ORIGINAL ARTICLE

Percutaneous Left Atrial Appendage Closure for Thromboembolic Prevention in Atrial Fibrillation

Cierre percutáneo de la orejuela izquierda para prevención tromboembólica en fibrilación auricular

ALDO G. CARRIZO[†, 1], MADHU NATARAJAN[2,3], SEBASTIAN RIBAS[1], JAMES VELIANOU[2], CARLOS A. MORILLO[1,3]

ABSTRACT

Background: Atrial fibrillation (AF) produces a five-fold increase in the risk of stroke, and the exclusion of the left atrial appendage (LAA), the main source of thrombi, is an interesting therapeutic option in patients with contraindication for oral anticoagulation.
Objectives: The goal of this study was to evaluate the initial experience, immediate results and outcome at 45 days of percutaneous closure of the LAA in patients with AF and high risk of thromboembolic events, in whom chronic oral anticoagulation was contraindicated.
Methods: Twenty-two patients with non-valvular AF and a CHA_2DS_2-Vasc ≥2 in whom there was contraindication or impossibility of long-term oral anticoagulation underwent percutaneous closure of the LAA with the WATCHMAN™ device. The patients were evaluated 45 days after the procedure by clinical assessment and transesophageal echocardiography.
Results: The implant was successful in 21 of 22 patients (95.4%). Median (interquartile range) age and CHA_2DS_2-VASc and HAS-BLED scores were 76 years (IQR 14.5), 5 (IQR 1.5) and 4 (IQR 1), respectively. Three (13.6%) periprocedural complications were observed: one cardiac tamponade requiring surgery, one concealed major bleeding and one pseudoaneurysm of the femoral artery. No device-related complications or thromboembolic events were observed during the 45-day follow-up. The LAA was adequately excluded in 95% of the cases.
Conclusions: In our initial experience, the procedure is feasible, with an acceptable risk, and can be considered a therapeutic option in patients with AF and high thromboembolic risk who cannot receive oral anticoagulation.

Key words: Atrial Fibrillation - Atrial Appendage - Stroke/prevention and control

RESUMEN

Introducción: La fibrilación auricular (FA) incrementa cinco veces el riesgo de accidente cerebrovascular y la orejuela auricular izquierda (OI) es la principal fuente de formación de trombos, por lo que su exclusión se presenta como una alternativa terapéutica interesante en pacientes con contraindicación para la anticoagulación oral.
Objetivos: Evaluar la experiencia inicial, los resultados del implante y la evolución a los 45 días del cierre percutáneo de la OI en pacientes con FA de riesgo tromboembólico alto en los cuales no podía emplearse la anticoagulación oral crónica.
Material y métodos: Veintidós pacientes con FA no valvular y CHA_2DS_2-Vasc ≥2 en los que la anticoagulación a largo plazo estaba contraindicada o era impracticable fueron sometidos al cierre percutáneo de la OI con el dispositivo WATCHMAN®. Los pacientes fueron evaluados a los 45 días mediante control clínico y con ecocardiografía transesofágica.
Resultados: El implante fue exitoso en 21 de los 22 pacientes (95,4%). Las medianas (rango intercuartil) de edad, CHA_2DS_2-VASc y HAS-BLED fueron 76 años (RIC 14,5), 5 (RIC 1,5) y 4 (RIC 1), respectivamente. Se observaron 3 (13,6%) complicaciones periprocedimiento: un taponamiento que requirió revisión quirúrgica, un sangrado mayor oculto y un seudoaneurisma femoral. Durante el seguimiento a 45 días no se observaron complicaciones relacionadas con el dispositivo ni eventos tromboembólicos. En el 95% de los casos, la OI se encontraba adecuadamente excluida.
Conclusiones: En nuestra experiencia inicial, el procedimiento es factible con un riesgo aceptable, constituyéndose en una alternativa terapéutica en pacientes con FA de riesgo tromboembólico alto que no pueden recibir anticoagulantes orales.

