

FOCUS ON LEFT ATRIAL APPENDAGE CLOSURE

STRUCTURAL

Percutaneous Left Atrial Appendage Closure With the Watchman Device



Long-Term Results Up to 5 Years

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ABSTRACT

OBJECTIVES The aim of this study was to evaluate long-term outcomes in patients with atrial fibrillation undergoing percutaneous left atrial appendage (LAA) closure with the Watchman device.

BACKGROUND Atrial fibrillation is one of the most common arrhythmias and is associated with a high risk for cardioembolic ischemic events, most notably stroke. Percutaneous LAA closure is an alternative to oral anticoagulation, because most thrombi originate from the LAA.

METHODS All consecutive patients with minimum CHADS₂ or CHA₂DS₂-VASc scores of 1 who underwent LAA closure with the Watchman device between June 2006 and August 2010 were eligible. Follow-up examinations were performed after 45 days to 3 months, 6 months, and 1 year and thereafter annually. Afterward, alternating office visits and telephone follow-up were performed every 6 months.

RESULTS A total of 102 patients were included. The mean age was 71.6 ± 8.8 years, and 37.3% were women. The mean CHADS₂ and CHA₂DS₂-VASc scores were 2.7 ± 1.3 and 4.3 ± 1.7, respectively. Procedural success was achieved in 96.1% of patients. During a mean follow-up period of 3.0 ± 1.6 years, the annual rates of transient ischemic attack, stroke, intracranial hemorrhage, and death were 0.7%, 0.7%, 1.1%, and 3.5%, respectively.

CONCLUSIONS LAA closure with the Watchman device is safe and feasible for stroke protection in patients with atrial fibrillation. Low ischemic events rates demonstrate its effectiveness during long-term follow-up.

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Atrial fibrillation (AF) increases the risk for stroke by approximately 5-fold compared with patients in sinus rhythm (1). Anticoagulation with vitamin K antagonists (VKAs) or anticoagulant agents such as factor Xa or direct thrombin inhibitors reduces the risk for cerebral embolic events; however, it is associated with significant complications, most commonly related to hemorrhage (2-5). Percutaneous left atrial appendage (LAA) occlusion with the Watchman device (Boston Scientific,

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ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

LAA = left atrial appendage

TEE = transesophageal
echocardiography

TIA = transient ischemic attack

VKA = vitamin K antagonist

Marlborough, Massachusetts) is an alternative to medical therapy in these patients because pathological studies have demonstrated that in patients with AF, at least 90% of all thrombi originate in the LAA (4).

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The PROTECT-AF (Watchman Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation) trial recently demonstrated noninferiority of device closure with the Watchman device in comparison with conventional anticoagulation with VKAs (6). Subsequently, percutaneous LAA closure was incorporated into current European guidelines, which describe LAA closure to be reasonable in patients with long-term contraindications to oral anticoagulation (7). However, data beyond the PROTECT-AF trial, specifically regarding long-term results, are pending. In this present analysis, we aimed to evaluate the long-term outcomes of patients with AF treated with the Watchman device on the basis of the real-world setting of a single center.

METHODS

This prospective single-center analysis included all consecutive patients who underwent implantation of the second-generation Watchman device between June 2006 and August 2010. All patients received and signed an informed consent document at least 24 h before the procedure. All examinations were performed in accordance with the Declaration of Helsinki (revisions of 2008 and 2013).

PATIENTS. Patients with nonvalvular AF and CHADS₂ or CHA₂DS₂-VASc scores of at least 1 were included. Echocardiographic criteria for implantation were an ejection fraction $\geq 30\%$ and the absence of severe mitral insufficiency, mitral stenosis, or thrombus formation in left atrium and/or in the LAA. Patients with large patent foramen ovales, defined as patent foramen ovales with atrial septal aneurysms (total excursion >15 mm or length ≥ 15 mm) or large shunts (substantial passage of bubbles within 3 beats) were excluded as well. Only patients whose LAA lengths were greater than their ostial diameters were included. Patients with intolerance to aspirin were excluded.

