Review of Percutaneous Left Atrial Appendage Closure for Non-valvular Atrial Fibrillation in Taiwan

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Abstract

Atrial fibrillation (AF) is the most common cardiac arrhythmia and approximately one fifth of ischemic strokes are caused by AF. Stroke prevention among patients with non-valvular AF (NVAF) and a CHA_2DS_2-VASc score ≥ 2 is indicatedwithoral anticoagulants, as recommended in clinical guidelines. However, some patients cannot be treated with anticoagulants, for a variety of reasons or multiple comorbidities. Left atrial appendage (LAA) closure has evolved as an effective strategy for stroke prevention among NVAF patients for whom oral anticoagulants are indicated, but cannot be tolerated in clinical practice. Currently, there is robust evidence based on randomized clinical trials with one percutaneous LAA closure device, and some registry data with other devices, regarding the safety and efficacy of this therapy. However, concerns have been raised about optimal patient selection, management of peri-procedural complications including device-related thrombus and residual leaks. In this review, we summarize and evaluate recently available evidence regarding percutaneous LAA closure in Taiwan with the aim of assisting health professionals in selecting the best management strategies.

Keywords: NVAF, ischemic stroke, atrial fibrillation, oral anticoagulation, CHA_2DS_2-VASc, LAA closure, LAA occluder

Introduction

Atrial fibrillation (AF) is the most common cardiac dysrhythmia, and its incidence is increasing.[1-3] Theprevalence rate of AF in most Asian countries is around 1% in the adult population, lower than that in white people (about 2%).[4] AF is associated with a significant risk of ischemic stroke, congestive heart failure, and overall mortality and presents an important health care challenge for cardiovascular and general clinicians. Approximately one fifth of ischemic strokes are caused by AF and oral anticoagulants (OAC), along with vitamin K antagonists (VKAs) or non-VKA oral anticoagulants (NOACs) markedly reduce ischemic stroke and mortality in patients with non-valvular AF (NVAF) and a CHA_2DS_2-VASc score (congestive heart failure,

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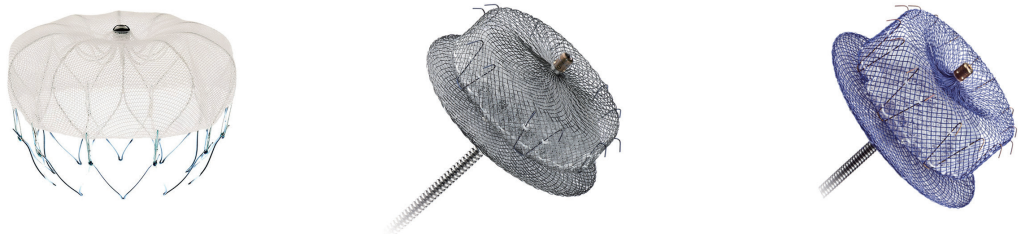
hypertension, age ≥75 years, diabetes, stroke/transient ischemic attack [TIA], vascular disease, age 65 to 74 years, sex category [female]) ≥ 2.[1,3,5,6] Other pharmacological interventions such as rhythm control and rate control improve AF-related symptoms and may preserve cardiac function, but have not demonstrated a reduction in long-term morbidity or mortality.[1,3] However, some patients cannot be treated with OAC for a variety of reasons, including absolute or relative contraindications due to high bleeding risk, patient noncompliance, drug interactions or multiple comorbidities even with a CHA_2DS_2-VASc score ≥ 2. The left atrial appendage (LAA) is the most common source of thrombus in AF patients with ischemic stroke, whereby echocardiography and autopsy studies have shown that more than 90% of thrombi in patients with NVAF and 57% of thrombi in patients with valvular AF originated from the LAA.[7-10] Specific LAA morphology, concomitant trabeculations, pectinate muscle morphology, inflammation, atrial remodeling, and a hypercoagulable state contribute to thrombogenicity.[11,12] Observational studies have demonstrated inconsistent results of surgical LAA excision or occlusion.[13] Percutaneous LAA closure with self-expanding devices which are trans-septally implanted in the LAA, have emerged as safe and effective alternatives for prevention of stroke and systemic embolism (SE) in NVAF patients indicated for OAC.[14,15] In Taiwan, currently available percutaneous LAA closure devices include Watchman (Boston Scientific, Marlborough, MA, USA), Amplatzer Cardiac Plug (ACP, Abbott Vascular, Santa Clara, CA, USA) and Amulet (Abbott Vascular, Abbott Park, IL, USA) (Picture 1). In this paper, we summarize and evaluate recently available evidence (Table 1 and 2) regarding percutaneous LAA closure with the aim of assisting health professionals in selecting the best management strategies.

