS ₂ -VASC score	4.5 ± 1.6	5.5 ± 1.5	4.3 ± 1.6	< .001
Predicted annual risk of thromboembolism, %	5.7 ± 2.8	7.4 ± 2.6	5.4 ± 2.7	< .001
HAS-BLED score	3.1 ± 1.2	3.9 ± 1.3	3.1 ± 1.2	< .001
Predicted annual risk of major bleeding, %	5.6 ± 2.8	7.3 ± 2.0	6.0 ± 2.2	< .001

RS, resistant stroke.

Values are expressed as mean ± standard deviation.

Table 4

Procedural success and major adverse events

Number of patients	Total (n = 1047)	RS (n = 115)	Others (n = 932)	P
Procedural success	1019 (97)	112 (97)	907 (97)	NS
Major adverse events	51 (4.9)	9 (7.8)	42 (4.5)	NS
Death	8 (0.8)	1 (0.9)	7 (0.8)	NS
Stroke	9 (0.9)	3 (2.6)	6 (0.6)	NS
Systemic embolism	0 (0.0)	0 (0.0)	0 (0.0)	NS
Myocardial infarction	1 (0.1)	0 (0.0)	1 (0.1)	NS
Cardiac tamponade	16 (1.5)	3 (2.6)	13 (1.4)	NS
Major bleeding	14 (1.3)	2 (1.7)	12 (1.3)	NS
Device embolization requiring surgery	2 (0.2)	0 (0.0)	2 (0.2)	NS
Device embolization snared	7 (0.7)	1 (0.9)	6 (0.6)	NS
Need for surgery*	0 (0.0)	0 (0.0)	0 (0.0)	NS

RS, resistant stroke.

Values are expressed as No. (%).

* Apart from device embolization.

Table 5

Antithrombotic medication at baseline and follow-up

Baseline					Follow-up			
Number of patients	Total n = 1047	RS n = 115	Others n = 932	P	Total n = 1001	RS	Others	P
Aspirin	641 (61.2)	71 (61.7)	570 (61.2)	NS	845 (84.4)	85 (76.6)	760 (85.4)	.016
Clopidogrel	232 (22.2)	24 (20.9)	208 (22.3)	NS	242 (24.2)	36 (32.4)	206 (23.1)	.031
Aspirin and clopidogrel	164 (15.7)	17 (14.8)	147 (15.8)	NS	189 (18.9)	24 (21.6)	165 (18.5)	NS
VKA	255 (24.4)	46 (40)	209 (22.4)	< .001	30 (3)	6 (5.4)	24 (2.7)	NS
NOAC	31 (3)	2 (1.7)	29 (3.1)	NS	14 (1.4)	3 (2.7)	11 (1.2)	NS
LMWH	168 (16)	6 (5.2)	162 (17.4)	.001	2 (0.4)	0 (0.0)	2 (0.4)	NS
Unknown	15 (1.4)	4 (3.5)	11 (1.2)	NS	19 (1.9)	4 (3.6)	15 (1.7)	NS

LMWH, low molecular weight heparin; NOAC, nonvitamin K antagonist oral anticoagulants; RS, resistant stroke; VKA, vitamin K antagonists.

Values are presented as No. (%).