DEVICE AND PROCEDURE. The Watchman LAA closure device has a self-expanding nitinol cage with a permeable polyester fabric on the surface and fixation barbs surrounding the perimeter. The device is delivered through a 12-F catheter requiring femoral

venous access and transseptal puncture with the insertion of a 14-F transseptal sheath. Five different sizes from 21 to 33 mm in 3-mm increments are available. A device slightly (8% to 20%) larger than the maximal LAA ostial diameter as measured by angiography and transesophageal echocardiography (TEE) was chosen. Compression grade was calculated (device diameter after implantation/diameter before implantation) to ensure safe position. The optimal compression grade was considered to range between 80% and 92%. Further procedural details have been published elsewhere (6).

After the procedure, patients were hospitalized for at least 1 day. Transthoracic echocardiography and electrocardiographic monitoring were performed to exclude pericardial effusion and potential arrhythmias.

MEDICATIONS. In the absence of contraindications to anticoagulation, VKAs were administered for 45 days with heparin bridging until the international normalized ratio was in a therapeutic range (2.0 to 3.0). Aspirin therapy (100 mg/day) was started on the day before implantation and continued lifelong. Clopidogrel was started at the 45-day follow-up visit and was continued until 6-month follow-up. Patients not eligible for anticoagulation ($n = 25$) were treated with lifelong aspirin (100 mg/day), which started the day before implantation, and clopidogrel (75 mg/day) starting from the day of implantation until completion of the 6-month follow-up. Endocarditis prophylaxis was recommended up to 6 months after implantation.

FOLLOW-UP. Follow-up examinations, including international normalized ratio monitoring (for anticoagulated patients) and electrocardiography, were performed between 45 days and 3 months (for non-anticoagulated patients) after implantation. At the same time, peridevice flow, device stability, and positioning were evaluated by TEE. Electrocardiography and TEE were repeated at the 6-month and 1-year follow-up visits. Follow-up via telephone was performed at month 9. After 1 year, another office follow-up visit was scheduled, including TEE, electrocardiography, and physical examination. Afterward, follow-up via telephone and office follow-up visits, including electrocardiography and physical examination, were performed alternately every 6 months.

STATISTICAL ANALYSIS. Data are presented as frequencies and percentages for categorical variables and mean \pm SD for continuous variables. For comparison of categorical variables, the Fisher exact test or

chi-square test was applied, whereas for continuous variables, the Mann-Whitney *U* test was used. These tests were calculated 2-tailed, and *p* values <0.05 were considered to indicate statistical significant. Furthermore, Kaplan-Meier analyses were performed. Statistical analysis was performed with Prism 6 (GraphPad Software, Inc., La Jolla, California).

RESULTS

BASELINE EVALUATION. One hundred two patients were eligible for this evaluation. The mean age was 71.6 ± 8.8 years, and 37.3% (38 of 102) were women. The mean CHADS₂, CHA₂DS₂-VASc, and HAS-BLED scores were 2.7 ± 1.3, 4.3 ± 1.7, and 2.9 ± 1.2, respectively. TEE of the LAA revealed a mean ostial diameter of 22.2 ± 3.5 mm and a mean length of 32.4 ± 6.8 mm. The LAA was multilobed in 54.9% of patients. Further baseline characteristics are presented in **Table 1**.

PROCEDURAL RESULTS. Successful implantation of the device was achieved in 96.1% of patients (98 of 102). In 4 patients, implantation was not possible because of unfavorable anatomic features. For adequate positioning, partial recapture were required in 26.5% of patients (27 of 102). Full recapture and subsequent replacement of the device because of inappropriate device size were needed in 31.4% (32 of 102). The mean compression grade after successful deployment was 84.9 ± 6.4%. Post-implantation TEE and fluoroscopic imaging demonstrated successful

closure of the LAA in 97 of 98 patients. In 1 patient, the device was deployed in 1 lobe of a multilobed appendage and could not be recaptured or repositioned adequately. Because of the uncovered lobe, the patient was advised to stay on VKA therapy. The mean procedure time was 54.5 ± 22.0 min. The mean total fluoroscopy time was 8.8 ± 3.8 min. The mean amount of contrast agent was 146.5 ± 52.5 ml. Dual-antiplatelet therapy was administered for 6 months in 41.8% of patients (41 of 98). All others (58.2% [57 of 98]) received VKAs for 45 days and dual-antiplatelet therapy afterward until completion of 6-month follow-up.