Watchman

The Watchman nitinol cage percutaneous LAA closure device is the most widely studied and has been approved by the Food and Drug Administration (FDA) in the United States since 2015 and reimbursed by Taiwan's National Health Insurance since 2016. The Watchman device consists of a self-expanding nitinol frame covered with a permeable polyethylene terephthalate (PET) membrane and includes 10 active fixation anchors. A fabric membrane filter made of PET covers the atrial surface of the device, preventing thrombi from escaping into the left atrial chamber and promoting endothelialization during the healing process.[16,17] This device is deployed transseptally using a dedicated 14 Fr sheath and a 12 Fr delivery catheter, usually under transesophageal echocardiography (TEE) and fluoroscopic guidance, but it can also be placed using intracardiac echocardiography. The PROTECT-AF study (Watchman Left Atrial Appendage Closure Device for Embolic Protection in Patients with Atrial Fibrillation) enrolled 707 patients with



Picture 1. Currently available devices for percutaneous left atrial appendage (LAA) closure in Taiwan. (A) Watchman (B) Amplatzer Cardiac Plug (C) Amulet.

Table 1. Major studies on percutaneous LAA closure devices: Watchman.

Characteristics	PROTECT-AF	PREVAIL	CAP registry	CAP2 registry	EWOLUTION	Post-FDA Approval
Study types	Randomized trial	Randomized trial	Prospective registry	Prospective registry	Prospective registry	Prospective registry
Enrolled patients	800	461	566	579	1021	3822
Randomized	463/244	269/138				
Implantation success rate (%)	91	95.1	95	94.8	98.5	95.6
$CHADS_2$ score	2.2 ± 1.2	2.6 ± 1.0	2.4 ± 1.2	2.7 ± 1.1	NA	NA
CHA_2DS_2-Vasc score	3.5 ± 1.6	4.0 ± 1.2	3.9 ± 1.5	4.5 ± 1.3	4.5 ± 1.6	NA
HAS-BLED score ≥3 (%)	19.9	29.7	36.2	28.3	40.0	NA
Anticoagulation	Warfarin for 45 days post implantation followed by aspirin and Plavix × 6 months then aspirin alone	Warfarin for 45 days post implantation followed by aspirin and Plavix × 6 months then aspirin alone	Warfarin for 45 days post implantation followed by aspirin and Plavix × 6 months then aspirin alone	Warfarin for 45 days post implantation followed by aspirin and Plavix × 6 months then aspirin alone	27% treated with OAC, 60% DAPT, 7% single APT, 6% without any therapy	NA
Ischemic stroke (%)	2.2/1.6	1.9/0.7	NA	NA	1.1	NA
Hemorrhagic stroke (%)	0.1/1.6	0.4/0	NA	NA	NA	NA
Major bleeding (%)	3.5/4.1	0.4/NA	0.7	NA	2.6	NA
Pericardial effusion/tamponade (%)	4.8/0	0.4/0	2.2	2.4	0.5	1.3
Device embolization (%)	0.6/0	0.7/0	0	0	0.2	0.2
Procedure related stroke (%)	1/0	0.4/0	0	NA	NA	0.1
Device-related thrombus	NA	NA	NA	NA	3.7	NA

APT = antiplatelet therapy; CAP = Continued Access to PROTECT AF; CAP2 = Continued Access to PREVAIL ; DAPT = dual antiplatelet therapy; FDA = Food and Drug Administration; LAA = left atrial appendage; NA = not available; OAC = oral anticoagulation; PROTECT-AF = The WATCHMAN LAA Closure Device for Embolic PROTECTion in Patients with Atrial Fibrillation; PREVAIL = Randomized Trial of LAA Closure vs. Warfarin for Stroke/Thromboembolic Prevention in Patients with Non-valvular Atrial Fibrillation; EWOLUTION = Design of a Registry to Evaluate Real-World Clinical Outcomes in Patients With AF and High Stroke Risk-Treated With the WATCHMAN Left Atrial Appendage Closure Technology
n/n=percutaneous LAA closure device/warfarin arms.

