VIA MEDICA

REVIEW

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Left atrial appendage closure: therapeutic option or solution?

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ABSTRACT

Atrial fibrillation (AF) is the most common type of arrhythmia. AF increases the risk of thromboembolic complications including stroke. Stroke in patients with AF is more severe compared with patients with sinus rhythm. Long-term oral anticoagulant therapy (OAT) is widely used in a large population of patients with AF to prevent arterial thromboembolic events, such as stroke and systemic embolism. However, it is well established that OAT significantly increases the risk of bleeding. Percutaneous left atrial appendage closure (LAAC) is an option for stroke prophylaxis in patients with nonvalvular AF and high risk of bleeding. This paper provides an overview of recent studies that address the effectiveness and safety of LAAC using the Amplatzer Cardiac Plaque and Watchman Left Atrial Appendage System. LAAC provides a superior choice of treatment in patients with absolute contraindication of systemic OAT, in cases of refusal of systemic OAT by a patient, and as a complementary treatment to anticoagulation in patients with embolic events despite adequate OAT. LAAC should be also considered as a therapeutic option for patients with high thromboembolic risk and very high bleeding risk on the basis of individual risk/benefit evaluation for OAT vs. alternative methods of treatment. In general, LAAC becomes more attractive with increasing thromboembolic risk. There is a need for further studies to address the question of whether LAAC is actually the best method for preventing thromboembolism for patients with moderate/high thromboembolic risk and relatively low bleeding risk, to determine the optimum antithrombotic or antiplatelet therapy in patients who underwent LAAC, as well as to conduct direct comparative analysis of LAAC and the use of new oral anticoagulant drugs (NOAC).

Key words: atrial fibrillation, left atrial appendage closure, stroke prevention, risk of bleeding, thromboembolic risk, oral anticoagulant therapy, vitamin K antagonist, drug anticoagulants non-vitamin K antagonist, Amplatzer Cardiac Plug, Watchman system

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Introduction

Atrial fibrillation (AF) is the most common type of arrhythmias, it affects about 2% to 3% of the European population and both: United States and Canada [1, 2]. Management of patients with AF is a common but still difficult clinical problem. AF increases the risk of thromboembolic complications, including stroke (patients with AF are almost five times more likely to have stroke compared with patients with sinus rhythm) [1, 2]. Moreover, the stroke in patients with AF is more severe.

Long-term oral anticoagulant therapy (OAT) is widely used in a large population of patients with AF to prevent arterial thromboembolic events, such as stroke and systemic embolism. Health care professionals in their everyday practice face a dilemma, while it is well established that OAT increases the risk of bleeding [3–7]. Because of that, this therapy is the most common, but not the safest or most effective for each patient. Currently physicians along with well-informed patients may choose one of several options for stroke prophylaxis. Until recently vitamin K antagonists (VKAs) were the only therapeutic option and have been recommended for thromboembolic prophylaxis in the group of high risk patients with AF [8, 9].

However, the use of VKAs is limited by an increased risk of bleeding (which results in high rates of drug discontinuation), narrow therapeutic range and diet interactions. Because of bleeding complications about 40% of patients qualified to warfarin do not receive therapy of proven efficacy [10, 11]. These patients were very often treated just with aspirin [12, 13].

Health care professionals have observed a turning point in the clinical development of new oral anticoagulant drugs (NOACs), currently known as drug anticoagulant non-vitamin K antagonists (DAnonVKAs), during the past decade [14]. The DAnonVKAs include: direct thrombin inhibitors (e.g dabigatran) and factor Xa inhibitors (e.g rivaroxaban, apixaban). Furthermore, multi-centre randomised controlled trials (RCT) demonstrated that DAnonVKAs are non-inferior or even superior compared with warfarin in both stroke and systemic embolism prevention, with reduced bleeding rates [11, 15–18]. Currently DAnonVKAs are used as a complementary therapy, but certainly in the future they will replace VKAs and heparins in the treatment and prevention of arterial as well as venous thromboembolism [14]. However, we all know that anticoagulation with VKAs as well as DAnonVKAs is associated with bleeding complications [3–7]. Nowadays there is an alternative strategy. Percutaneous left atrial appendage closure (LAAC) is the third option of stroke prophylaxis in patients with nonvalvular AF. The idea is based on the finding, further improved by autopsy and echocardiographic studies, that in patients with nonvalvular AF about 90% of thrombi are localised in the left atrial appendage (LAA) [19].

There are two the most popular systems used to close LAA: the Watchman LAAC system (Boston Scientific Corporation, Saint Paul, Minnesota), and Amplatzer Cardiac Plug (ACP) (St. Jude Medical, Minneapolis, Minnesota) including its second generation Amulet (Figs. 1–4) [20–23]. The European Society of Cardiology (ESC) implemented a class II B recommendation for LAAC for patients with nonvalvular AF, who are either contraindicated or unsuitable for long-term OAT-owing to high bleeding risk (HAS-BLED score equal to 3 or more), or as an alternative treatment [24–27]. According to the European Heart Rhythm Association (EHRA) and European Association of Percutaneous Cardiovascular Interventions (EAPCI), LAAC is recommended in patients with AF and indication for OAT for stroke/embolism prevention (with CHA_2DS_2-VASc score > 1 point) and: increased risk of bleeding (HAS-BLED score 3 points or more), contraindications for OAT, or refusal of treatment with OAT [1].