Procedure-related adverse events occurred in 8.8% of patients (9 of 102). Three patients had hemodynamically relevant pericardial effusions and underwent successful pericardiocentesis. Four patients had evidence of hemodynamically nonrelevant pericardial effusions, which were treated conservatively. One patient had an allergic exanthema, and 1 patient had minor post-procedural femoral bleeding.

Comparison of procedural parameters and procedure-related complications did not show any statistically relevant differences between the first 51 and second 51 consecutive patients. Further results are presented in **Table 2**.

FOLLOW-UP OUTCOMES. The mean follow-up duration for 96 patients (after inclusion, 2 patients refused to undergo follow-up visits at our center) was 3.0 ± 1.6 years, with a maximum of 5 years and a total of 276.6 documented patient-years. During this period, there was no evidence of relevant residual peridevice leakage ≥5 mm, except in the patient with the uncovered lobe mentioned previously. In 2 patients, thrombus formation was detected on the device 3 and 6 months after the procedure, respectively. Both patients were asymptomatic and

TABLE 1 Baseline Characteristics (n = 102)

Age (yrs)	71.6 ± 8.8
CHADS ₂ score	2.7 ± 1.3
CHA ₂ DS ₂ -VASc score	4.3 ± 1.7
1	19.6% (20)
2	33.3% (34)
3	16.7% (17)
4	21.6% (22)
5	8.8% (9)
6-9	0.0% (0)
Congestive heart failure	36.3% (37)
Hypertension	91.2% (93)
Age 65-74 yrs	43.1% (44)
Age ≥75 yrs	39.2% (40)
Diabetes	27.5% (28)
History of stroke	17.6% (18)
History of TIA	22.5% (23)
Vascular disease	45.1% (46)
Women	37.3% (38)

Values are mean ± SD or % (n).
 TIA = transient ischemic attack.

TABLE 2 Comparison of Procedural Findings Between the First and Second Consecutive Halves of the Cohort

Variable	Total Cohort (n = 102)	First Half (n = 51)	Second Half (n = 51)	<i>p</i> Value (First vs Second Cohort)
Mean procedure time (min)	54.5 ± 22.0	53.3 ± 24.1	55.6 ± 19.8	0.2920
Fluoroscopy time (min)	8.8 ± 3.8	9.1 ± 3.7	8.6 ± 3.9	0.4293
Amount of contrast agent (ml)	146.5 ± 52.5	143.9 ± 49.4	149.1 ± 55.8	0.4911
Need for full recapture	31.4% (32)	25.5% (13)	37.3% (19)	0.2004
Mean number of devices deployed per procedures	1.3 ± 0.6	1.2 ± 0.6	1.4 ± 0.6	0.1464
Procedure failure	3.9% (4)	3.9% (2)	3.9% (2)	1.0000
Procedure-related complications	8.8% (9)	11.8% (6)	5.9% (3)	0.4874

Values are mean ± SD or % (n).

were treated with low-molecular weight heparin. At the next follow-up visits, the thrombi were dissolved.

Two patients had ischemic strokes more than 12 months after implantation. Two further patients had transient ischemic attacks (TIAs), 1 patient 1 month and the other patient more than 12 months after the procedure. Three patients had evidence of intracranial bleeding, 1 patient while on VKA and aspirin, the second patient while on aspirin and clopidogrel therapy, and the third patient while on aspirin therapy only. The latter patient died 26 months after the procedure.

The rate of cerebral ischemia (including TIA and stroke) during follow-up was 1.4 per year, and the combined rate of cerebral ischemia and intracranial bleeding was 2.5 per year. Survival free of stroke or TIA of any origin was 92.7% (89 of 96).