Palabras clave: Fibrilación auricular - Apéndice atrial - Accidente cerebrovascular/prevención y control

Rev Argent Cardiol 2015;83:512-518. http://dx.doi.org/10.7775/rac.v83.i6.7272
SEE RELATED ARTICLE: Rev Argent Cardiol 2015;83:499-500. http://dx.doi.org/10.7775/rac.v83.i6.7612

Received: 09/28/2015 - *Accepted:* 10/21/2015

Address for reprints: Dr. Aldo Carrizo - 237 Barton St E, 4W Floor - Hamilton, Ontario, Canada. L8L 2X2 - e-mail: carrizo@HHSC.CA

[†] To apply as Full Member of the Argentine Society of Cardiology
[1] Cardiac Arrhythmia and Pacemaker Unit, Hamilton Health Sciences, McMaster University. Ontario, Canada
[2] Heart Investigation Unit, Hamilton Health Sciences, McMaster University. Ontario, Canada
[3] Population Health Research Institute. Ontario, Canada

Abbreviations

TEE	Transesophageal echocardiography	**PASS**	Position, Anchor, Size and Seal
AF	Atrial fibrillation	**IQR**	Interquartile range
FDA	Food and Drug Administration	**INR**	International normalized ratio
LAA	Left atrial appendage	**ACT**	Activated clotting time

INTRODUCTION

Atrial fibrillation (AF) has become a global public health problem, as its incidence has increased partly due to population aging. (1) Atrial fibrillation is associated with an increased risk of ischemic stroke. In patients with AF, the annual risk of stroke is approximately 5% and varies with the associated risk factors. (2, 3) For this reason, several investigations have been developed over the past years to prevent the thromboembolic complications associated with AF.

Warfarin has proved to reduce the risk of stroke (RR 60%) and is substantially more efficient than aspirin (RR 20%). (4) Bleeding is the major complication associated with these drugs and may be catastrophic as in the case of intracranial hemorrhage. In addition, long-term administration of these agents is limited by several barriers resulting in poor tolerance or no administration. In average, 50% of patients discontinue anticoagulation therapy 2 years after initiation, 50% do not achieve optimal INR values and the remaining 50% who have a clear indication of anticoagulation are not receiving treatment. (5-7)

These limitations have led to the development of new oral anticoagulants which include direct thrombin inhibitors (dabigatran) (8) and Xa factor inhibitors (rivaroxaban, apixaban and endoxaban). (9-11) These drugs were found to be noninferior to warfarin in the prevention of stroke, with additional practical advantages as rapid onset of action, lower interaction with food or medications and lack of need for regular anticoagulant monitoring.

However, between 13% and 36% of patients with AF have contraindication for chronic oral anticoagulation, (12, 13) which associated with high thromboembolic risk constitutes a real dilemma in clinical practice.

Therefore, non-pharmacological strategies, either surgery or percutaneous interventions, have been developed and are used in patients with contraindication for oral anticoagulation. Several studies based on necropsy material, echocardiography or surgical findings have demonstrated that in non valvular AF most thrombi (90%) originate in the left atrial appendage (LAA). (14-16) Thus, these interventions focus on preventing the passage of LAA thrombi into the systemic circulation producing catastrophic thromboembolic events.

Among the various percutaneous techniques, only the LARIAT® device (SentreHEART, Redwood City, CA) (17) and, more recently the WATCHMAN™ device (Boston Scientific, Natick, MA) (18) have been approved by the Food and Drug Administration (FDA) in the United States.

The ASAP registry, which included patients with AF and contraindication for oral anticoagulation, reported 77% reduction in the risk of stroke after percutaneous closure of the LAA with the WATCHMAN™ device. The rate of procedure-related adverse events was 8.7%. (19)

The aim of this study was to report our initial experience, including periprocedural complications, and at 45 days of LAA percutaneous closure with the WATCHMAN™ device in patients with AF and CHA_2DS_2-VASc score ≥2 with contraindication for oral anticoagulation.