Left atrial appendage closure procedure

Before the procedure all patients should undergo transoesophageal echocardiography (TEE) to assess the anatomical type of this structure and to rule out thrombus inside LAA [1, 23]. In most cases the device implantation is performed under general anaesthesia with TEE and fluoroscopic guidance [1, 23]. Before the procedure patients are given a loading dose of aspirin (325 mg), and just before deployment of the closure device intravenous heparin is also administrated to achieve an activated clotting time > 250 seconds. The most frequent vascular access to this procedure is the right femoral vein. Then trans-septal puncture is performed at the inferoposterior region of the interatrial septum. Subsequently the operator has to measure the widest anatomic orifice and the depth of LAA, then the closure device is implanted according to the manufacturer's recommendation [1]. Device size is based on the widest landing zone dimensions [23]. The Watchman device is available in sizes from 21 to 33 mm, and it consists of

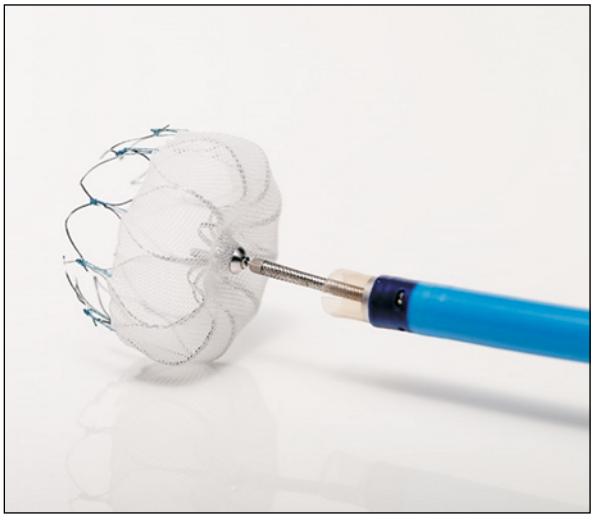

Figure 1. Watchman™ Left Atrial Appendage Closure Device (adapted from the official website of Boston Scientific) [65]

Figure 2. Watchman™ Left Atrial Appendage Closure Device (adapted from the official website of Boston Scientific) [65]

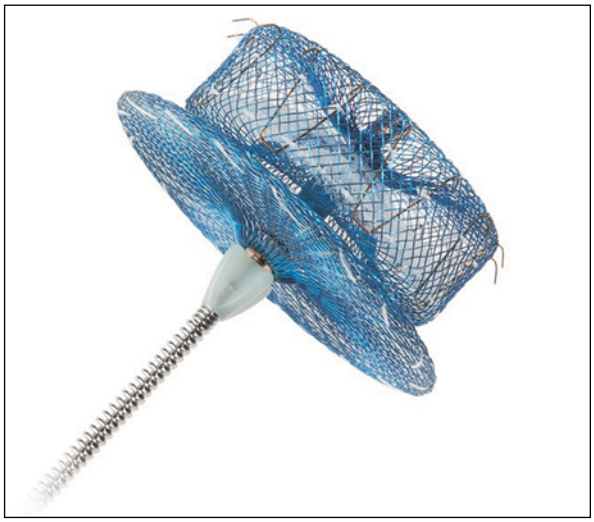

Figure 3. AMPLATZER™ AMULET™ LEFT ATRIAL APPENDAGE OCCLUDER (adapted from the official website of St Jude Medical) [66]

Figure 4. AMPLATZER™ CARDIAC PLUG (adapted from the official website of St Jude Medical) [66]

a nitinol frame with a microporous fabric cover [28]. On the day of procedure or the day after and on the day of discharge a transthoracic echocardiogram (TTE) is obtained [1, 23]. After the procedure patients are on a daily dose of aspirin 100 mg and should continue anticoagulation treatment for at least 45 days [using VKAs with heparin bridging until the international normalised ratio (INR) is in the therapeutic range 2–3] [28]. A scheduled TEE is performed 45 days after the procedure, to assess the position of the device and the presence of peridevice residual flow, and the patients with jet width less than 5 mm are allowed to discontinue OAT. These patients are recommended to take dual antiplatelet therapy (DAPT) (aspirin and clopidogrel) for six months, until the follow up visit. If a TEE during this visit does not confirm the presence of device-related thrombus, monotherapy with aspirin is recommended lifelong [28].