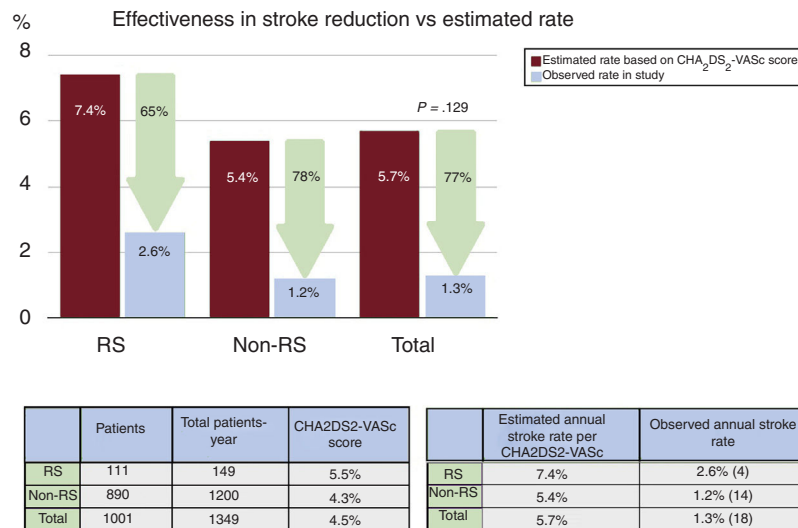


Figure 1. Effectiveness of left atrial appendage occlusion in reduction of thromboembolism based on annual rate predicted by CHA₂DS₂-VASc score during follow-up. Patients with resistant stroke (RS) are compared with patients without RS.

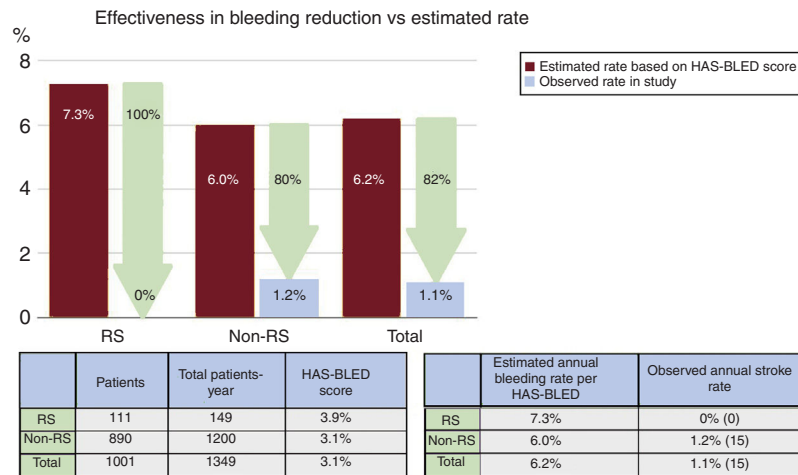


Figure 2. Effectiveness of left atrial appendage occlusion in reduction of bleeding based on annual rate predicted by HAS-BLED score during follow-up. Patients with resistant stroke (RS) are compared with patients without RS.

advantages not only by improving cardioembolic stroke prevention but also by reducing bleeding events. Several studies on NOAC have shown a reduction in thromboembolic events by about 20% over warfarin therapy.⁶ In these studies, about 20% of patients had a previous stroke or TIA, which correlates with advanced age, the most

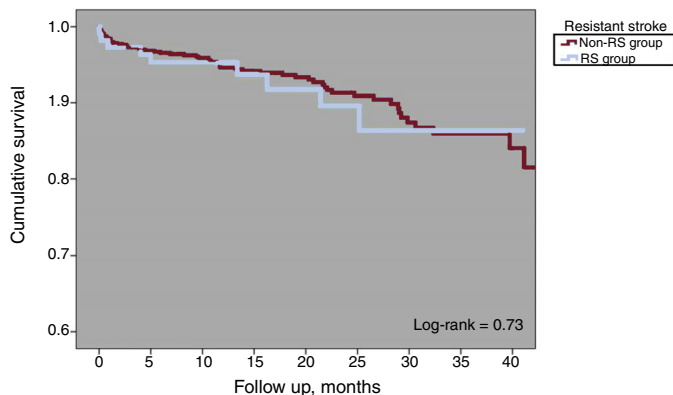


Figure 3. Kaplan-Meier cumulative survival curve of resistant stroke (RS) patients and nonresistant stroke patients.

important risk factor for stroke in patients with atrial fibrillation. NOAC therapy as secondary prevention has been found to be noninferior to warfarin in the subgroup of patients with previous stroke or TIA. Despite NOAC therapy, these patients have a residual rate of stroke or systemic embolism between 2.0 to 2.8 per 100 patient-year of follow-up, which is higher than that of patients without previous stroke or TIA.^{14–16} Therefore, in this group of patients, with high residual risk of stroke despite OAC treatment, LAAO could play a promising role in reducing the risk of thromboembolic events.²