Table 2. Major studies on percutaneous LAA closure devices: Amplatzer Cardiac Plug and Amulet.

Characteristics	Tzikas et al.[26]	Landmesser et al. [28]
Study types	Retrospective registry, ACP	Prospective registry, Amulet
Enrolled patients	1047	1088
Implantation success rate (%)	97.3	99.0
CHA_2DS_2-Vasc score	4.5 ± 1.6	4.2 ± 1.6
HAS-BLED score	3.1 ± 1.2	3.3 ± 1.1
Antithrombotic therapy at discharge	No use: 8.3% Single APT: 34.7% DAPT: 15.7% OAC (alone or with APT): 25.2%	No use: 2% Single APT: 23% DAPT: 54.3% OAC (alone or with APT): 18.9%
Procedure-related stroke (%)	0.9	0.2
Procedure-related death (%)	0.8	0.2
Procedure-related Major bleeding (%)	1.2	2.4
One year all-cause mortality (%)	4.2	NA
One year major bleeding rate (%)	2.1	NA
Pericardial effusion/tamponade (%)	1.2	1.2
Device embolization (%)	0.7	0.1
Major vascular complication (%)	0.4	0.9
Device-related thrombus	0.3	1.5

ACP = Amplatzer Cardiac Plug; APT = antiplatelet therapy; DAPT = dual antiplatelet therapy; LAA = left atrial appendage; NA = not available; OAC = oral anticoagulation.

NVAF and a $CHADS_2$ risk score of 1 or more (ie, at least one of the following: previous stroke or TIA, congestive heart failure, diabetesmellitus, hypertension, or were 75 years or older) randomized to either the Watchman device (n = 463) or continued warfarin (n = 244) in a 2:1 ratio.[14] After device implantation, warfarin was continued for 45 days, but discontinued if a TEE showed a small peri-deviceleak (residual jet <5 mm), followed by clopidogrel for 4.5 months and life-long aspirin. Successful device implantation was recorded in 88% of subjects, where as TEE criteria for warfarin discontinuation were met in 86% and 92% at 45 days and 6 months, respectively. Efficacy was assessed by a primary composite endpoint of stroke, cardiovascular death, and SE with a one-sided probability criterion of non-inferiority for the intervention of at least 97.5%, by use of a two-fold non-inferiority margin. Serious adverse events (SAEs) that constituted the primary endpoint for safety included major bleeding, pericardial effusion, and device embolization. After 1065 patient-years (PY) of follow-up, the primary efficacy event rate was 3.0 per 100 PY (95% credible interval [CrI] 1.9-4.5) in the intervention group and 4.9 per 100 PY (2.8-7.1) in the control group (rate ratio [RR] 0.62, 95% CrI 0.35-1.25). Primary safety events were more frequent in the intervention group than in the control group (7.4 per 100 PY, 95% CrI 5.5-9.7, vs 4.4 per 100 PY, 95% CrI 2.5-6.7; RR 1.69, 1.01-3.19). The PROTECT-AF study concluded that the efficacy of the Watchman device was non-inferior to that of warfarin therapy with a higher