Results from studies with Amplatzer Cardiac Plug

The largest study using the ACP (St Jude Medical) for LAAC conducted by Tzikas (*Left atrial appendage occlusion for stroke prevention in atrial fibrillation: multi-centre experience with the AMPLATZER Cardiac Plug*) has shown a high procedural success rate and favourable outcomes for prevention of AF-related thromboembolism [29]. It was a multi-centre, prospective study that included data from 1047 patients with AF, who underwent LAAC with ACP between 2008 and 2013 at 22 centres. Clinical 13-month follow-up was completed in 98.2% of the patients. The aim of the study was to assess the safety, feasibility, and efficacy of LAAC with the ACP in a real-world patient population with AF. The indications for LAAC were: previous major bleeding (47% of patients), high risk of bleeding (35% of patients), and coronary stenting mandating triple therapy (22% of patients). In 16% of cases one of the indications was a stroke on VKAs. Tzikas reported a 97.3% procedural success rate [29].

Periprocedural serious adverse events (SAEs) occurred in 4.97% of the patients. There were 0.8% procedure-related deaths, 0.9% strokes, 0.4% transient ischaemic attacks (TIA), 1.2% cardiac tamponades, and 1.2% of major bleedings. During the 13-month of follow-up there were nine strokes (0.9%), and 0.9% of TIA, one-year all-cause mortality was reported as 4.2%, and none of the deaths was reported as related with the LAAC procedure. A peri-device leak was found in 11.6% of the patients, on average seven months after procedure. The annually rate of systemic thromboembolism and major bleeding events was, respectively, 2.3% and 2.1%. What is interesting, Tzikas reported for LAAC a 59% annual reduction rate for prevention of AF-related thromboembolism as compared to the rate predicted by the CHA_2DS_2-VASc score and a 61% annual reduction in major bleeding events as compared to the rate predicted by the HAS-BLED score [29].

Urena and others have designed a trial (*Percutaneous left atrial appendage closure with the AMPLATZER cardiac plug device in patients with nonvalvular atrial fibrillation and contraindications to anticoagulation therapy*) to assess efficacy and safety of LAAC with ACP in patients with nonvalvular AF and absolute contraindications to OAT [the most common are, respectively, intracranial haemorrhage (34.6%), gastrointestinal bleeding (23.1%) or spontaneous haematoma of abdominal

muscles (13.5%)] [30]. A total of 52 patients at mean age 74.8 years, who underwent LAAC with ACP, were enrolled to this study in seven Canadian centres. The mean time of follow-up was 20 ± 5 months. All the patients were followed-up at least for 12 months. The mean $CHADS_2$ score was 3. After the procedure patients received DAPT for 1–3 months and then single antiplatelet therapy (APT). A TEE was performed at the six-month follow-up in 74% of patients. Urena reported procedural a success rate of 98.1%. The main complications were: device embolisation (1.9% of patients) and pericardial effusion (1.9% of patients). There were no cases of periprocedural stroke. Peridevice leak was observed in 16.2% of patients at the six-month follow-up (as evaluated by TEE). There were no cases of device thrombosis [30].

During clinical follow-up the rate of death was 5.8%. The rates of stroke and systemic embolism were 1.9% and 0%, respectively. The rate of major bleeding was 1.9%, and the rate of pericardial effusion was also 1.9%. Summarising, in patients with nonvalvular AF and absolute contraindications to anticoagulation, LAAC with ACP followed by DAPT and then APT was associated with a low rate of embolic and bleeding events after a mean follow-up of 20 months [30].

*Left atrial appendage closure with **A**mplatzer **C**ardiac **P**lug for stroke prevention in atrial fibrillation: Initial Asia-Pacific experience* (ACP) is a register, which assessed initial safety, efficacy, and one-year clinical outcomes after LAAC [31]. In 20 patients (age 68 ± 9 years) with non valvular AF with high risk of thromboembolic event ($CHADS_2$ score 2.3 ± 1.3) such as with contraindications to OAT, the LAAC procedure was successfully performed in 95% of patients, and 5% of procedures were stopped due to catheter-related thrombus. There were 10% more periprocedural complications, including TEE-related oesophageal injury (5%) and coronary artery air embolism (5%). During the follow up (12.7 ± 3.1 months) there was no reported death, stroke, or device-related thrombus [31].

However, there is no randomised trial in which the safety and efficacy of ACP were assessed [31].

Results of studies with the Watchman Left Atrial Appendage System

The first randomised study evaluating the efficacy and safety of LAAC with a Watchman device was the *Watchman Left Atrial Appendage Closure (LAAC) Device for Embolic PROTECTion in Patients with **A**trial **F**ibrillation* (PROTECT AF) trial. This study demonstrated the superiority of the Watchman LAAC system compared to warfarin for the combined end point of stroke, systemic embolism, and cardiovascular death after 3.8 years of follow-up [28, 31–40]. This method, dedicated to patients with the highest risk of bleeding complications, has proven to be even more effective than VKAs in this group of patients. It was a multi-centre, randomised (2:1 allocation to either Watchman device implantation or warfarin therapy), unblinded, Bayesian-designed study conducted at 59 hospitals [32]. A total of 707 patients with nonvalvular AF and at least one additional stroke risk factor ($CHADS_2$ score ≥ 1) were enrolled into the study [28, 32, 41]. In total 485 patients underwent device implantation in this trial [31, 32].

