Editorial

Percutaneous left atrial appendage closure: here to stay

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Submitted Jul 05, 2016. Accepted for publication Jul 14, 2016.
doi: 10.21037/jtd.2016.08.99
View this article at: http://dx.doi.org/10.21037/jtd.2016.08.99

Stroke prevention has long been perceived as the Achilles heel in the management of atrial fibrillation (AF). In recent years, percutaneous left atrial appendage (LAA) closure, a novel catheter-based therapy designed to occlude the primary nidus responsible for cardioembolic events is emerging as a safe and effective alternative, amidst the multiple limitations encountered with conventional oral anticoagulants (OAC), particularly warfarin (1). Long-term use of warfarin, albeit efficacious (2), is often overshadowed by the need for continuous monitoring and dose adjustments, narrow therapeutic window, food and drug interactions, and most importantly undesirable bleeding hazards. The introduction of direct OAC remains inadequate to address these shortcomings due to the persistent major bleeding complications (3-5).

Presently, the WATCHMAN device (Boston Scientific, Marlborough, MA) is the most commonly utilized LAA occlusion device in contemporary practice, with its efficacy and safety demonstrated by several studies. The device is composed of a self-expanding nitinol frame, and is covered with permeable polyethylene terephthalate membrane and anchoring fixation barbs for stability. It was recently approved by the US Food and Drug Administration for clinical use in non-valvular AF patients who are deemed to have significant stroke risk and with an appropriate rationale to seek an alternative therapy to OAC.

Despite early success with this novel therapy (6), it was not until PROTECT-AF (WATCHMAN Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation), the pivotal randomized trial, which drew the attention of medical community to the crucial contribution of percutaneous LAA closure in stroke prevention with the WATCHMAN device, demonstrating non-inferiority to warfarin in the management of non-valvular AF patients. At the initial 1,065 patient-years of follow-up, the cumulative primary efficacy end point of stroke, systemic embolism and cardiovascular death in patients implanted with WATCHMAN was non-inferior compared to the control cohort [3 *vs*. 4.9 events per 100 patient-years; risk ratio (RR) =0.62; confidence interval (CI), 0.35–1.25] (7). With longer-term follow-up of 3.8±1.7 years, the primary efficacy event-rates were 2.3 per 100 patient-years (95% CI, 1.7–3.2) with WATCHMAN and 3.8 per 100 patient-years (95% CI, 2.5–4.9) with warfarin, meeting both the superiority and non-inferiority criteria. There was a 40% risk reduction (RR =0.6; 95% CI, 0.41–1.05) of all cause stroke, systemic embolism, cardiovascular and unexplained death with WATCHMAN. There was also 85% reduction in hemorrhagic stroke (RR =0.15; 95% CI, 0.03–0.49), 63% reduction in disabling stroke (RR =0.37; 95% CI, 0.15–1.00), 60% reduction in cardiovascular death (RR =0.4; 95% CI, 0.23–0.82), and 34% reduction in all-cause mortality (RR =0.66; 95% CI, 0.45–0.98) (8).

In the December 2015 issue of *JACC Cardiovascular Interventions*, Wiebe and colleagues reported their 5-year experience of LAA closure with WATCHMAN at their institution. In this prospective single centre study of 102 consecutive non-valvular AF patients (mean CHADS2, CHA_2DS_2-VASc and HAS-BLED scores of 2.7±1.3, 4.3±1.7 and 2.9±1.2, respectively) who were implanted with the second-generation WATCHMAN, the authors reported a 96.1% procedural success rate. Procedure-related complications, predominantly non-fatal pericardial effusion were identified in 8.8% of the study cohort. However, there was no statistical difference in event-rates between the first and second halves of patients to reflect a learning curve. The annual incidence of cerebral ischemia inclusive

of stroke and transient ischemic attack (TIA) was 1.4% per year, which was substantially lower than the predicted stroke risk based on CHA_2S_2-VASc score and was consistent with contemporary studies (8). The rates of major bleeding and death were 2.1% and 3.5% per annum at follow-up to 5 years, respectively. Adequate lobe coverage (<5 mm residual peri-device leak) was achieved in all patients except one. Thrombus formation on the device was detected in 2 of 41 patients who received dual antiplatelet therapy (DAPT) after their procedures. The authors concluded that LAA closure with WATCHMAN to be safe and conferred effective long-term cardioembolic protection in light of the low ischemic event-rates observed (9).

