2-Year Outcomes of Left Atrial Appendage Occlusion With WATCHMAN in Japanese Atrial Fibrillation Patients

Masahide Harada, MD, PhD

Atrial fibrillation (AF) causes stagnant blood flow within the left atrium, leading to thrombus formation and cardiogenic stroke. Almost 90% of all thrombi localize in the left atrial appendage (LAA). Oral anticoagulation (OAC) prevents LAA thrombus in patients with non-valvular AF (NVAF), but these drugs are unfavorable in NVAF patients with higher bleeding risk, presenting physicians with a therapeutic dilemma.

WATCHMAN (Boston Scientific, St. Paul, MN, USA) is the most extensively studied LAA occlusion (LAAO) device and the only one that has been approved in Japan. In North American and European trials, LAAO with the WATCHMAN demonstrated stroke prevention in NVAF patients, comparable to warfarin with additional reductions in major bleeding and death (Figure 1). However, little information is available regarding Asian patients.

Aonuma et al conducted the SALUTE trial, a multicenter single-arm prospective registry, to evaluate the safety and efficacy of LAAO with the WATCHMAN in Japanese NVAF patients (n=42). After implantation of the device, warfarin was administered for 45 days and was stopped when effective LAAO (peri-device flow ≤5 mm) was confirmed by transesophageal echocardiography. Thienopyridine and aspirin were then prescribed, allowing time for endothelialization on the device surface. The first results...
Although recognized as effective for LAAO, even small peri-device flow (≤5 mm) may affect thrombus formation especially after discontinuation of warfarin. The percentage of complete LAAO appeared to be lower in the SALUTE trial (59.5%) compared with previous studies (e.g., 91.4% in the EWOLUTION trial). A previous study demonstrated that peri-device flow did not increase thromboembolic risk during 1-year follow-up, but there was a case of thrombus associated with peri-device flow 2 years after implantation. The association between incomplete LAAO and thromboembolic risks remains to be elucidated. In the WASP registry, Asian patients had a larger LAA ostial diameter than non-Asian patients (23.4 ± 4.1 mm vs. 21.2 ± 3.1 mm) and a similar diameter was reported in the SALUTE trial (23.6 ± 2.6 mm). Appropriate positioning of a correctly sized device may be particularly important in Asian patients with their larger LAA to avoid peri-device leakage and thromboembolic events.

Another potential explanation of the ischemic stroke is device-related thrombus (DRT); that is, thrombus created on the device surface. Implantation of foreign material increases thrombogenesis. In the SALUTE trial, 2 patients had DRT and restarted warfarin treatment; DRT resolved and no thromboembolic events occurred. However, the time course of DRT is still not understood. Endothelialization may take longer to fully cover the device surface. DRT can occur even in patients without peri-device leakage. A recent study reported that the incidence of DRT was low (3.8%) but that it was significantly associated with ischemic stroke risk. The optimal management of DRT should be examined. Nevertheless, 3 patients with ischemic stroke in the SALUTE trial recovered without any physical disability.

Table 1. Pivotal studies of left atrial appendage occlusion with the WATCHMAN device. *18-month event rate. **Events included ischemic stroke, transient ischemic attack, and systemic embolism. †Pooled data from patients with Amplatzer cardiac plug and WATCHMAN. Event rates estimated from the original data in the study. RCT, randomized controlled study.

| Region          | North America/Europe | Asia |
|-----------------|----------------------|------|
| Study           | PROTECT† | PREVAIL‡ | EWOLUTION§ | WASP (Asian cohort)† | Korean Registry‡ | SALUTE¶ |
| Study year      | 2005-2008 | 2010-2013 | 2013-2015 | 2014-2015 | 2010-2015 | 2017 |
| Study design    | RCT | RCT | Registry | Registry | Registry | Registry |
| Follow-up period, months | 18 | 12 | 24 (median) | 24 | 22 | 24 |
| No. of patients with Watchman, n | 463 | 269 | 1021 | 107 | 46 | 42 |
| Age, y          | 72 | 74 | 73 | 71 | 66 | 73 |
| CHADS2 score, points | 2.2 | 2.6 | 2.8 | 2.5 | 2.7 | 2.5 |
| CHA2DS2-VASc score, points | 3.4 | 3.8 | 4.5 | 4.1 | 4.1 | 3.6 |
| HAS-BLED score, points | — | — | 2.3 | 2.2 | 2.8 | 2.9 |
| Implantation success, % | 91 | 95 | 99 | 99 | 98 | 100 |
| Ischemic stroke, % | 2.2 | 1.9* | 1.3 | 1.0** | 2.3† | 3.6‡ |
| Major bleeding, % | 3.5 | 0.4* | 2.7 | 1.0 | 0.6† | 2.4‡ |