Patients on aspirin and VKAs for 45 days and afterward on aspirin and clopidogrel until 6 months after the procedure (n = 55) did not show any evidence of thrombi on the LAA occluder and had no ischemic events during this period. In those patients who received aspirin and clopidogrel for 6 months (n = 41), thrombi on the LAA occluder occurred in 2 cases, and 1 ischemic event was noted during this time (0 of 55 vs. 2 of 41).

Severe bleeding complications requiring hospitalization occurred in 6 patients, and the annual rate was 2.1%. Besides the previously mentioned intracranial hemorrhages, 1 patient was admitted to the hospital 1 month after the procedure (while on aspirin and VKA) because of a TIA, and this patient experienced severe pharyngeal bleeding during TEE and subsequently died. Another patient died of severe gastrointestinal bleeding more than 12 months after the procedure while on aspirin. One patient

was hospitalized because of melena more than 2 years after the implantation. At that time, the patient was on aspirin and clopidogrel because of coronary artery disease.

A total of 7 further patients died during follow-up, resulting in an annual rate of 3.5%. One patient committed suicide, 2 patients died of cancer, and 1 patient died of pulmonary embolism. One patient died of global respiratory insufficiency related to severe chronic obstructive pulmonary disease and pneumonia, and in 2 patients the causes of death remained unknown. An overview of long-term outcome is presented in [Table 3](#) and [Figure 1](#).

DISCUSSION

The presented results show that percutaneous LAA closure with the Watchman device can be performed with high procedural success and a low rate of severe procedure-related adverse events. The evaluation of procedural characteristics in the first and second consecutive halves of the cohort did not reveal clear evidence of a learning curve, as no statistically relevant difference were detected. Nevertheless, a trend toward fewer procedure-related complications in the second group was noted (11.8% vs. 5.9%, $p = 0.4874$), which was not statistically relevant, most probably because of the small number of patients. In addition, a learning curve with the Watchman device was observed in a large study of 1,002 patients, with a significant increase of procedural success and a reduction of procedure-related adverse events over time (8).

At present, there is a lack of long-term data, as most of the existing data were derived from the PROTECT-AF trial. To the best of our knowledge, this study had the longest follow-up duration besides PROTECT-AF so far. Sick et al. (9) were the first to describe data with a follow-up period of approximately 2 years in 66 patients treated with the Watchman device, and only 2 TIAs occurred. Another investigation of 58 patients found 1 stroke in 25 months of follow-up (10). Moreover, long-term data with the former percutaneous LAA transcatheter occlusion device (ev3 Inc., Plymouth, Minnesota) exist. Investigations of the percutaneous LAA transcatheter occlusion device with 58 and 73 patients and follow-up periods of 4 and 2 years, respectively, demonstrated annual stroke rates of 3.8% and 0%, respectively (11,12). In addition, a study of 134 patients treated with the Amplatzer Cardiac Plug, with a mean follow-up duration of almost 2 years (680 days), was performed, and an annual stroke rate of 0.8% was observed (13). However, there are substantial