rate of adverse safety events in the intervention group than in the control group, whereby events in the intervention group were mainly a result of peri-procedural complications. Most adverse events were related to the implant procedure, which included major bleeding, pericardial effusion, and stroke in 3.5%, 4.8%, and 1.1%, respectively. After 1588 PY of follow-up (mean 2.3 ± 1.1 years), the primary efficacy event rates were 3.0% and 4.3% per 100 PY in the Watchman and warfarin groups, respectively (relative risk 0.71; 95% confidence interval [CI], 0.44%–1.30% per year), which met the criteria for non-inferiority. There were more primary safety events in the Watchman group (5.5% per year; 95% CI, 4.2%–7.1% per year) than in the control group (3.6% per year; 95% CI, 2.2%–5.3% per year; relative risk 1.53; 95% CI, 0.95–2.70).[18] The influence of experience on the safety of percutaneous LAA closure using the Watchman device has been analyzed in another study which included patients in the PROTECT-AF trial (542 patients) and those from a subsequent non-randomized CAP (Continued Access to PROTECT AF) registry of patients undergoing Watchman implantation (460 patients).[19] The safety end point included bleeding- and procedure-related events (pericardial effusion, stroke, device embolization). There was a significant decline in the rate of procedure- or device-related safety events within 7 days of the procedure across the 2 studies, with 7.7% and 3.7% of patients, respectively, experiencing events (p = 0.007), and between the first and second halves of PROTECT-AF and CAP, with 10.0%, 5.5%, and 3.7% of patients, respectively, experiencing events (p = 0.006). The rate of serious pericardial effusion within 7 days of implantation, which had made up >50% of the safety events in the PROTECT-AF trial, was lower in the CAP Registry (5.0% versus 2.2%, respectively; p = 0.019). There was a similar experience-related improvement in procedure-related stroke (0.9% versus 0%, respectively; p = 0.039). Finally, the functional impact of these safety events, as defined by significant disability or death, was statistically superior in the Watchman group compared with the warfarin group in the PROTECT-AF trial. This remained true whether significance was defined as a change in the modified Rankin score of ≥1, ≥2, or ≥3 (1.8 versus 4.3 events per 100 PY; relative risk, 0.43; 95% CI, 0.24-0.82; 1.5 versus 3.7 events per 100 PY; relative risk, 0.41; 95% CI, 0.22-0.82; and 1.4 versus 3.3 events per 100 P; relative risk, 0.43; 95% CI, 0.22-0.88, respectively). Therefore, it was concluded that there is a significant improvement in the safety of the Watchman LAA closure with increased operator experience, as with all interventional procedures. The PREVAIL study (Randomized Trial of LAA Closure vs. Warfarin for Stroke/Thromboembolic Prevention in Patients with Non-valvular Atrial Fibrillation) was conducted to answer someof the safety concerns raised by the FDA on the basis of the PROTECT-AF study.[20] The PREVAIL study included patients with NVAF who had a $CHADS_2$ score ≥ 2 or 1 and another risk factor, randomly assigned (in a 2:1 ratio) to undergo percutaneous LAA closure and subsequent discontinuation of warfarin (intervention group, n = 269) or receive chronic warfarin therapy (control group, n = 138). At 18 months, the rate of the first co-primary efficacy endpoint including stroke, SE, and cardiovascular/unexplained death was 0.064 in the device group versus 0.063 in the control group (RR 1.07, 95% CrI: 0.57-1.89) and did not achieve the pre-specified criteria for non-inferiority (upper boundary of 95% CrI ≥ 1.75). The rate for the second co-primary efficacy endpoint (stroke or SE >7 days' post-randomization) was 0.0253 versus 0.0200 (risk difference 0.0053, 95% CrI: -0.0190-0.0273), achieving non-inferiority. Early safety events occurred in 2.2% of the Watchman arm, significantly lower than in PROTECT-AF, satisfying the pre-specified safety performance goal. Even using a broader, more inclusive definition of adverse effects, these still were lower in the PREVAIL trial than in the PROTECT-AF (4.2% vs. 8.7%; p = 0.004). Pericardial effusions requiring surgical repair decreased from 1.6% to