METHODS

Study design and patient selection

This prospective, non- randomized study evaluated implant safety and efficacy and the short-term outcome of patients undergoing percutaneous closure of the LAA with the WATCHMAN™ device. Twenty-two patients with AF and high thromboembolic risk (CHA_2DS_2-VASc ≥2) in whom oral anticoagulation was contraindicated (history of spontaneous major bleeding, current anticoagulant or antiplatelet therapy, hematologic disorders with bleeding predisposition) or impossibility to receive anticoagulants (patient's refusal to treatment or labile therapeutic range) were selected between November 2013 and August 2015 at the Hamilton General Hospital.

Patients with severe heart valve disease, nickel allergy, active infection, recent bleeding or any other condition preventing the use of anticoagulants, aspirin or clopidogrel for a minimum of 45 days were excluded from the study. Patients were considered unsuitable to take part in the study if they had undergone surgical repair or percutaneous device closure of atrial septal defects or patent foramen ovale, presented intracardiac thrombi or had an unfavorable LAA anatomy (maximum LAA ostium diameter <17 mm or LAA depth >31 mm) measured by transesophageal echocardiograhy (TEE).

Details of implant and follow-up

The WATCHMAN™ left atrial appendage closure device consists of three components: a transseptal access sheath, a delivery system catheter and the device itself mounted on the catheter. The WATCHMAN™ device is a self-expanding nitinol frame with fixation barbs and a polyester fabric which covers the atrium-facing surface of the device (Figure 1). The system is available in five sizes: 21, 24, 27, 30, and 33 mm. The device size must be 10-20% larger than the maximum LAA ostium diameter. The ostium diameter and the LAA depth were measured using TEE in different angles (0º, 45º, 90º and 135º) (Figure 2).

The implant was performed under general anesthesia

with angiographic and transesophageal and intracardiac echocardiographic guidance. In all cases the left atrium was accessed via a transseptal approach. Once in the left atrium, an initial intravenous heparin bolus (1000 U/kg) was administered and activated clotting time (ACT) controls were performed every 20 minutes. The aim was to maintain ACT between 250 and 350 s, using additional heparin boluses as necessary.

Once the device was deployed, the correct positioning was evaluated using the PASS criteria (position, anchor, size, seal). Position: the device position had to be distal or at the LAA ostium; anchor: the stability was tested by traction movements; size: the device size should be 8% to 20% smaller then the original size, and seal: angiographic and TEE assessment of the LAA ostium was performed to evaluate any peri-device flow.

If all the criteria were met, the device was released (Figure 3); if not, the device was recaptured and repositioned. If needed, another device with a different diameter was chosen.

The patients were hospitalized and discharged on the following day, if possible. Before being discharged, all the patients underwent transthoracic echocardiography to rule out pericardial effusion, thrombi or device migration. Oral anticoagulants with or without aspirin, or aspirin plus clopidogrel could be prescribed according to the patient's characteristics and clinical criteria.

All patients were evaluated at 45 days by clinical assessment and TEE. The position of the device was again assessed, particularly the adequate LAA occlusion through peri-device flow assessment. Oral anticoagulation or dual antiplatelet therapy was discontinued if peri-device flow was absent or minimal (<3 mm) and the patient remained only with aspirin treatment for at least 12 months after implantation.