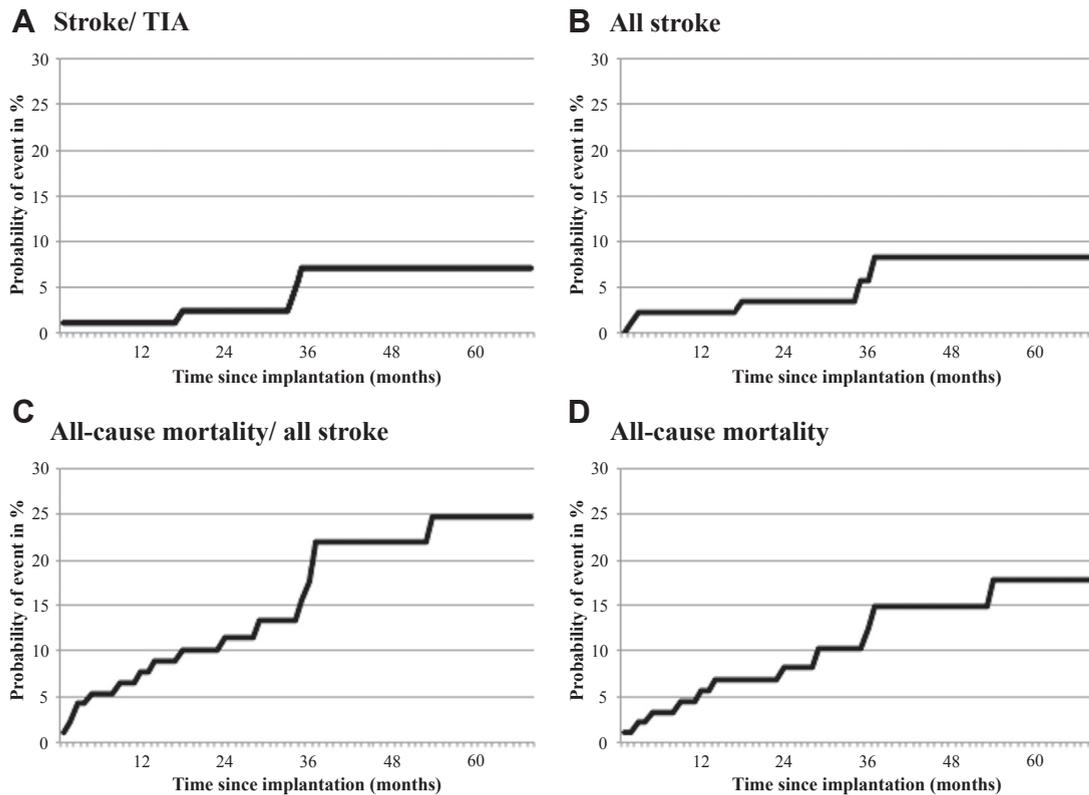
TABLE 3 Follow-Up Outcomes

Follow-up time	3.0 ± 1.6
Total patient-yrs	276.6
Post-procedural DAPT for 6 months	41.8% (41/98)
Post-procedural VKA and aspirin for 45 days	58.2% (57/98)
Device-associated thrombus	2.1% (2/96)
Stroke/TIA	1.4%
Stroke	0.7%
TIA	0.7%
Intracranial hemorrhage	1.1%
Total major bleeding complications	2.1%
Deaths	3.5%

Values are mean ± SD, % (n/N), or % per year.

DAPT = dual-antiplatelet therapy; TIA = transient ischemic attack; VKA = vitamin K antagonist.

FIGURE 1 Kaplan-Meier Curves of Incidence of Endpoints



Time (months)	0	12	24	36	48	60
Patients at risk	96	80	65	40	34	18

Incidence of stroke and transient ischemic attack (TIA) (A), hemorrhagic and ischemic stroke (B), all-cause mortality and all-cause stroke (C), and all-cause mortality (D) for all patients with successful Watchman implantation are illustrated over time.

differences in the design of the occluders and in the post-procedural medications. Furthermore, the percutaneous LAA transcatheter occlusion device is no longer available.

Two randomized controlled trials compared oral anticoagulation with VKAs and LAA closure with the Watchman device, and noninferiority in terms of stroke prevention was demonstrated in both (6,14). In the previously mentioned PROTECT-AF trial, 463 patients were treated with the Watchman device. The observed stroke rates consistently decreased over time: 2.2%, 1.9%, and 1.4% per 100 patient-years after 18 months, 2.3 years, and 3.8 years, respectively (6,15,16). According to the mean CHADS₂ score of 2.7 in this population, the estimated annual stroke risk for patients not taking

oral anticoagulation is between 2.5% and 5.3% and for patients on VKAs is between 1.3% and 2.2%, respectively (17). These results are consistent with our findings: in our investigation, the observed annual rate of ischemic stroke was 0.7%, and the combined rate for ischemic stroke and TIA was 1.4%. Even if both deaths of unknown cause were considered cerebral ischemic cardioembolic events, the yearly rate would have been 2.1%. Taking the event of cerebral bleeding into account as well, the calculated yearly rate of cerebral events of any cause would have been 3.2%. These results are substantially lower than predicted for patients without anticoagulation. Additionally the rate of actually observed ischemic events is even lower than expected for patients under VKA therapy.