0.4% (p = 0.027), and those requiring pericardiocentesis decreased from 2.9% to 1.5% (p = 0.36), although the number of events was small. The PREVAIL trail concluded that percutaneous LAA closure using the Watchman device was non-inferior to warfarin for ischemic stroke prevention or SE > 7 days' post-procedure. Although non-inferiority was not achieved for overall efficacy, event rates were low and numerically comparable in both arms and procedural safety was significantly improved. The trial also provided additional data that the Watchman device is a reasonable alternative to warfarin therapy for stroke prevention in patients with NVAF who do not have an absolute contraindication to short-term warfarin therapy. Despite not meeting the first co-primary efficacy endpoint, the FDA Circulatory System Advisory Panel reviewed the data from both of thesetrials (PROTECT-AF and PREVAIL) in entirety, judged the device to be safe, and approved the percutaneous LAA closure device, Watchman, for routine clinical practice in 2015. The EWOLUTION (Design of a Registry to Evaluate Real-World Clinical Outcomes in Patients With AF and High Stroke Risk-Treated With the WATCHMAN Left Atrial Appendage Closure Technology) registry provides large-scale post-marketing data from more than one thousand participants regarding procedural success and complications, and long-term patient outcomes, including bleeding and incidence of stroke/TIA.[21,22] The EWOLUTION registry enrolled subjects at high risk of stroke (average $CHADS_2$ score: 2.8 ± 1.3, CHA_2DS_2-VASc score: 4.5 ± 1.6) and moderate-to-high risk of bleeding (average HAS-BLED score [hypertension, abnormal renal/liver function, stroke, bleeding history orpredisposition, labile international normalized ratio, elderly, drugs/alcohol concomitantly]: 2.3 ± 1.2). 45.4% of patients had a history of TIA, ischemic stroke, or haemorrhagic stroke; 62% of patients were judged unsuitable for NOAC by physicians. The Watchman device was successfully deployed in 98.5% of patients with no flow or minimal residual flow achieved in 99.3% of implanted patients. The overall 30-day mortality rate was 0.7%. The most common SAE occurring within 30 days of the procedure was major bleeding requiring transfusion. Incidence of SAEs within 30 days was significantly lower for subjects judged to be ineligible for OAC compared with those eligible for OAC (6.5 vs. 10.2%, p = 0.042). This 30-day data showed that percutaneous LAA closure with the WATCHMAN device has a high success rate with low peri-procedural risk, even in a population with a higher risk of stroke and bleeding, and multiple co-morbidities. Improvement in implantation techniques has led to a reduction of peri-procedural complications previously limiting the net clinical benefit of the procedure. Longer 1-year data of the EWOLUTION registry showed that the Watchman implant succeeded in 1005 patients (98.5%), without leaks >5 mm in 1002 patients (99.7%) with at least 1 TEE follow-up in 875 patients (87%). Antiplatelet therapy was used in 784 (83%), while VKAs were used in only 75 (8%). 1-year mortality rate was 9.8%, reflecting the advanced age and co-morbidities in this enrolled population.[23] Device-related thrombus was observed in 28 patients at routine TEE (3.7%) and was not correlated with the drug regimen (p = 0.14). Ischemic stroke rate was 1.1% (relative risk 84% vs estimated historical data); the major bleeding rate was 2.6% and was predominantly (2.3%) non-procedure/device related. Percutaneous LAA closure with the Watchman device has a high implant and sealing success rate.1-year data of the EWOLUTION registry showed that stroke risk reduction appears to be safe and effective with an ischemic stroke rate as low as 1.1%, even though 73% of patients had a contraindicationto and were not using OAC. 5-year outcomes after percutaneous LAA closure from the PREVAIL and PROTECT-AF trials enrolled 1,114 patients for 4,343 PY and demonstrated that the Watchman provides stroke prevention in NVAF comparable to warfarin (all-stroke/SE; hazard ratio [HR]: 0.961; p = 0.87), with additional reductions in hemorrhagic stroke, disabling/fatalstroke,

cardiovascular/unexplained death, all-cause death, and post-procedure bleeding (HR: 0.20; p = 0.0022; HR: 0.45; p = 0.03; HR: 0.59; p = 0.027; HR: 0.73; p = 0.035; HR: 0.48; p = 0.0003, respectively).[24] Four real-world registries or meta-analysis demonstrated safety and feasibility with post-procedural dual antiplatelet therapy (DAPT), without using OAC. The ASAP (ASA Plavix Feasibility Study With WATCHMAN Left Atrial Appendage Closure Technology), a multicenter, prospective, nonrandomized study, enrolled 150 patients with NVAF and $CHADS_2$ score ≥ 1, who were considered ineligible for warfarin, where by history of hemorrhagic/bleeding tendencies (93%) was the most common reason.[25] The primary efficacy endpoint included combined events of ischemic stroke, hemorrhagic stroke, SE, and cardiovascular/unexplained death. The ASAP study demonstrated an ischemic stroke rate of 1.7%/year with a 77% relativerisk reduction of stroke, adjusted for a predicted stroke risk of 7.3% for the $CHADS_2$ score and successfully confirmed that management with aspirin and 6 months of clopidogrel was safe and feasible after the Watchman percutaneous LAA closure. 1-year data from the EWOLUTION registry further shows that 60% of patients were treated with DAPT, 7% with single antiplatelet, 11% with a NOAC, and 16% with VKA. During follow-up, discontinuation of clopidogrel and OAC occurred, resulting in 84% of patients receiving antiplatelet therapy (55% single and 28% DAPT) and 9% taking no medications. The average time to discontinue DAPT was 6 months, but a large proportionof patients (25%) used a short DAPT regimen (≤ 3 months). The annual rate of ischemic stroke was 1.1%, which translates into an 84% risk reduction, as compared with the calculated stroke rate of 7.2% without the use of OAC for similar CHA_2DS_2-VASc scores. There were no differences in death, stroke, or bleeding rates observed between patients with or without a contraindication for anticoagulation, and there was no relation to the type of OAC used.[21,23] Follow-up TEE revealed adequate sealing (no residual jet >5 mm) in 99% of patients. Device-related thrombus was present in 3.7% of patients but was not correlated with the drug regimen. Preliminary results at 2-year follow-up from the EWOLUTION registry were presented at the European Society of Cardiology (ESC) Congress 2018 and showed consistent findings as compared with the 1-year follow-up data but the manuscript is not yet available. Summarized data of the Watchman device is listed in Table 1.