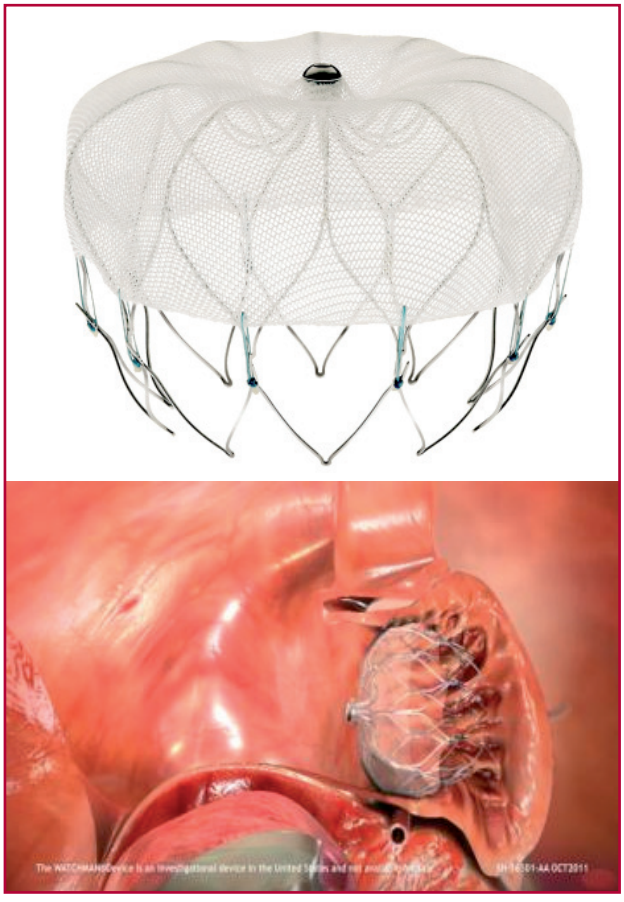

Fig. 1. WATCHMAN™ device. Image courtesy of Boston Scientific, MN. Reproduced with permission.

Events analyzed

The acute implant success and device stability at 45 days was analyzed. All the complications related with the procedure, the presence of thromboembolic complications and hemorrhages related with this population were reported. Stroke was defined as a non-traumatic focal neurological deficit lasting more than 24 hours confirmed by imaging tests. Transient ischemic attack was defined as the sudden onset of a non-traumatic focal neurological deficit lasting less than 24 hours. Systemic embolism was defined as the vascular occlusion of an extremity or organ with clinical and radiological documentation in the absence of another likely mechanism (e.g. trauma). Major bleeding was considered following the criteria of the International Society on Thrombosis and Haemostasis; (20) all other bleedings were considered minor.

Statistical analysis

A descriptive analysis of the different variables was performed. Continuous variables are expressed as median and interquartile range (IQR) and categorical variables as numbers and percentages. IBM SPSS 22.0 statistical package (SPSS Inc., Chicago, Illinois, USA) was used for statistical analysis.

Ethical considerations

The study was conducted following the recommendations of the Declaration of Helsinki and all the patients gave their informed consent. The device has not been approved by the Public Health Agency of Canada yet; therefore, each case was submitted to a "special access" request.

RESULTS

Population characteristics

Twenty-two patients with AF underwent percutaneous closure of the LAA. Median age was 76 years

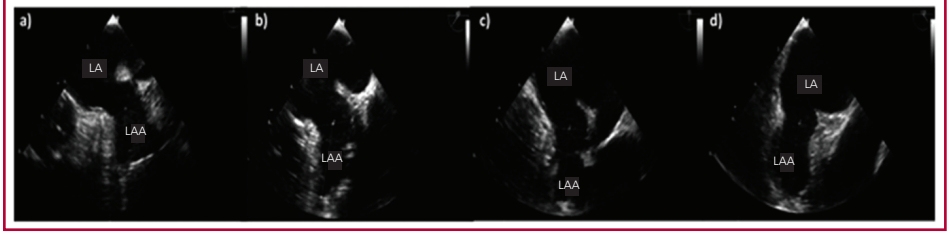

Fig. 2. Measurement of the left atrial appendage size and depth with transesophageal echocardiography at 0° (a), 45° (b), 90° (c) and 135° (d) before device implantation. LA: Left atrium LAA; left atrial appendage.