The management of patients with RS is challenging because, as shown in this study, they are characterized by a high thromboembolic risk by the CHA₂DS₂-VASc score, as well as for bleeding according to the HAS-BLED score. In this study, LAAO was associated with a reduction in the rate of stroke after comparison of observed and expected rates according to the CHA₂DS₂-VASc score and with reduced bleeding events in the follow-up. The reduction of stroke or TIA at follow-up compared with the expected incidence according to the CHA₂DS₂-VASc score (65%) was in agreement with previous studies.^{1,17–20} The reduction in bleeding events after LAAO was remarkable, with no major bleeding events occurring during follow-up in the RS group. Given the small number of events, this could represent a statistical bias,

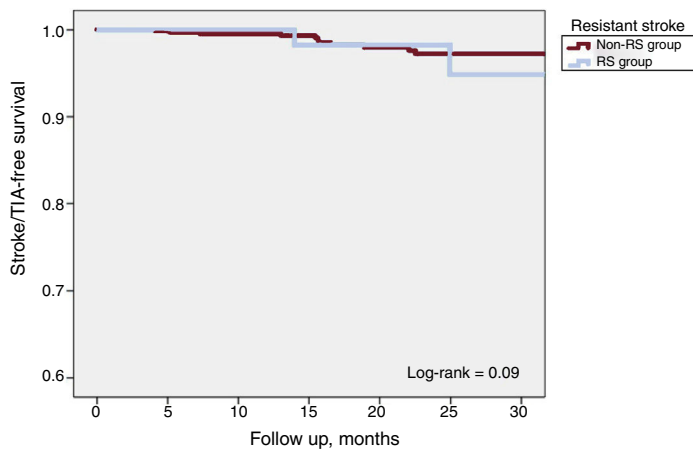


Figure 4. Survival free of stroke or transient ischemic attack (TIA) after left atrial appendage occlusion. Kaplan-Meier analysis showing the effect of resistant stroke (RS) on stroke- or TIA-free survival.

although as demonstrated in previous studies, LAAO significantly reduced bleeding beyond the immediate periprocedural period, and especially after discontinuation of adjuvant anticoagulant or antiplatelet treatment.²¹ We can speculate that when the indication for LAAO is not a contraindication for OAC, as in the RS group, the bleeding events after LAAO are really low. In contrast, in the non-RS group the indication for LAAO in many patients was a contraindication for OAC (due to previous bleeding) so the bleeding rates are higher, independently of the drug-regime used after LAAO. When deciding the strategy for stroke prevention, it is necessary to take into account the favorable effect of LAAO in reducing bleeding events in the long-term, especially if the indication for LAAO is not a contraindication for OAC or previous bleeding. On the other hand, the HAS-BLED score has been developed to predict the risk of bleeding in patients treated with OAC therapy. It would be reasonable to consider whether this score is adequate to predict bleeding events in patients with some resistance to oral anticoagulants, such as patients with RS.

In patients who experienced a stroke despite OAC therapy, it is necessary to investigate the cause of the stroke. The most frequent cause is an INR below the therapeutic range, but as described in previous studies, patients often have additional potential etiologies for stroke.^{22–24} In our study, we highlight the heterogeneity in the baseline treatment of patients with RS and the low use of NOAC (probably related to enrolment between 2008 and 2013).

Based on the effectiveness of LAAO in reducing stroke and bleeding, together with the low risk of periprocedural adverse events, we believe that LAAO should be considered in the secondary prevention of stroke in RS patients.

Limitations

The present study has several limitations that should be acknowledged. This is a subanalysis of the Amplatzer Cardiac Plug registry, which was a nonrandomized, retrospective, observational study with no control group. The retrospective nature of the study is a major limitation, which may lead to underestimation of event rates, especially during follow-up. Importantly, the presence of a control group in the study, treated with OAC after the RS, would be a better comparator of the rate of ischemic and hemorrhagic events than that calculated by CHA₂DS₂-VASC and HAS-BLED. Another important limitation of the study is that, despite the significant reduction in the RR of stroke in patients with RS, these patients have a higher absolute risk of stroke than patients without RS. Although the study was not designed for this purpose, after LAAO,

stroke reduction RR seems to be more important among patients without RS than among patients with RS.