There are a few limitations with this study that should be considered when interpreting their data. Firstly, the results were based on a single-centre observational registry with a considerably smaller population in contrast to contemporary WATCHMAN trials. Data from single centre experience are vulnerable to unsuspected confounders leading to selection bias, and at the same time lacked generalizability of the therapy to clinical practice across the board. Furthermore, post-procedural antithrombotic regimen was not standardized, and may potentially influence the overall outcomes of the device under investigation. On the other hand, the enrolment of consecutive patients reduced selection bias, and the extended period of follow-up is one of the longest available in published literature. Overall, it was a commendable initiative by the authors to elucidate real world experience on the long-term performance of LAA closure with WATCHMAN.

Like all emerging technology, the procedural/device-related limitations need to be explored and balanced with efficacy data, to evaluate the suitability of adopting new technologies. Early experience from PROTECT-AF alerted us to several safety concerns with LAA closure. An estimated 4.8% of the procedures in the trial were complicated by severe peri-procedural pericardial effusion requiring intervention, mostly on the same day of the procedure, thus prolonging the length of hospitalization. Procedure-related stroke as a consequence of air embolism accounted for 1.1% of the cases. Major bleeding (3.5%) and device embolization (0.6%) were also reported. Overall, higher incidence of primary safety events (8.7%) was recorded in the intervention group (7.4 *vs*. 4.4 per 100 patient-years; RR =1.69). Fortunately, with increasing experience, there have been improvements in safety event-rates reported in subsequent studies, 4.2% in the Continued Access Protocol (CAP) registry and 4.5% in the PREVAIL (Prospective Randomized Evaluation of the WATCHMAN Left Atrial Appendage Closure Device in Patients with Atrial Fibrillation versus Long-term Warfarin Therapy) study. Serious pericardial effusion warranting surgical drainage (0.2% in CAP, 0.4% in PREVAIL, *vs*. 1.6% PROTECT-AF, P=0.03) and procedure-related stroke (0% CAP, 0.7% PREVAIL, *vs*. 1.1% PROTECT-AF, P=0.02) were both lower in the newer WATCHMAN studies (10,11).

In reality, about 30–40% of eligible AF patients are not treated with appropriate stroke preventative therapy due to bleeding propensity (12). Currently, both the European Society of Cardiology and the American Heart Association/American Stroke Association endorsed percutaneous LAA closure with a weak class IIB recommendation for patients deemed high cardioembolic risk who have contraindication to long-term OAC (13,14). Irrespective of the guidelines, patient selection varies geographically and eligibility criteria appear to be diverse. According to the European Heart Rhythm Association survey of 33 European centres, a number of indications have been identified to influence the selection process, including contraindication to OAC (94%), HAS-BLED ≥3 (55%), embolic events despite OAC (55%), end-stage renal failure (30%), triple antithrombotic therapy (24%) and intention to cease OAC after pulmonary vein isolation (15%). One centre even considered LAA closure as a substitute to OAC in the absence of elevated bleeding risk (15).

