

Ten years from the first left atrial appendage closure in Serbia

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Abstract

Atrial fibrillation (AF) is the most common arrhythmia, and stroke is the major complication of AF. Over 90% of thrombi associated with atrial fibrillation are located in the left atrial appendage (LAA). Oral anticoagulant therapy represents the first line of therapy as thromboembolic prophylaxis in patients with nonvalvular atrial fibrillation. As an alternative to anticoagulant therapy, in certain groups of patients with AF closure of the LAA with the Watchman occluder (LAAC) is used in thromboembolic prophylaxis. The efficacy and safety of LAAC was investigated in three randomized clinical trials and compared with standard anticoagulant therapy (PROTECT-AF, PREVAIL, and PRAGUE). The results of the studies indicate that LAAC represents a good alternative to anticoagulant therapy in certain groups of patients, but that additional studies are necessary.

Key words

atrial fibrillation, left atrial appendage occlude, Watchman device

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and stroke is the most debilitating complication of AF.¹⁻⁴ AF-related strokes are more disabling, more likely to recur, and are associated with higher mortality rates than non-AF-associated strokes.² In AF, blood stagnates among left atrial appendage (LAA) pectinate muscles leading to thrombus and stroke⁵ and LAA is source of at least 90% of AF-related thrombus. Oral anticoagulation remains an effective standard of care for the prevention of stroke in AF, but is associated with major and minor bleeding, challenging adherence, and drug interactions.⁶ Trials comparing novel direct oral anticoagulants (DOACs) with warfarin for AF-associated stroke prevention provide comparative efficacy and safety data on both the DOACs as well as warfarin.^{7,8} Despite advances in anticoagulation, the persistent risk of stroke, bleeding, patient compliance, and other major adverse cardiovascular events leaves relevant unmet clinical need for alternative AF-associated stroke prevention.⁴ The series of Watchman (Boston Scientific, Natick, MA) trials demonstrated that Watchman device provides similar stroke prevention efficacy as warfarin.^{4,9}

Watchman trials

Up to date, 3 randomized controlled trials (RCTs) comparing LAAC to anticoagulation have been published.^{10,11,12,13} The PROTECT-AF Trial¹⁰ randomized 707 patients in a 2:1 ratio of Watchman vs. warfarin, with a primary combined endpoint of all stroke, systemic thromboembolism, and

cardiovascular death. At initial analysis, the trial met its noninferiority primary efficacy endpoint with an incidence of all stroke, cardiovascular death, or systemic embolism of 3% with the device and 4.9% with warfarin therapy, a benefit which proved durable with longer-term follow up (the primary efficacy event rate was 3.0 per 100 patient-years (95% CI: 1.9-4.5) in the device group and 4.9 per 100 patient-years (2.8-7.1) in the control group (RR: 0.62, 95% CI: 0.35-1.25).⁹ This study has been questioned for several reasons: device/procedure-associated adverse events, the inclusion of moderate risk (CHADS₂ =1) patients, and a relatively short follow up).^{4,9}

The PREVAIL trial¹¹ was designed to address the controversies of PROTECT-AF. Like PROTECT-AF, PREVAIL randomized 407 patients in a 2:1 ratio to Watchman and warfarin with a composite noninferiority endpoint. PREVAIL was designed to enroll a higher risk patient cohort than PROTECT-AF including significant participation of unexperienced operators. First co-primary efficacy endpoint (stroke, SE, and CV/unexplained death) event rate at 18 months was 6.4% in the device group vs 6.3% in the control group (RR 1.07 [95% CrI: 0.57-1.89]).¹¹ Stroke was more common among patients randomized to the device than those to warfarin in the PREVAIL trial (2.5% vs. 2.0% (risk difference 0.5% [95% CI: 0.019 to 0.027])). Adverse events in this study was lower than PROTECT AF (4.2% vs 8.7%; p=0.004).

A patient-level meta-analysis of the PROTECT-AF and PREVAIL trials¹² aggregated the entire five year results of both studies. The primary composite endpoint was similar between groups. The ischemic stroke/SE rate was numerically higher with LAAC, but this difference did

not reach statistical significance (HR: 1.71; $p=0.080$). However, differences in hemorrhagic stroke, disabling/fatal stroke, cardiovascular/unexplained death, all-cause death, and post-procedure bleeding all favored LAAC (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).¹² PRAGUE trial¹³ remains the only RCT to date that compared LAAC with direct oral anticoagulant (DOAC). The noninferiority of LAAC compared with DOAC was documented in the PRAGUE trial. The annualized rate of the primary composite outcome (stroke, TIA, SE, CV death, major or non-major clinically relevant bleeding, or procedure-/device-related complications) was 10.9% with LAAC and 13.4% with DOAC (sHR: 0.84; 95% CI: 0.53–1.31; $p=0.44$; $p=0.004$ for noninferiority). Major LAAC-related complications occurred in 9 (4.5%) patients.¹³ The main limitation of the trial is that the noninferiority of LAAC was only powered for a composite endpoint that combined ischemic and bleedings events as well as procedural complications. The study was, however, underpowered to assess the impact of LAAC on lowering ischemic events, which is the presumed mechanism of action of the LAAC procedure.¹⁰