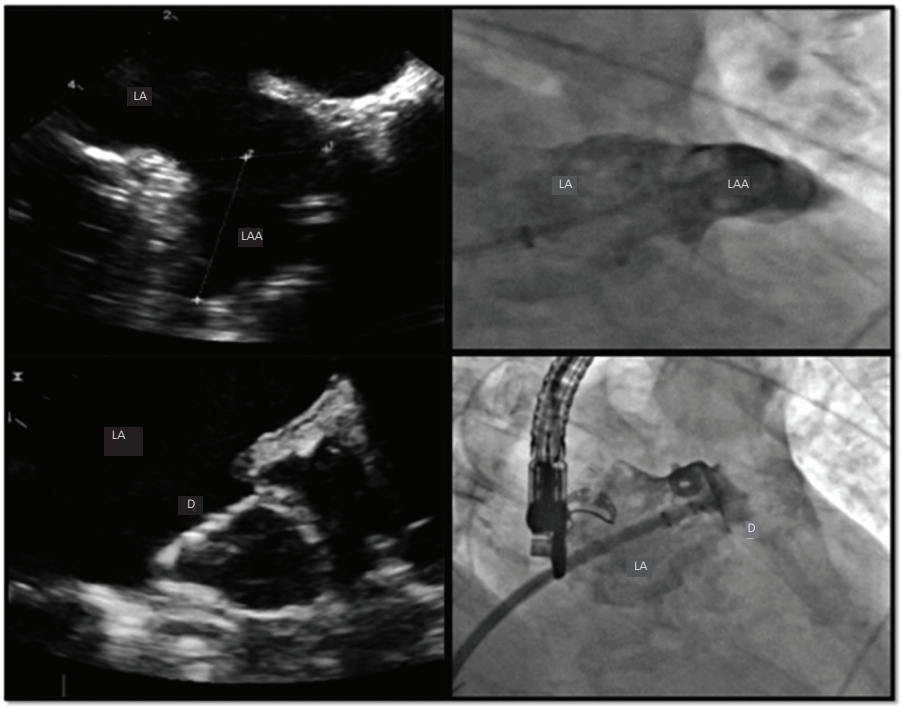

Fig. 3. Transesophageal echocardiography and angiography images obtained before (upper image) and after (lower image) device implantation. LA: Left atrium LAA; left atrial appendage. D: Device

(IQR 14.5), 64% were men and 64% presented persistent or permanent AF. Median CHA_2DS_2-VASc score was 5 (IQR 1.5) and median HAS-BLED score was 4 (IQR 1). The principal baseline characteristics of the study population are described in Table 1.

The most common indication was history of major bleeding in 16 patients (73%), 7 of which (44%) were receiving anticoagulants. The remaining 6 patients (27%) had a history of repeated minor bleeding during antithrombotic therapy and the following conditions: 2 had severe renal dysfunction requiring dialysis and labile therapeutic range, 1 autoimmune idiopathic thrombocytopenic purpura, 1 Rendu-Osler-Weber disease, 1 underwent drug-eluting stent implantation and required prolonged dual antiplatelet therapy and the remaining patient refused to receive chronic oral anticoagulation.

Success of the procedure

The device was successfully implanted in 21 of 22 patients (95.4%). The remaining patient presented cardiac tamponade during cannulation of the LAA before advancing the device and the procedure was aborted. The PASS criteria were successfully achieved in 11 patients (52%) during the first positioning. In the remaining patients, the device was recaptured and repositioned without complications. In one case the device size had to be changed. Table 2 summarizes the characteristics and the outcomes of the implant.

Seven patients (32%) were hospitalized for >1 day: 3 due to procedure-related complications, 1 due to the anesthesiologist's recommendation in a patient with severe chronic obstructive pulmonary disease and 3 for social issues.

Acute complications (0-7 days after device implantation)

Three complications (13.6%) were observed within the first 7 days after implantation. One patient presented cardiac tamponade requiring surgery and died five days later due to sepsis. Another patient had a pseudoaneurysm of the femoral artery that was treated with thrombin injection. The third patient presented a sudden fall in hemoglobin levels requiring transfusion of 2 units of red blood cells, with no evidence of the site of bleeding (see Table 2).

None of the patients presented cardiac effusion, device migration or device-related thrombi in the echocardiogram performed before discharge.

Complications during follow-up (45 days)

The 21 patients discharged completed clinical follow-up and TEE at 45 days. No device-related complications or thromboembolic events were observed. Two patients presented minor bleeding requiring modification of the antithrombotic treatment.

Transesophageal echocardiography did not demonstrate thrombi associated with the device or device migration. The LAA was correctly sealed in 95% of the patients (absence of residual or peri-device flow <3 mm) (see Table 2).