ACP

ACP is the first-generation device specifically developed for percutaneous LAA closure and comprises a self-expanding double-disc nitinol platform with a proximal disc, distal lobe, and six pairs of distal wires for stabilization (Figure 1). There have been no randomized controlled trials (RCTs) comparing the ACP device with OAC, and only observational studies are available. Tzikas et al. reported the largest multicenter experience withthe CAP device, including 1,047 patients with NVAF treated in 22 centers.[26] Overall, procedural success was 97.3% and peri-procedural major adverse events were 4.97%. The annual rate of SE was 2.3% (31/1349 PY), which is a 59% risk reduction adjusted for a predicted stroke risk of 5.6%/year for the CHA_2DS_2-VASc score. The annual rate of major bleeding was 2.1% (28/1349 PY), which is a 61% risk reduction adjusted for a predicted bleeding risk of 5.34%/year. During follow-up, aspirin monotherapy increased from 31% to 63.7%, whereas VKA decreased from 16% to 1.6%, showing that the ACP device could be a useful strategy inpatients who are not eligible for OAC and who can besafely managed with DAPT. The ACP device is currently not FDA-approved in the United States but is available in Europe. 4-year follow up data using the ACP device in 134 NVAF patients with long-term OAC contraindication from cumulative experience of 2 Italian centers revealed similar reduced annual rates of SE and major bleeding (2.5% and 1.3%) respectively.[27]

Amulet

The Amulet device is the second generation of ACP with improvements in the implantation apparatus to promote ease of deployment, safety, and efficacy. A global prospective registry of a large cohort of NVAF patients (n = 1088) at high risk for ischemic stroke as well as bleeding, implanted with the Amulet device demonstrated a high implantation successrate (99.0%) and major adverse events during implantation and subsequent hospitalization were 3.2%.[28] Patients were discharged on a single antiplatelet agent (23.0%), DAPT (54.3%) or an OAC (18.9%). TEE follow-up showed adequate (<3 mm jet) occlusion of the LAA in 98.2% of patients and device-related thrombus in 1.5% of patients. This large real-world prospective registry of percutaneous LAA closure using the Amulet device confirms a high implant success rate, a low peri-procedural complication rate, good closure rates and low rates of device-associated thrombus in a population with a high risk of stroke and bleeding. However, there are no RCTs comparing the Amulet device with OAC. In the United States, the ongoing Amulet–IDE (AMPLATZER Amulet LAA Occluder Trial) clinicaltrial (NCT02879448) is currently being randomized to evaluate safety and efficacy for stroke prevention in patients with NVAF. The Amulet device is currently not FDA-approved in the United States but is available in Europe. Comparative studies have shown similar results obtained with the ACP and Amulet devices in terms of safety, implantation success and appropriate closure of the LAA.[29,30] The Amulet device is associated with shorter fluoroscopy times and radiation dosages, reduced use of contrast-dye, lower recapture rates, and less peri-device leaks as compared to the ACP device.[31]

Which patients with NVAF should be considered for percutaneous LAA closure?