The major inclusion criteria to this study were: age 18 years or older; paroxysmal, persistent, or permanent nonvalvular AF; $CHADS_2$ risk score (age ≥ 75 years, hypertension, diabetes, heart failure or left ventricular systolic dysfunction, prior transient ischaemic attack or stroke) result equal to 1 or more points; and contraindications to long-term anticoagulation with warfarin [32, 41]. Whereas major exclusion criteria were: an atrial septal defect, permeable foramen ovale with atrial septal aneurysm, mechanical valve prosthesis, left ventricular ejection fraction (LVEF) less than 30%, mobile aortic atheroma, and symptomatic carotid disease. A composite efficacy end point included: stroke, systemic embolism, and cardiovascular/unexplained death. The primary composite safety end point included: major bleeding events (intracranial or bleeding requiring transfusion) and procedure-related events in the device group (pericardial effusion requiring intervention or prolonged hospitalisation, procedure-related stroke, or device embolisation) [32, 41].

The treatment schedule was the same as previously described. All of these patients underwent TEE at five time points: baseline, intraprocedurally, 45 days, 6 months, and 12 months after implantation [28, 32]. TEE was performed at 45 days to assess device position and peridevice flow [32, 41]. In patients with jet width less than 5 mm, oral anticoagulation with warfarin was discontinued and replaced by DAPT (aspirin 81 to 325 mg and clopidogrel 75 mg) until the six-month follow up visit [32, 41]. If there was no thrombus on the device in TEE repeated six months after the procedure clopidogrel was discontinued and aspirin was recommended life-long [28, 32].

After the first year, follow-up visits occurred twice yearly, with neurological assessments at 12 months, and annually thereafter or whenever a neurological event was suspected [32, 41]. The mean $CHADS_2$ scores among patients in the warfarin group and the device group were 2.3 points and 2.2 points, respectively. Approximately two-fifths of the patients had paroxysmal AF, and in most cases, this arrhythmia was present for one year or longer. This analysis reflects a mean (SD) follow up of 3.8 (1.7) years (range, 0–6.5 years). Successful implantation of a Watchman device was

reported in 88% of patients [32, 41, 42]. After the 45-day, 6-month, and 12-month TEE estimation warfarin was discontinued for 86.8%, 92.2%, and 93.2% of patients, respectively [32, 41]. There were 8.4% of primary efficacy events in the LAAC group and 13.9% in the warfarin patients. The rates of all strokes (5.6% in device group vs. 8.2% in the warfarin group) and ischaemic stroke (5.2% in device patients vs. 4.1% warfarin patients) did not differ significantly between both groups [41]. More haemorrhagic strokes occurred in the warfarin group (4.0% of patients) than in the device group (0.6% of patients). In the post-procedural analysis there were 1.3% of procedure-related strokes in the device group, which was probably caused by technical complications of the device implantation, suggesting that stroke prevention after LAAC occurs over time. There were deaths from any cause: in the warfarin group 18.0%, and 12.3% in the device group ($p = 0.04$). Moreover, more cardiovascular deaths occurred in the warfarin group (9.0%) than in the device group (3.7%) [32, 41].

What made this new method so promising was a reduction in the number of haemorrhagic stroke-related deaths in the device group (0.4%) compared with the warfarin group (3.3%, $p=0.004$) [41]. Nevertheless, we have to take into account that LAAC is associated with early post procedure complications, such as periprocedural events, as well as complications related to OAT after the procedure. The long-term (3.8 years) follow-up of patients randomised in the PROTECT AF trial showed that in patients with nonvalvular AF, LAAC with Watchman device reduced the relative risk of the composite endpoint of cardiovascular death, systemic embolism, and stroke by 40% (1.5% absolute reduction) compared with anticoagulation with warfarin [41]. Long-term follow-up confirmed that there was a decrease in the relative risk of all-cause mortality, in favour of the strategy based on the Watchman LAA system (34% relative reduction, 5.7% absolute reduction). The all-cause mortality rate in the group treated with warfarin was 21.5% compared with 14.5% in the Watchman LAA system group for an absolute reduction at five years of 7.0%. The rate of ischaemic stroke in the Watchman LAA system group (1.4%/year) was not significantly higher than in the warfarin treated patients (1.1%/year, $p = 0.49$). Of interest, there was no significant difference in composite safety outcome between groups [41]. Pericardial effusion with tamponade was frequent (2%), but what is more important, it was not a lethal complication [41, 43–45]. Procedure-related strokes were probably due to embolism of thrombus or air during device implantation procedure.