In addition to the randomized trials, the nonrandomized studies continued access registries - Continued Access to PROTECT-AF (CAP) and Continued Access to PREVAIL (CAP2) included 566 and 578 Watchman implanted patients, respectively. Without a randomized comparison cohort, the CAP registries were compared to anticipated rates of stroke in the absence of oral anticoagulation based on validated stroke prediction scores. The rates of ischemic stroke were 78% and 69% lower than predicted in the absence of oral anticoagulation in the CAP and CAP2 registries, respectively.^{14,15}

There is a few non-randomized trials for LAAC. The third-generation Watchman FLX was evaluated in the PINNACLE FLX Trial which included 400 patients.¹⁶ The PINNACLE FLX primary safety endpoint of all-cause death, ischemic stroke, systemic embolism, or device/procedure-related adverse events requiring surgery or major endovascular intervention within seven days following the procedure was observed in 0.5% of patients. Implantation success was achieved in 98.8% of patients. The primary efficacy rate of effective LAAC, defined as any peri-device flow <5 mm demonstrated by TEE at 12 months, was achieved in all patients. Similar results were noticed in other nonrandomized trials as SUPRASS, CHAMPION-AF, etc.

Clinical guidelines

The 2019 American College of Cardiology Focused Update on the Management of Atrial Fibrillation assigns that left atrial appendage device occlusion, together with LAA surgical ligation/excision, received a class IIB recommendation, with the note that that LAA occlusion may be considered in patients with AF at increased risk of stroke who have contraindications to long-term anticoagulation.⁶ In our country, the first LAAC was implanted on April 24, 2014, during the BASIC 8+ congress (2 LAAC), and in 2015 year, one more LAAC (BASIC 9+). Our initial results with Watchman LAAC are promising providing real alter-

native in patients with non-valvular AF and contraindication for long-term oral anticoagulation therapy and high bleeding risk.¹⁷

Conclusion

LAAC represents a promising alternative to oral anticoagulation in selected patients with non-valvular AF who have contraindications for long-term anticoagulation.

References

1. Virani SS, Alonso A, Benjamin EJ, et al. Heart disease and stroke statistics-2020 update: a report from the American heart association. *Circulation* 2020;141(9):e139–e596.
2. Alkhouli M, Noseworthy PA, Rihal CS, et al. Stroke prevention in nonvalvular atrial fibrillation: a stakeholder perspective. *J Am Coll Cardiol* 2018;71(24):2790–2801.
3. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham study. *Stroke* 1991; 22(8):983–988.
4. Tandar A, Nielsen J, Whisenand B. Left atrial appendage closure review: Addressing unmet needs of AF mediated stroke prevention with evolving science. *Structural Heart* 2021;5(1):3–10.
5. Al-Saady NM, Obel OA, Camm AJ. Left atrial appendage: structure, function, and role in thromboembolism. *Heart* 1999;82 (5): 547–554.
6. January CT, Wann SL, Calkins H, et al. 2019 AHA/ACC/HRS focused update of the 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 clinical practice guidelines and the heart rhythm society. *J Am Coll Cardiol* 2019;74(1):104–132.
7. Granger CB, Alexander JH, McMurray JJV, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011; 365(11):981–992.
8. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009; 361(12):1139–1151.
9. Alkhouli M, Ellis C, Daniels M et al. Left atrial appendage occlusion. Current advances and remaining challenges. *JACC: Advances*. 2022;1(5).
10. 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):720–729.
11. 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.
12. 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):2964–2975.
13. Osmancik P, Herman D, Neuzil P, et al. 4-Year outcomes after left atrial appendage closure versus nonwarfarin oral anticoagulation for atrial fibrillation. *J Am Coll Cardiol* 2022;79:1–14.
14. 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. *Circulation* 2011;123(4):417–424.
15. Holmes DR Jr., Reddy VY, Gordon NT, et al. Long-term safety and efficacy in continued access left atrial appendage closure registries. *J Am Coll Cardiol* 2019;74(23):2878–2889.
16. Doshi S, Sadhu A, Horton RP, et al. Primary outcome evaluation of a next generation left atrial appendage closure device: the Pinnacle FLX trial. *Heart Rhythm* 2020;17(5):74.
17. Nedeljkovic M, Beleslin B, Tesic M, et al. Left atrial appendage closure with Watchman device in prevention of thromboembolic complication in patient with atrial fibrillation: First experience in Serbia. *Vojnosanit Pregl* 2017; 74(4): 378–385.

Sažetak

Deset godina od prve ugradnje okludera u aurikulu leve pretkomore

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Atrijalna fibrilacija (AF) je najčešća aritmija, a moždani udar je najveća komplikacija AF. Preko 90% tromba povezanih sa atrijalnom fibrilacijom lokalizovano je u aurikuli leve pretkome (LAA). Oralna antikoagulatna terapija predstavlja prvu liniju terapije kao tromboembolijska profilaksa kod pacijenata sa nevalvularnom atrijalnom fibrilacijom. Kao alternativa antikoagulatne terapije kod pojedinih grupa pacijenata u tromboembolijskoj profilaksi AF primenju se zatvaranje aurikule leve pretkome Watchman okluderom. Efikasnost i bezbednost zatvaranja LAA praćena je u tri randomizovane studije i poređena sa antikoagulatnom terapijom (PROTECT-AF, PREVAIL i PRAGUE studije). Rezultati studija ukazuju da zatvaranje LAA predstavlja dobru alternativu antikoagulante terapije kod određenih grupa pacijenata, ali da su dodatna istraživanja neophodna.

Ključne reči: atrijalna fibrilacija, okluder leve aurikule, Watchman uređaj