Patients with NVAF and CHA_2DS_2-VASc scores ≥ 2 are indicated to receive NOACs or VKAs for stroke prevention. However, there is adiscrepancy in real-world practice, where eligible patients are deemed ineligible for OAC due to absolute or relative contraindications or high bleeding risk. NOACs use in such patients ineligible for OAC remains limited and has shown a higher risk of recurrent major bleeding, especially gastrointestinal bleeding. In theory, these patients arepotentially suitable for percutaneous LAA closure.However, RCTs of the Watchman device were conducted in patients eligible for warfarin. The EWOLUTION registry supported the benefit of the Watchman device in patients deemed ineligible for OAC, and a significant proportion of patients were treated with DAPT, with substantial reductions in stroke and major bleeding. NVAF patients with high HAS-BLED scores may benefit from percutaneous LAA closure, as studies have consistently shown a significant reduction in risk of major bleeding which could translateinto a survival benefit. Also, NVAF patients with high CHA_2DS_2-VASc scores and without any bleeding contraindications still have ischemic stroke despite OAC use, as demonstrated in the RCTs of currently available NOACs and such patients might potentially benefit from combination therapy with percutaneous LAA closure and OAC. However, there are currently no data to support such a strategy in thesehigh-risk patients.

Post-procedural antithrombotic therapy

The major challenge associated with percutaneous LAA closure is managing post-procedural antithrombotic therapy and bleeding risk. Recent studies have revealed that the incidence of device-related thrombus with the percutaneous LAA closure is around 4%. If athrombus is confirmed on follow-up TEE, patients should continue OAC, and follow-up TEE in 3 to 6 months is recommended.As current understanding of coagulation and bleeding mechanisms at a molecular and cellular level

continues to develop, future targeted therapies may change theclinical practice dramatically.

Post-procedural leaks

The incidence of reported leaks hasranged from 0% to 63%, depending on the type of LAA device and the frequency and modality of monitoring. Using competent imaging modalities and adequate device sizing are keys to reduce peri-device leaks. Currently, continued surveillance with TEE and temporary initiation of anticoagulation are recommended.

Conclusions

AF is a major cause of ischemic stroke. 90% of embolic thrombi in patients with NVAF originate from the LAA. Percutaneous LAA closure is an effective interventional alternative to prevent ischemic stroke in patients with high risk of bleeding or prior bleeding history.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Chiang CE, Wu TJ, Ueng KC, et al. 2016 Guidelines of the Taiwan Heart Rhythm Society and the Taiwan Society of Cardiology for the management of atrial fibrillation. *J Formos Med Assoc* 2016;115(11):893-952.
2. Kotecha D, Breithardt G, Camm AJ, et al. Integrating new approaches to atrial fibrillation management: the 6th AFNET/EHRA Consensus Conference. *Europace* 2018;20(3):395-407.
3. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Europace* 2016;18(11):1609-78.
4. Lip GYH, Brechin CM, Lane DA. The global burden of atrial fibrillation and stroke: a systematic review of the epidemiology of atrial fibrillation in regions outside North America and Europe. *Chest* 2012;142(6):1489-98.
5. Hart RG, Diener HC, Coutts SB, et al. Embolic strokes of undetermined source: the case for a new clinical construct. *Lancet Neurol* 2014;13(4):429-38.
6. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS Guideline for the management of patients with atrial fibrillation: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *Circulation* 2014;130:e199-e267.
7. Aberg H. Atrial fibrillation. I. A study of atrial thrombosis and systemic embolism in a necropsy material. *Acta Med Scand* 1969;185(5):373-9.
8. Leung DY, Black IW, Cranney GB, et al. Prognostic implications of left atrial spontaneous echo contrast in nonvalvular atrial fibrillation. *J Am Coll Cardiol* 1994;24(3):755-62.
9. Blackshear JL, Odell JA. Appendage obliteration to reduce stroke in cardiac surgical patients with atrial fibrillation. *Ann Thorac Surg* 1996;61(2):755-9.
10. Manning WJ, Silverman DI, Keighley CS, et al. Transesophageal echocardiographically facilitated early cardioversion from atrial fibrillation using short-term anticoagulation: final results of a prospective 4.5-year study. *J Am Coll Cardiol* 1995;25(6):1354-61.
11. Naksuk N, Padmanabhan D, Yogeswaran V, et al. Left atrial appendage: embryology, anatomy, physiology, arrhythmia and therapeutic intervention. *JACC Clin Electrophysiol* 2016;2(4):403-12.
12. Mitusch R, Siemens HJ, Garbe M, et al. Detection of a hypercoagulable state in nonvalvular atrial fibrillation and the effect of anticoagulant therapy. *Thromb Haemost* 1996;75(2):219-23.
13. Dawson AG, Asopa S, Dunning J. Should patients undergoing cardiac surgery with atrial fibrillation have left atrial appendage exclusion? *Interact Cardiovasc Thorac Surg* 2010;10(2):306-11.
14. 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(9689):534-42.
15. Bartus K, Han FT, Bednarek J, et al. Percutaneous left atrial appendage suture ligation using the LARIAT device in patients with atrial fibrillation: initial clinical experience. *J Am Coll Cardiol* 2013;62(2):108-18.
16. Schwartz RS, Holmes DR, Van Tassel RA, et al. Left atrial appendage obliteration: mechanisms of healing and intracardiac integration. *JACC Cardiovasc Interv* 2010;3(8):870-7.
17. Kar S, Hou D, Jones R, et al. Impact of Watchman and Amplatzer devices on left atrial appendage adjacent