After nearly four years of follow-up, the investigators demonstrated that percutaneous LAAC met criteria for both non-inferiority and superiority, compared with warfarin therapy, for preventing the combined outcome of cardiovascular death, stroke, and systemic embolism, as well as superiority for all-cause and cardiovascular mortality [41]. Summarising, when we analyse the risk of death, intracranial haemorrhage, all strokes, major bleeding, and pericardial tamponade, we found clinical benefit from LAAC with Watchman device compared to warfarin in thromboembolic prophylaxis in patients with nonvalvular AF [41, 46].

As we know well, the PROTECT AF trial has several limitations: first of all, there were no patients enrolled to this trial with absolute contraindications to warfarin (because of mandatory post-procedural transition anticoagulant therapy with warfarin). Second, there were no data comparing the safety and efficacy of the DAnon-VKAs versus LAAC with Watchman device. Third, one of the exclusion criteria was LVEF less than 30%, which is a huge study limitation, because unlike anticoagulants, LAAC would not prevent thromboembolism from the left ventricle. In this trial, patients and physicians were not blinded to treatment assignment, because of the study design. According to the PROTECT-AF results, health care professionals emphasised that the Watchman system is an alternative therapeutic strategy, involving not just a procedure of device implantation, but moreover six months of anticoagulation or antithrombotic pharmaceutical intervention (or both) because of that, this trial does not address patients with absolute contraindications to warfarin, who are incapable of transition to OAT [41].

CAP (*Continued Access Protocol*) is a continuation of the observations performed in the PROTECT AF trial. The aim of the study was the assessment of periprocedural complications regarding the experience of the operator in performing the LAAC procedure. This register included patients in the PROTECT AF trial, who underwent LAAC (542 patients) and those from a following nonrandomised registry of patients undergoing Watchman implantation (Continued Access Protocol [CAP] Registry; 460 patients) [47]. The safety endpoints were procedure-related events (device embolisation, stroke, and pericardial effusion) and bleeding complications. There was a significant decline in the rate of procedure- or device-related safety events within seven days after the procedure comparing the PROTECT-AF Trial and CAP: respectively, 7.7% and 3.7% of patients ($p = 0.007$). The rate of pericardial effusion within a week after LAAC was lower in the CAP Registry (2.2% vs. 5.0% in the PROTECT-AF Trial; $p = 0.019$). However, in the case of procedure-related stroke, the results between these two trials were similar (0.9% in PROTECT-AF trial versus 0% in CAP Registry; $p = 0.039$) [47].

PREVAIL (*Prospective Randomised Evaluation of the Watchman Left Atrial Appendage Closure Device in Patients With Atrial Fibrillation Versus Long-Term Warfarin*

Therapy) is an another randomised trial that assessed the efficacy and safety of the LAAC. The aim of study was to assess the safety and efficacy of LAAC for stroke prevention in patients with nonvalvular AF compared with long-term warfarin therapy. Patients were randomly assigned (2:1) to undergo LAAC (269) or receive chronic warfarin therapy (138) [48].

The inclusion criteria were a $CHADS_2$ score of one point if they also had any of the higher-risk characteristics: female age ≥ 75 years, ejection fraction ≥ 30% but < 35%, age 65 to 74 years and either: diabetes or coronary disease, and age ≥ 65 years with congestive heart failure. Whereas exclusion criteria were as follows: contraindication to aspirin or warfarin, indication for long-term OAT other than AF, previous stroke/transient ischaemic attack within 90 days of enrolment, symptomatic carotid disease, or a patent foramen ovale or atrial septal defect requiring treatment. The coprimary efficacy endpoints were: stroke, systemic embolism, and cardiovascular/unexplained death, whereas the second coprimary efficacy endpoint was a composite of stroke or systemic embolism excluding the week after randomisation. The third coprimary endpoint was early safety, which consisted of all-cause death, iscahemic stroke, systemic embolism, or device-/procedure-related events (requiring open cardiovascular surgery or major endovascular intervention between randomisation, and within the first week after the procedure). The results of the study were reported after 18 months from randomisation, and the rate of the first coprimary efficacy endpoint was 0.064 in the device group compared with 0.063 in the control group and did not achieve the criteria of non-inferiority. The rate for the second coprimary endpoint was 0.0253 vs. 0.0200, which achieved the criteria of non-inferiority. Whereas the second coprimary endpoint occurred in 2.2% of the Watchman arm, significantly lower than in PROTECT AF. Summarising, LAAC was non-inferior to warfarin for ischaemic stroke prevention or systemic embolism (excluding a week after procedure). However, non-inferiority was not achieved for overall efficacy, and event rates were comparable in both groups [48].

The EVOLUTION of thromboembolism prophylaxis in patients with nonvalvular AF, the EWOLUTION Registry

The EWOLUTION registry is an observational, prospective, single-arm, multi-centre study, which was designed to collect real-world outcome data. In this study, the authors collected preoperative and operative data of patients who received a Watchman LAAC system and had been treated according to the standard medical practice of the investigational medical centres. Approximately 1000 patients were enrolled at up to 70 medical centres in Europe, Russia, and in the Middle East, and they were followed for two years. In this trial the following endpoints were assessed: Watchman implant procedure (successes and complications), bleeding events, incidence of stroke and TIA, other thromboembolic events, and death [48].