Antithrombotic therapy

Eighty-six percent of the patients were discharged with oral anticoagulants plus or without aspirin, 2

Table 1. Baseline population characteristics

	n=22
Age, years, median (IQR)	76 (14.5)
Male gender, n (%)	14 (64)
BMI (kg/m2), median (IQR)	27 (8.7)
AF, type	
Paroxysmal, n (%)	8 (36)
Persistent/permanent, n (%)	14 (64)
Hypertension, n (%)	18 (82)
Diabetes, n (%)	7 (32)
Coronary artery disease, n (%)	8 (36)
Previous thromboembolism	9 (41)
Stroke, n (%)	5 (23)
TIA, n (%)	2 (9)
PE, n (%)	2 (9)
Pacemaker, n (%)	5 (23)
Renal dysfunction, n (%)	7 (32)
Creatinine clearance* (ml/min), median, (IQR)	64 (37)
$CHADS_2$, median (IQR)	3 (2)
$CHADS_2$	
1	1 (4.5)
2	6 (27)
3	9 (41)
4	5 (23)
5	1 (4.5)
$CHADS_2$-VASc , median (IQR)	5 (1.5)
CHA_2DS_2-VASc, n (%)	
2	1 (4.5)
3	4 (18)
4	5 (23)
5	7 (32)
6	4 (18)
7	1 (4.5)

IQR: Interquartile range. BMI: Body mass index. AF: Atrial fibrillation. TIA: Transient ischemic attack. PE: Peripheral embolism. *Cockroft-Gault formula.

(9.5%) with dual antiplatelet therapy and 1 (4.5%) with triple antithrombotic therapy. Most patients continued with this regime for 45 days and then with aspirin indefinitely. Four patients had different managements. One patient discontinued warfarin and another patient discontinued clopidogrel prematurely due to minor bleeding. A third patient continued with dual antiplatelet therapy due to peri-device flow >3 mm. In the last patient, who was receiving triple antithrombotic therapy, warfarin was discontinued and the patient remained with dual antiplatelet therapy.

DISCUSSION

In our initial experience in highly selected patients with non-valvular AF with high thromboembolic risk and contraindication for anticoagulation, percutaneous closure of the LAA was an effective and safe procedure. The acute success rate achieved during implantation was similar to those reported by the main studies (90.9% PROTECT AF; 94.3% CAP; 95.1% PREVAIL). (21, 22) In almost half of the patients, the PASS criteria were not met in the first attempt to deliver the device. However, we could easily reposition the device in all the cases.

Regarding procedure safety, our study included a population with severe comorbidities, with a $CHADS_2$ score of 3±0.9, greater than the one reported by previous studies (2.2±1.2 PROTECT AF; 2.5±1.2 CAP; 2.6±1.0 PREVAIL), (21, 22) and high risk of bleeding (about 8% per year). Two of the 3 complications reported within the first 7 days after the procedure were resolved with minimal invasive measures which did not present any relevant functional impact. Only one procedure had to be aborted due to cardiac tamponade while the LAA was cannulated. The patient underwent cardiac surgery immediately and died of septic shock 5 days later. It is important to remark the importance of performing these procedures in centers with cardiovascular surgery facilities. Interestingly, the LAA size of this case was the smallest of the series (17.5 × 23 mm). Probably the small size could have limited the space for manipulating the instruments. Pericardial effusion requiring intervention is the most common complication reported in multicenter studies (4% PROTECT AF; 2.2% CAP; 1.9% PREVAIL). (21, 22) Other complications as procedure-related stroke, device-associated thrombi or device migration are rare and were not observed in our series.

At 45-day follow-up, none of the patients presented thromboembolic events or device-related complications. The device was adequately positioned in all the cases. In one patient who presented peri-device flow >3 mm, dual antiplatelet therapy was continued. A retrospective analysis based on the PROTECT AF trial shows that 32% of patients have a certain degree of peri-device flow which does not increase the risk of thromboembolism. (23) However, this finding should be interpreted with caution due to the low event rate.