structures and healing response in a canine model. *JACC Cardiovasc Interv* 2014;7(7):801-9.
18. Reddy VY, Doshi SK, Sievert H, et al. Percutaneous left atrial appendage closure for stroke prophylaxis in patients with atrial fibrillation: 2.3-Year Follow-up of the PROTECT AF (Watchman Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation) Trial. *Circulation* 2013;127(6):720-9.
19. Reddy VY, Holmes D, Doshi SK, et al. Safety of percutaneous left atrial appendage closure: results from the Watchman Left Atrial Appendage System for Embolic Protection in Patients with AF (PROTECT AF) clinical trial and the Continued Access Registry. *Circulatio*n 2011;123(4):417-24.
20. Holmes DR, Jr., Kar S, Price MJ, 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):1-12.
21. Boersma LV, Schmidt B, Betts TR, et al. EWOLUTION: Design of a registry to evaluate real-world clinical outcomes in patients with AF and high stroke risk-treated with the WATCHMAN left atrial appendage closure technology. *Catheter Cardiovasc Interv* 2016;88(3):460-5.
22. Boersma LV, Schmidt B, Betts TR, et al. Implant success and safety of left atrial appendage closure with the WATCHMAN device: peri-procedural outcomes from the EWOLUTION registry. *Eur Heart J* 2016;37(31):2465-74.
23. Boersma LV, Ince H, Kische S, et al. Efficacy and safety of left atrial appendage closure with WATCHMAN in patients with or without contraindication to oral anticoagulation: 1-Year follow-up outcome data of the EWOLUTION trial. *Heart Rhythm* 2017;14(9):1302-08.
24. Reddy VY, Doshi SK, Kar S, et al. 5-Year outcomes after left atrial appendage closure: from the PREVAIL and PROTECT AF Trials. *J Am Coll Cardiol* 2017;70(24):2964-75.
25. Reddy VY, Mobius-Winkler S, Miller MA, et al. Left atrial appendage closure with the Watchman device in patients with a contraindication for oral anticoagulation: the ASAP study (ASA Plavix Feasibility Study With Watchman Left Atrial Appendage Closure Technology). *J Am Coll Cardiol* 2013;61(25):2551-6.
26. Tzikas A, Shakir S, Gafoor S, et al. Left atrial appendage occlusion for stroke prevention in atrial fibrillation: multicentre experience with the AMPLATZER Cardiac Plug. *EuroIntervention* 2016;11(10):1170-9.
27. Santoro G, Meucci F, Stolcova M, et al. Percutaneous left atrial appendage occlusion in patients with non-valvular atrial fibrillation: implantation and up to four years follow-up of the AMPLATZER Cardiac Plug. *EuroIntervention* 2016;11(10):1188-94.
28. Landmesser U, Schmidt B, Nielsen-Kudsk JE, et al. Left atrial appendage occlusion with the AMPLATZER Amulet device: periprocedural and early clinical/echocardiographic data from a global prospective observational study. *EuroIntervention* 2017;13(7):867-76.
29. Gloekler S, Shakir S, Doblies J, et al. Early results of first versus second generation Amplatzer occluders for left atrial appendage closure in patients with atrial fibrillation. *Clin Res Cardiol* 2015;104(8):656-65.
30. Abualsaud A, Freixa X, Tzikas A, et al. Side-by-side comparison of LAA occlusion performance with the Amplatzer Cardiac Plug and Amplatzer Amulet. *J Invasive Cardiol* 2016;28(1):34-8.
31. Al-Kassou B, Omran H. Comparison of the feasibility and safety of first- versus second-generation AMPLATZER Occluders for left atrial appendage cosure. *Biomed Res Int* 2017;2017:1519362.