The inclusion criteria into the EWOLUTION Registry were: patient eligible for a LAAC with Watchman device according to current guidelines; patient willing and capable of providing informed consent; age 18 years or older. The major exclusion criteria were: patient currently enrolled in another registry or study (exception: participating in a mandatory governmental registry, or an observational registry with no associated treatment); woman who is potential childbearing, or plans on becoming pregnant; patient is unable or not willing to complete follow up visits and examinations. The first post-procedure visit is performed 1–3 months after the LAAC with Watchman device. During the visit TEE or computed tomography (CT) scan is performed to assess residual flow around the device, and to confirm the absence of thrombus prior to discontinuing OAT (VKAs or similar therapies). Follow-up office visits are recommended once a year throughout the first two years. Enrolment for the EWOLUTION Registry started in the autumn of 2013, and the study is expected to be completed in the autumn of 2017 [48].

Preliminary analyses of this trial are intended to focus on three endpoints: procedural success, complications related to the procedure, and incidence of stroke or TIA. Specified covariates may affect these endpoints, which is why the following variables were assessed: gender, age (age of 80 years or more), AF pattern, history of major bleeding, TIA, or stroke; HAS BLED score (3 points or more), $CHADS_2$ score (3 points or more), CHA_2DS_2-VASc score (5 points or more), therapy after implantation (warfarin, DAnonVKAs, or antiplatelet drugs), and the presence of multiple procedures (compared with Watchman implantation procedure alone) [48]. About 60% of the patients enrolled to the trial were male, and the mean age was 73 years [49]. Nearly half of the patients had a history of either ischaemic stroke (19.7% of patients), haemorrhagic stroke (15% of patients), or TIA (10.7% of patients). All the patients enrolled to this trial were at high risk of thromboembolic complications-based on the $CHADS_2$ and CHA_2DS_2-VASc risk scores, with an average $CHADS_2$ score of 2.8+1.3 and CHA_2DS_2-VASc score of 4.5+1.6. Nevertheless, more than half of the patients (62%) were deemed ineligible for OAT, due to such factors as bleeding history, high bleeding risk, inability to monitor OAT, or co-morbidities. Patients were at moderate-to-high risk of bleeding (40% of subjects

had a high risk of bleeding with a HAS-BLED score of 3 or more), and the average HAS-BLED score was 2.3+1.2, but what is even more important - almost one-third of patients had a history of major bleeding (31.2%) [49]. Because of the above-mentioned contraindications, at baseline only 31% of patients were on OAT [50]. Other patients enrolled to this registry were on DAPT (21% of patients) or on APT (22% of patients), and 27% of them were not taking any form of anticoagulant [49]. After LAAC with Watchman device implantation, anticoagulation was used in line with Watchman device recommendations for the first 3–6 months. However, the important finding of this register is the fact that after Watchman implantation only 27% of patients were on OAT, 59% of subjects were on DAPT, and 7% were on APT, whereas 6% of them were without any type of antiplatelet therapy. A total of 1019 patients underwent LAAC procedure with Watchman device, with the success rate 98.5%. When we compared the preliminary data from the EWOLUTION trial with that previously reported from earlier studies, we noticed that the rate of successful implantations was higher [PROTECT-AF 90.9%, and CAP (94.4%), PREVAIL (95.1%), CAP 2 94.8%]. The two most common reasons for the deployment failures were: mismatch between the LAA dimensions and the size of Watchman device or unfavourable anatomy of LAA. In 99.3% of implanted patients the procedure of LAAC was successful because there was no or minimal residual flow around the device (defined as 5 mm measured in periprocedural TEE). SAEs related to procedure and/or device occurred at a rate of 2.8% within the first week after implantation, and it was lower than in any of the previous Watchman LAAC studies (PROTECT-AF 8.7%, CAP 4.1%, PREVAIL 4.2%). Within the first 24 hours after procedure, 28.5% patients experienced SAEs, and 81% of them seem to be related to the LAAC procedure [major bleeding, pericardial effusion (leading to one tamponade), vascular damage to the groin, periprocedural air embolism, device embolisation, and reinterventions because of incomplete LAA seal] [49].

Within the first week after procedure, there were three deaths, but none of them reported as associated with the LAAC procedure. There were four additional deaths within the first month, which resulted in 0.7% mortality rate within the first month (one of them was reported to be associated with the procedure — air embolism on the day of the procedure). Within the first month, the SAE rate was 7.9%, with an SAE rate of 3.6% reported as associated with procedure and/or device. The most common SAE was major bleeding requiring transfusion, both related to groin access (pseudoaneurysms, laceration of veins), and due to gastrointestinal bleeding. In these patients, who suffered from major bleeding (with HAS-BLED score ranged from 1 to 5) OAT was used in 18% of patients, APT in 29% of patients, and DAPT in 41% of patients, whereas 12 % of patients were not treated with any form of anticoagulation. There were three patients with an ischaemic stroke, none of them resulting in death, and two of them with complete recovery. In these three patients, two were on DAPT ($CHADS_2$ scores were 2 and 3; CHA_2DS_2-VASc scores were 3 and 5), while one patient with very high risk ($CHADS_2$ score was 5; CHA_2DS_2-VASc score was 8) was on clopidogrel alone. One case of stroke was reported as procedure related [49].