Currently, several devices are available for LAA closure, but the WATCHMAN™ device has been the most extensively studied and has been granted European regulatory approval since 2005. Recently, and after the publication of the PREVAIL study, the FDA has approved the device in the United States in patients with non-valvular AF and high thromboembolic risk, and in those with concern about long-term anticoagulant treatment due to high risk of bleeding. In the PREVAIL study, 407 patients with AF and no contraindication for anticoagulation were randomized to LAA occlusion with the WATCHMAN™ device or to warfarin therapy. (22) The WATCHMAN™ device did not reach the noninferior criterion; however, the study showed a reduction in device-related complications compared with the PROTECT AF trial. Therefore, at present anticoagulation remains the mainstay treatment for the prevention of thromboembolic complications in patients with AF, while percutaneous

Successful implant	21/22 (95.4%)
Repositioning	10/21 (48%)
Successful	10/10 (100%)
Procedure time (min), median (IQR)	76 (14)
Fluoroscopy time (min), median (IQR)	23.5 (10)
LAA*	
Maximum LAA ostium diameter (mm), median (IQR)	22 (4)
Maximum depth (mm), median (IQR)	30 (8)
Spontaneous contrast	16/22 (73%)
Size of the devices implanted	
21 mm	2/21 (9%)
24 mm	6/21 (29%)
27 mm	9/21 (43%)
30 mm	3/21 (14%)
33 mm	1/21 (5%)
General anesthesia	22/22 (100%)
TEE	22/22 (100%)
ICE	22/22 (100%)
Transseptal puncture	22/22 (100%)
Days of hospitalization, median (IQR)	1 (1)
>1 day	7/22 (32%)
Periprocedure complications	
Embolism/device migration	0/22 (0%)
Cardiac tamponade**	1/22 (4.5%)
Stroke	0/22 (0%)
Major bleeding	1/22 (4.5%)
Vascular access	1/22 (4.5%)
Complications at 45 days	
Embolism/device migration	0/21 (0%)
Stroke	0/21 (0%)
Major bleeding	0/21 (0%)
Minor bleeding	2/21 (9.5%)
Peri-device flow at 45 days by TEE	
Absent	12/21 (57%)
1-3 mm	8/21(38%)
>3 mm	1/21 (5%)

Table 2. Details of the procedure and follow-up

min: Minutes. IQR: Interquartile range. LAA:Left atrial appendage. mm: Millimeters. TEE: Transesophageal echocardiogram. ICE: Intracardiac echocardiogram. *Evaluated by TEE. **The patient died at day 5 due to sepsis.

closure of the LAA is a valid treatment for patients unsuitable for oral anticoagulation.

Study limitations

This is a small prospective cohort with a low rate of events that reports the complications, feasibility and efficacy of percutaneous closure of the LAA with the WATCHMAN™ device. The short follow-up period and the sample size limit our observations.

CONCLUSIONS

In our initial experience, and in a population with severe comorbidities, percutaneous closure of the LAA is a feasible procedure with an acceptable risk. Thus, the procedure is a valid option in patients with AF and high thromboembolic risk in whom oral anticoagulation is contraindicated or not feasible

Acknowledgments

The authors are grateful to Nicole Campbell, specialist in Electrophysiology and Structural Heart Pathology at Boston Scientific, for her contribution during the procedures.

Conflicts of interest

A.C. has received a Boston Scientific educational grant and C.M. is a consultant for Boston Scientific. (See authors' conflicts of interest forms in the website/Supplementary material).

REFERENCES

1. Miyasaka Y, Barnes ME, Gersh BJ, Cha SS, Bailey KR, Abhayaratna WP, et al. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota 1980 to 2000, and implications on the projections for future prevalence. Circulation 2006;114:119-25. http://doi.org/cs8qvt

2. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham study. Stroke 1991;22:983-8. http://doi.org/dhwbwv

3. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Analysis of pooled data from five randomized controlled trials. Arch Intern Med 1994;154:1449-57. http://doi.org/d2285f

4. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Ann Intern Med 2007;146:857-67. http://doi.org/2nb

