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Review article

Ten years from the first left atrial appendage closure in Serbia

Milan A Nedeljkovic[1,2], Milorad Tesic[1,2], Dusan Ruzicic[3], Branko Beleslin[1,2]

[1]University Clinical Center of Serbia, Cardiology Clinic, Belgrade, [2]Medical Faculty, University of Belgrade, [3]Health Center Valjevo, Department of invasive cardiology, Valjevo

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.

Kew 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 stroke[5] 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 Trial[10] 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 trial[11] 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 trials(12) 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

Corresponding address: Milan Nedeljkovic, University Clinical Center of Serbia, Cardiology Clinic, Belgrade. E-mail: milanned@hotmail.com

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 trial[13] 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 LAAO 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 LACC (BASIC 9+). Our initial results with Watchman LAAC are promising providing real alternative in patients with non-valvular AF and contraindication for long-term oral anticoagulation therapy and high bleeding risk.[17]

Conslusion

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

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Sažetak

Deset godina od prve ugradnje okludera u aurikulu leve pretkomore

Milan A Nedeljković[1,2], Milorad Tesić[1,2], Dušan Ružičić[3], Branko Beleslin[1,2]

[1]Univerzitetski Klinički centar Srbije, Klinika za kardiologiju, Beograd, [2]Medicinski fakultet, Univerzitet u Beogradu, [3]Zdravstveni centar Valjevo, Odeljenje invazivne kardiologije

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*