We have no data on the possible causes for stroke despite anticoagulation (eg, INR out of range, left atrial thrombus despite anticoagulation, thrombi on an artificial heart valve, right-to-left shunt), nor about the level of INR if the patient had been treated with VKA. With respect to antithrombotic treatment at baseline, we have no data on the type of anticoagulant, only if it was VKA, NOAC, or low molecular-weight heparin. We have no transesophageal echocardiogram data before the procedure nor was transesophageal echocardiogram follow-up available for all patients.

CONCLUSIONS

Patients with previous RS and indication for percutaneous LAAO had similar procedural outcomes to those of with patients without RS. According to the results of this study, LAAO could be safely performed in this group of patients, who have a high risk of thromboembolic and bleeding events. In this study, patients with RS had a significant reduction in stroke and TIA with no major bleeding events during the follow-up period, despite their overall high bleeding risk. Adequately powered controlled trials are needed to further investigate the use of LAAO in patients who experience a stroke despite OAC therapy. In this regard, robust data on the comparative efficacy of LAAO vs NOAC are of the utmost importance.

CONFLICTS OF INTEREST

I. Cruz-González, X. Freixa, S. Gaafoor, H. Omran, S. Berti, G. Santoro, J. Nielsen-Kudsk, U. Landmesser, A. Aminian, M. Costa, and R. Ibrahim are consultants and proctors for Abbott. A. Tzikas, H. Sievert, P. Kanagaratnam, W. Schillinger, B. Meier, and J.W. Park are consultants, proctors, and have received research grants from Abbott. I. Cruz-González and M. Costa are proctors and consultants for Boston Scientific. I. Cruz-González is a proctor for Lifetech. S. Berti is a proctor for Edwards Lifesciences. F. Nietlispach is a consultant for Abbott, Edwards Lifesciences and Medtronic. The other authors have no conflicts of interest to declare.

WHAT IS KNOWN ABOUT THE TOPIC?

- LAAO is an alternative to OAC therapy for the prevention of stroke in patients with nonvalvular atrial fibrillation.
- There have been no previous analyses of the role of LAAO as secondary prevention, among patients who have had a stroke despite OAC therapy (RS).

WHAT DOES THIS STUDY ADD?

- In this study, LAAO in RS patients had a procedural success rate of 97.0% and 4.5% rate of major periprocedural adverse events without significant differences with the non-RS group.
- LAAO in RS patients provided a favorable outcome with an annual risk reduction in stroke or TIA of 65% and a 100% annual risk reduction in major bleeding events during follow-up.
- Adequately powered controlled trials are needed to further investigate the use of LAAO in RS patients, with appropriate comparison of the classical treatment strategy vs the strategy that would add LAAO.