5. Birman-Deych E, Radford MJ, Nilasena DS, Gage BF. Use and effectiveness of warfarin in Medicare beneficiaries with atrial fibrillation. Stroke 2006;37:1070-4. http://doi.org/chm6kb

6. Hylek EM, Evans-Molina C, Shea C, Henault LE, Regan S. Major hemorrhage and tolerability of warfarin in the first year of therapy among elderly patients with atrial fibrillation. Circulation 2007;115:2689-96. http://doi.org/cc6t59

7. Connolly SJ, Pogue J, Eikelboom J, Flaker G, Commerford P, Franzosi MG, 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;118:2029-37. http://doi.org/bm85mf

8. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009;361:1139-51. http://doi.org/bcqddq

9. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011;365:883-91. http://doi.org/bbcf6w

10. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, et al. ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2011;365:981-92. http://doi.org/d937xk

11. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, et al. ENGAGE AF-TIMI 48 Investigators. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2013;369:2093-104. http://doi.org/qqn

12. O'Brien EC, Holmes DN, Ansell JE, Allen LA, Hylek E, Kowey PR, et al. Physician practices regarding contraindications to oral anticoagulation in atrial fibrillation: Findings from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) registry. Am Heart J 2014;167:601-9. http://doi.org/8kx

13. Roel VC, Moukarzel JA, Zaidel EJ, Galli MA, Da Rosa W, Leiva R, et al. Estrategias antitrombóticas en fibrilación auricular. Registro CONAREC XIX. Rev Argent Cardiol 2015;83:178-9. http://doi.org/8kz

14. Alberg H. Atrial fibrillation: a study of atrial thrombus and systemic embolism in a necropsy material. Acta Med Scand 1969;185:373-9. http://doi.org/dnrcgr

15. Stoddard MF, Dawkins PR, Price CR, Ammash NM. Left atrial appendage thrombus is not uncommon in patients with acute atrial fibrillation and a recent embolic event: a transesophageal echocardiographic study. J Am Coll Cardiol 1995;25:452-9. http://doi.org/fdr34b

16. Blackshear JL, Odell JA. Appendage obliteration to reduce stroke in cardiac surgical patients with atrial fibrillation. Ann Thorac Surg 1996;61:755-9. http://doi.org/b6mngc

17. Bartus K, Bednarek J, Myc J, et al. Feasibility of closed-chest ligation of the left atrial appendage in humans. Heart Rhythm 2011;8:188-93. http://doi.org/fkc4kx

18. 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;374:534-42. http://doi.org/bkjfjd

19. Reddy VY, Möbius-Winkler S, Miller MA, Neuzil P, Shchuler G, Wiebe J, et al. Left atrial appendage closure with the Watchman device in patients with a contraindication for oral anticoagulation: ASA Plavix Feasibility Study with Watchman Left Atrial Appendage Closure Technology (ASAP Study). J Am Coll Cardiol 2013;61:2551-6. http://doi.org/f2fm5h

20. Schulman S, Angeras U, Bergqvist D, Eriksson B, Lassen MR, Fisher W, on behalf of the Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in surgical patients. J Thromb Haemost 2010;8:202-4. http://doi.org/fq82sb

21. Reddy VY, Holmes D, Doshi SK, Neuzil P, Kar S. The safety of percutaneous left atrial appendage closure: results from PROTECT AF and the Continued Access Registry. Circulation 2011;123:417-24. http://doi.org/bfbj99

22. Holmes DR Jr, Kar S, Price MJ, Whisenant B, Sievert H, Doshi SK, et al. Prospective randomized evaluation of the Watchman Left Atrial Appendage Closure device in patients with atrial fibrillation versus long-term warfarin therapy: the PREVAIL trial. J Am Coll Cardiol 2014;64:1-12. http://doi.org/f2sthm

23. Viles-Gonzalez JF, Kar S, Douglas P, Dukkipati S, Feldman T, Horton R, et al. The clinical impact of incomplete left atrial appendage closure with the Watchman Device in patients with atrial fibrillation: a PROTECT AF (percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation) substudy. J Am Coll Cardiol 2012;59:923-9. http://doi.org/f2ncbq