Summarising, the incidence of SAEs (related or not to the procedure) did not appear to be associated with $CHADS_2$ or CHA_2DS_2-VASc scores, and there were no significant differences in incidence of SAEs between patients on OAT after LAAC with Watchman device compared with patients not on OAT after implantation ($p = 0.39$). What is more, the incidence of SAEs throughout the first month was significantly lower in patients ineligible for OAT compared with patients eligible for OAT (6.5 vs. 10.2%, $p = 0.042$). In patients with HAS-BLED score less than 3 compared with those with score 3 or more, the incidence of SAEs throughout first month showed a trend towards higher event rates with a higher risk (6.6 vs. 9.9%, respectively, $p = 0.078$). As expected, bleeding complications occurred more often in patients with a HAS BLED score 3 or more compared with the patients with lower HAS BLED score result (1.7 vs. 4.0%, $p = 0.029$). Comparing to previous studies, the EWOLUTION registry suggests a relationship between the number of implants and parameters such as successful implantation and complete LAA seal. Nevertheless, there was no significant correlation between number of implantations and periprocedural SAEs ($p = 0.33$ at 30 days and $p = 0.12$ at 7 days) [49].

The EWOLUTION registry shows that LAAC can be successfully and safely performed in an wide group of patients, including those with the highest risk of stroke. The average $CHADS_2$ score of 2.8 and CHA_2DS_2-VASc score of 4.5 in the EWOLUTION registry were higher compared with patients enrolled to either the PROTECT AF (average $CHADS_2$ of 2.2 and CHA_2DS_2-VASc of 3.4) or PREVAIL ($CHADS_2$ score of 2.6 and CHA_2DS_2-VASc of 4.0) trials [50]. Whereas, according to bleeding risk, 40% of the EWOLUTION population had a HAS BLED score 3 or more, compared with 30% of PREVAIL patients, and only 20% of PROTECT AF subjects [35, 50]. Regarding SAEs: the rate of SAEs within the first seven days in the EWOLUTION registry was lower than in any of the previous Watchman LAAC studies (PROTECT-AF 8.7%, CAP 4.1%, PREVAIL 4.2%) [35, 50]. Generally, the 30-day procedure- or device-related SAE rate was assessed as 3.6% [50]. The rate of procedural/device-related strokes was assessed as 0.1% through the first month in this registry, compared with 0.9% in the

PROTECT AF and 0.4% in PREVAIL study [48, 50–53]. This result might simply be due to less intense use of anticoagulation in VKA-ineligible patients [50]. There is a theory that some events such as groin bleeding or pericardial effusion, have increased likelihood because of OAT use, although it was not statistically different due to the low event rate. The limitations of the analysis performed in the EWOLUTION registry include: the observational nature of the design and the relatively short follow-up of 30 days [50].

Until now the randomised trials collected data of patients qualified to LAAC with Watchman device, who continued VKA for at least 45 days after procedure [50, 52, 53]. Before the publication of first results of the EWOLUTION registry, we had a small number of data regarding patients with absolute contraindications to oral anticoagulation (only from small registries) [53–55]. Nevertheless, the most important fact is that the EWOLUTION registry, which includes the patients with and without an absolute contraindication to anticoagulation, gave us data to assess the benefits and the risk carried by the LAAC with Watchman device in these two distinct groups of patients [50]. Furthermore, this registry can become a basis to plan other studies regarding optimisation of post-procedural pharmacological therapy. To the EWOLUTION registry were enrolled over 600 patients deemed to be ineligible for OAT, and 738 patients who were not prescribed OAT following the procedure [50]. The various post-implantation strategies of therapy with VKAs, DAnonVKAs, or heparin-derivatives (different drugs are used because of, for example, the patient's contraindications), and antiplatelet therapy will be assessed to establish optimal management of anticoagulation in a population of the patients with a high bleeding risk [49].

The ASAP Study (*ASA Plavix Feasibility Study With Watchman Left Atrial Appendage Closure Technology*) was a non-randomised trial assessing the safety and efficacy of LAAC in patients with nonvalvular AF ineligible for warfarin therapy. In this trial, after LAAC with Watchman, patients were administered a thienopyridine antiplatelet agent (clopidogrel or ticlopidine) for six months and lifelong aspirin. This registry has demonstrated that the Watchman device implantation is safe without a warfarin transition. Presumably in the future, also thanks to this registry, several post-implantation options of anticoagulant or antiplatelet therapy in the early period after the procedure, when sealing and re-endothelialisation take place, will be used [56].