Figure 2. Pivotal studies of left atrial appendage occlusion with the WATCHMAN device. *18-month event rate. **Events included ischemic stroke, transient ischemic attack, and systemic embolism. †Pooled data from patients with Amplatzer cardiac plug and WATCHMAN. Event rates estimated from the original data in the study. RCT, randomized controlled study.
as reported in previous studies, which may be an advantage of LAAO with the WATCHMAN.\textsuperscript{4,6} LAAO with the WATCHMAN has shown long-term benefit over warfarin therapy and will be an alternative to conventional OAC in NVAF patients.\textsuperscript{4} However, there are still unresolved issues with this treatment. First, non-vitamin K-dependent oral anticoagulants (NOACs) have become the standard for OAC in NVAF patients, but there are no direct comparisons of the WATCHMAN and NOACs. Second, the LAA is a nest for thrombus but may also play a role in neurohormonal and hemodynamic regulation. In a recent study, epicardial LAAO (Lariat, LAA exclusion) decreased blood pressure compared with endocardial LAAO (WATCHMAN, LAA occlusion).\textsuperscript{12} The physiological role of the LAA needs to be examined. Third, the LAA is a potential arrhythmogenic substrate and hybrid ablation therapy combined with WATCHMAN treatment may improve the outcomes. Fourth, there are different stroke/bleeding epidemiologies among races; region-specific optimization of LAAO treatment is required. As the SALUTE trial reported, it would be worthwhile to examine Asian-specific responses to LAAO with the WATCHMAN to ensure that this technology is successfully deployed in Asia.

Disclosures
M.H. received speaker fees from Nippon Boehringer Ingelheim, Daiichi-Sankyo, and Johnson & Johnson.

References
1. Holmes DR, Reddy VY, Turi ZG, Doshi SK, Sievert H, Buchbinder M, 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.
2. 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 subjects with atrial fibrillation versus long-term warfarin therapy: The PREVAIL trial. J Am Coll Cardiol 2014; 64: 1–12.
3. Boersma LV, Ince H, Kische S, Pokushalov E, Schmitz T, Schmidt B, et al. Evaluating real-world clinical outcomes in atrial fibrillation patients receiving the WATCHMAN left atrial appendage closure technology: Final 2-year outcome data of the EVOLUTION Trial focusing on history of stroke and hemorrhage. Circ Arrhythm Electrophysiol 2019; 12: e006841.
4. Reddy VY, Doshi SK, Kar S, Gibson DN, Price MJ, Huber K, et al. 5-Year outcomes after left atrial appendage closure: From the PREVAIL and PROTECT AF trials. J Am Coll Cardiol 2017; 70: 2964–2975.
5. Aonuma K, Yamasaki H, Nakamura M, Ootomo T, Takayama M, Ando K, et al. Percutaneous WATCHMAN left atrial appendage closure for Japanese Patients with nonvalvular atrial fibrillation at increased risk of thromboembolism: First results from the SALUTE trial. Circ J 2018; 82: 2946–2953.
6. Aonuma K, Yamasaki H, Nakamura M, Matsamoto T, Takayama M, Ando K, et al. Efficacy and safety of left atrial appendage closure with WATCHMAN in Japanese nonvalvular atrial fibrillation patients: Final 2-years follow-up outcome data from the SALUTE trial. Circ J 2020; 84: 1237–1243.
7. Phillips KP, Santoso T, Sanders P, Alison J, Chan JLK, Pak HN, et al. Left atrial appendage closure with WATCHMAN in Asian patients: 2-year outcomes from the WASP registry. Int J Cardiol Heart Vasc 2019; 23: 100358.
8. Kim JS, Lee H, Suh Y, Pak HN, Hong GR, Shim CY, et al. Left atrial appendage occlusion in non-valvular atrial fibrillation in a Korean multi-center registry. Circ J 2016; 80: 1123–1130.
9. 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 sub-study. J Am Coll Cardiol 2012; 59: 923–929.
10. Sasko B, Ritter O, Bramlage P, Riediger F. Late left atrial appendage closure device displacement and massive thrombus formation: A case report. Eur Heart J Case Rep 2020; 4: 1–5.
11. Dukkipati SR, Kar S, Holmes DR, Doshi SK, Swarup V, Gibson DN, et al. Device-related thrombus after left atrial appendage closure: Incidence, predictors, and outcomes. Circulation 2018; 138: 874–885.
12. Lakhtireddy D, Turagam M, Afzal MR, Rajasingh J, Atkins D, Dawn B, et al. Left atrial appendage closure and systemic homeostasis: The LAA HOMEOSTASIS study. J Am Coll Cardiol 2018; 71: 135–144.