REFERENCES

1. Tzikas A, Shakir S, Gafoor S, et al. Left atrial occlusion for stroke prevention in atrial fibrillation: multicentre experience with the AMPLATZER Cardiac Plug. *EuroIntervention*. 2016;11:1170–1179.
2. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J*. 2016;37:2893–2962.
3. Segers VFM, Heidbuchel H. Evidence and Indications for Percutaneous Closure of the Left Atrial Appendage. *Rev Esp Cardiol*. 2018;71:700–702.
4. Friberg L, Hammar N, Rosenqvist M. Stroke in paroxysmal atrial fibrillation: report from the Stockholm Cohort of Atrial Fibrillation. *Eur Heart J*. 2010;31:967–975.
5. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med*. 2007;146:857–867.
6. Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet*. 2014;383:955–962.
7. Kappetein AP, Head SJ, Généreux P, et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. *J Am Coll Cardiol*. 2012;60:1438–1454.
8. Friberg L, Rosenqvist M, Lip GY. Evaluation of risk stratification schemes for ischaemic stroke and bleeding in 182 678 patients with atrial fibrillation: the Swedish Atrial Fibrillation cohort study. *Eur Heart J*. 2012;33:1500–1510.
9. Lip GY, Nieuwlaar R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euroheart survey on atrial fibrillation. *Chest*. 2010;137:263–272.
10. Lip GY, Frison L, Halperin JL, Lane DA. Comparative validation of a novel risk score for predicting bleeding risk in anticoagulated patients with atrial fibrillation: the HAS-BLED (Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly) score. *J Am Coll Cardiol*. 2011;57:173–180.
11. Bungard TJ, Ghali WA, Teo KK, McAlister FA, Tsuyuki RT. Why do patients with atrial fibrillation not receive warfarin? *Arch Intern Med*. 2000;160:41–46.
12. Deitelzweig SB, Buysman E, Pinsky B, et al. Warfarin use and stroke risk among patients with non-valvular atrial fibrillation in a large managed care population. *Clin Ther*. 2013;35:1201–1210.
13. Connolly SJ, Pogue J, Eikelboom J, et al. Benefit of oral anticoagulant over antiplatelet therapy in atrial fibrillation depends on the quality of international normalized ratio control achieved by centers and countries as measured by time in therapeutic range. *Circulation*. 2008;118:2029–2037.
14. Easton JD, Lopes RD, Bahit MC, et al. Apixaban compared with warfarin in patients with atrial fibrillation and previous stroke or transient ischaemic attack: a subgroup analysis of the ARISTOTLE trial. *Lancet Neurol*. 2012;11:503–511.
15. Diener HC, Connolly SJ, Ezekowitz MD, et al. Dabigatran compared with warfarin in patients with atrial fibrillation and previous transient ischaemic attack or stroke: a subgroup analysis of the RE-LY trial. *Lancet Neurol*. 2010;9:1157–1163.
16. Hankey GJ, Patel MR, Stevens SR, et al. Rivaroxaban compared with warfarin in patients with atrial fibrillation and previous stroke or transient ischaemic attack: a subgroup analysis of ROCKET AF. *Lancet Neurol*. 2012;11:315–322.
17. López-Mínguez JR, Asensio JM, Gragera JE, et al. Two-year clinical outcome from the Iberian registry patients after left atrial appendage closure. *Heart*. 2015;101:877–883.
18. Urena M, Rodes-Cabau J, Freixa X, et al. Percutaneous left atrial appendage closure with the AMPLATZER cardiac plug device in patients with nonvalvular atrial fibrillation and contraindications to anticoagulation therapy. *J Am Coll Cardiol*. 2013;62:96–102.
19. Holmes DR, Reddy VY, Turi ZG, et al. Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomised non-inferiority trial. *Lancet*. 2009;374:534–542.
20. López-Mínguez JR, Nogales-Asensio JM, Infante De Oliveira E, et al. Long-term event reduction after left atrial appendage closure. Results of the Iberian registry II. *Rev Esp Cardiol*. 2019;73:449–455.
21. Price MJ, Reddy VY, Valderrábano M, et al. Bleeding outcomes after left atrial appendage closure compared with long-term warfarin: a pooled, patient-level analysis of the WATCHMAN Randomized Trial Experience. *JACC Cardiovasc Interv*. 2015;8:1925–1932.
22. Hart RG, Pearce LA, Miller VT, et al. Cardioembolic vs. noncardioembolic strokes in atrial fibrillation: frequency and effect of antithrombotic agents in the stroke prevention in atrial fibrillation studies. *Cerebrovasc Dis*. 2000;10:39–43.
23. Pujol-Lereis VA, Ameriso S, Povedano GP, Ameriso SF. Ischemic stroke in patients with atrial fibrillation receiving oral anticoagulation. *J Neurol Sci*. 2013;15:139–142.
24. Cano LM, Cardona P, Quesada H, Lara B, Rubio F. Ischaemic stroke in patients treated with oral anticoagulants. *Neurología*. 2016;31:395–400.