Another crucial aspect in the evolution of LAA closure is the practice of post-procedural antithrombotic therapy. Currently, the ideal combination remains unknown since there is lack of randomized comparative study. Historically, PROTECT-AF advocated warfarin post-implant, transitioning to DAPT at 45 days after the procedure, provided there is no significant residual peri-device leak. The alternative of antiplatelet therapy without OAC in the immediate post-implant period is increasingly preferred. The ASAP (ASA Plavix Feasibility Study with Watchman Left Atrial Appendage Closure Technology) registry utilized DAPT for 6 months post-implant without OAC, in an AF population with contraindications to OAC (16). The combined incidence of all-cause stroke and systemic embolism with WATCHMAN was 2.3% per year, indicating a dramatic 77% reduction in observed annual ischemic stroke rate based on the $CHADS_2$ score of the patient cohort. Interestingly, there was no significant difference in the proportion of device-related thrombus when compared to PROTECT-AF with the OAC protocol post-implant. In the study by Wiebe *et al*., patients (n=41) receiving DAPT after their procedures had notably low

rates of intracranial bleeding and ischemic events (stroke and TIA) of 0.5% and 1.1% per annum, which also helped support the safety of antiplatelet therapy post-LAA closure during device endothelialisation period (10,16).

Additional contemporary real world data from the EWOLUTION registry was recently published. This large multicentre prospective non-randomized study enrolled over 1,000 patients (mean $CHADS_2$, CHA_2DS_2-VASc and HAS-BLED scores 2.8±1.3, 4.5±1.6 and 2.3±1.2, respectively), and included 62% of patients considered inappropriate for chronic OAC. Almost 60% were treated with DAPT post-procedure. This latest study with WATCHMAN showed an impressive 98.5% procedural success rate, together with the lowest serious procedure-related safety adverse events at 7 days post-implantation at 2.8% (compared to 8.7% with PROTECT-AF, 4.1% with CAP registry, and 4.2% with PREVAIL). Furthermore, in this high-risk population, 30-day ischemic stroke events occurred in only 0.29%. As a whole, these results are of great importance in consolidating the therapeutic role of WATCHMAN for stroke prevention in the real world, especially in the cohort of patients considered ineligible for OAC (17).

The improved procedural success rates in contemporary series highlight the learning curve observed with WATCHMAN implantation, which is anticipated as operators acquire new skillsets and adopt implant strategies that minimize complications (10,17). There are also evidence that the required skillsets can be transferred successfully to new centres and operators with appropriate training (11,17). Hence, concern over under-performance related to the learning curve is unjustified, and should not be the obstacle for adoption of this novel therapy particularly in new sites.

In conclusion, we are starting to witness a global acceptance of LAA closure as a feasible stroke preventative therapy in non-valvular AF patients at risk for cardioembolic events, especially those with contraindications to long-term OAC. Data from randomized controlled trials and real-world registries have helped elucidate the safety and efficacy of this therapy. Future studies with longer-term efficacy data, and comparative trials against direct OAC and between different LAA closure devices are desirable to address current knowledge gaps.

Acknowledgements

None.

Footnote

Provenance: This is an invited Editorial commissioned by the Section Editor Yue Liu (Associate professor, Department of Cardiology, The First Affiliated Hospital of Harbin Medical University, Harbin, China).

Conflicts of Interest: J Saw received unrestricted research grant supports (from the Canadian Institutes of Health Research, University of British Columbia Division of Cardiology, AstraZeneca, Abbott Vascular, St Jude Medical, Boston Scientific, and Servier), speaker honoraria (AstraZeneca, St Jude Medical, Boston Scientific, Bayer and Sunovion), consultancy and advisory board honoraria (AstraZeneca, St Jude Medical, Boston Scientific, and Abbott Vascular), and proctorship honoraria (St Jude Medical and Boston Scientific). L Eng has no conflicts of interest to declare.

Comment on: Wiebe J, Franke J, Lehn K, *et al*. Percutaneous Left Atrial Appendage Closure With the Watchman Device: Long-Term Results Up to 5 Years. JACC Cardiovasc Interv 2015;8:1915-21.

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Cite this article as: Eng L, Saw J. Percutaneous left atrial appendage closure: here to stay. J Thorac Dis 2016;8(9):2420-2423. doi: 10.21037/jtd.2016.08.99