Certainly it must be noted that the post-procedural anticoagulant therapy regime of the analyzed population was inconsistent in contrast to both randomized studies. Nevertheless, because of this fact, some secondary findings were detected. During the first 6 months, no relevant differences between both groups were found with regard to the occurrence of thrombi on the LAA occluder, ischemic events, and cerebral bleeding. The ASAP (ASA Plavix Feasibility Study With Watchman Left Atrial Appendage Closure Technology) trial evaluated 150 patients with a mean CHA₂DS₂-VASc score of 4.4 treated with the Watchman and contraindications to VKAs in a nonrandomized fashion, who received dual-antiplatelet therapy for 6 months, followed by aspirin monotherapy. During 14.4 months of follow-up, the annual stroke rate was 1.7%, and 0.6% experienced cerebral hemorrhages per year (18). These results are comparable with our findings, because the annual rates of cranial bleeding and ischemic events (TIA and stroke) were 0.5% and 1.1% per year in patients treated with dual-antiplatelet therapy only.

According to the mean HAS-BLED score of 2.9 ± 1.2 , our patient population was at a high bleeding risk according to current European Society of Cardiology guidelines. The theoretical annual bleeding rate under anticoagulation was 3.74% (7,19). The actual observed major bleeding rate was 2.1% per year, which was substantially lower than expected. This observation may be affected by patient selection and by discontinuation of oral anticoagulation or dual-antiplatelet therapy. Nevertheless, LAA closure seems to be reasonable to prevent severe bleeding complications, especially in high-risk patients. However, post-procedural antiplatelet and anticoagulant medications are heterogeneous within different studies. The optimal medication and duration have not been determined thus far. Thus, the impact of different post-procedural regimes on long-term outcome is not clear and may need further evaluation in a randomized fashion. New anticoagulant agents and shorter dual-antiplatelet therapy durations should be considered, as data on safe LAA closure with minimal antiplatelet therapy are sparse, and several patients show contraindications to contemporary anticoagulant therapy (20).

STUDY LIMITATIONS. Some limitations apply to our investigation. Different post-procedural anticoagulant and antiplatelet regimes were used within the first 45 days after implantation. Their impact on long-term results has not been evaluated so far and may be not interpretable in this particular cohort, because of

its relatively small sample size. Furthermore, 2 patients withdrew consent and 2 patients died of unknown causes. In these patients, cardioembolic events and bleeding complications could not be ruled out with full certainty. Although data were entered in a prospective, non-randomized manner, the present study is subject to the characteristic shortcomings of a single-center registry. Nevertheless, its clinical practice-based approach over a period of up to 5 years is also 1 of the main values of this present study. The all-comer population of patients undergoing LAA closure allows long-term analysis of those who, for various reasons, would have been excluded by contemporary study protocols.

CONCLUSIONS

Our findings suggest that low procedural complication rates with the Watchman device may result in a more pronounced benefit of percutaneous LAA occlusion than previously expected. Long-term data from our study confirm the safety and efficacy of LAA occlusion with the Watchman device for stroke protection, irrespective of the post-procedural anticoagulant regime. Thus, LAA occlusion represents a reasonable alternative to oral anticoagulation.

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PERSPECTIVES

WHAT IS KNOWN? Percutaneous LAA closure offers a reasonable alternative to oral anticoagulation because its safety and efficiency have been demonstrated in a randomized controlled trial. However, long-term data are lacking.

WHAT IS NEW? The follow-up up to 5 years in the present cohort reveals annualized rates of TIA or stroke of 1.4% and of major bleeding complications of 2.1% per year and suggests sufficient long-term stroke protection with a reasonable safety profile.

WHAT IS NEXT? Further long-term data, especially those derived from randomized controlled trials, will be needed to support these findings, and additional studies regarding optimal post-procedural anticoagulant and antiplatelet therapy will be required as well.

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