Left atrial appendage closure vs. the new oral anticoagulant drugs

We already know that the Watchman LAAC system is non-inferior compared to warfarin for the combined endpoint including stroke, systemic embolism, and cardiovascular death, but now we would like to answer the question: what about DAnonVKAs [28, 31–34]? Koifman et al. performed a meta-analysis to compare the safety and efficacy of DAnonVKAs versus the LAAC with Watchman device in patients with nonvalvular AF, in terms of haemorrhagic complications, stroke preventions, and all-cause mortality [55]. Trials that were included to this meta-analysis compared the Watchman device with warfarin therapy and DAnonVKAs in patients with nonvalvular AF (14 studies of 246,005 patients: 124,823 treated with warfarin, 120,450 treated with DAnonVKAs, and 732 patients had a Watchman LAAC system implanted) [11, 15–17, 55, 57–64]. There were 12 trials (five of them were RCTs) including 244,891 patients and comparing DAnonVKAs with warfarin. There were also two studies (both RCTs) including 1114 patients in which the Watchman LAAC system was compared with warfarin therapy. The mean age of patients included to these trials was 72 ± 9 years; 53% of them were male; and mean $CHADS_2$ score was 2.1 ± 1.6 points [55]. The analysis showed that there was a trend toward reduction in total stroke in patients after LAAC; however, this method did not significantly reduce the risk of total stroke compared with therapy with warfarin (OR = 0.67) [57]. What is more, there was a trend toward increased risk of ischaemic stroke with the Watchman LAAC device compared with warfarin (OR 1.64), but it was not statistically significant [55]. As we already know, DAnonVKAs are associated with a significant reduction in the total number of strokes compared with warfarin (OR = 0.78), even in cases of ischaemic stroke (OR 0.63). Regarding major bleeding, there was a trend toward a reduction of bleeding events after LAAC with Watchman compared with warfarin (OR = 0.62). Concluding, both of the new options: DAnonVKAs (OR 0.46) and the Watchman LAAC system (OR 0.21), significantly decrease the risk of haemorrhagic stroke compared with warfarin. Regarding major bleeding, these both strategies were comparable, and there was no difference between DAnonVKAs compared with the Watchman device (OR 1.25). Now the question arises: what is better in this battle? What is surprising, this meta-analysis showed that the LAAC with Watchman did not significantly reduce the risk of haemorrhagic stroke compared with DAnonVKAs (OR 0.44, 95% CI 0.09–2.14) [55]. When we compare all-cause mortality, there was a trend toward reduction for DAnonVKAs (OR = 0.66) and even a weaker trend for Watchman device (OR = 0.79) compared with warfarin [48]. DAnonVKAs led to a significant reduction in all-cause mortality (OR 0.89), significant reduction in haemorrhagic stroke (OR 0.45), and a trend towards reduction in total stroke (OR 0.84) and major bleeding (OR 0.79) vs. warfarin, when limiting the included

studies to RCTs only. LAAC Watchman device, compared with warfarin, led to a significant reduction in haemorrhagic stroke (OR 0.19) and a trend towards reduction in all-cause mortality (OR 0.68). Koifman et al. emphasised that, when we limit the included trials into to RCTs, there was again no significant difference between DAnonVKAs and Watchman device in regard to any outcome [55].

Conclusions

In recent years significant progress has been made in the treatment of patients with nonvalvular AF, especially in cases with high bleeding risk. This progress is associated primarily with the introduction of new methods, including LAAC and NOAC drugs, which aim at preventing thromboembolic events. In particular, LAAC has proven to be effective in a preventive role and is also relatively safe. Thus, by providing improved capabilities, LAAC significantly enhances a traditional suite of antithrombotic treatment procedures that have been based mainly on warfarin.

One of the most difficult challenges of traditional drug-based therapies has been the necessity to evaluate the balance between the risk of thrombotic and haemorrhagic complications. At present LAAC is known to provide a superior choice of treatment in patients with AF and thromboembolic risk in a few situations such as absolute contraindication of systemic OAT, refusal by a patient of systemic OAT, and as a complementary treatment to anticoagulation in patients with embolic events despite adequate OAT. In addition, as a result of individual risk/benefit evaluation for OAT vs. alternative methods of treatment, LAAC should be considered as a therapeutic option for patients with high thromboembolic risk and very high bleeding risk.

In general, LAAC treatment becomes more attractive with increasing thromboembolic risk. One of the outstanding challenges that remains to be addressed in future studies is the question whether LAAC is actually the best method for preventing thromboembolism for patients with moderate/high thromboembolic risk and relatively low bleeding risk. Another challenging question is to determine the optimum antithrombotic or antiplatelet therapy in patients who underwent LAAC, especially in patients with high bleeding risk.

Finally, there is a need to conduct direct comparative studies of LAAC and NOAC-based methods of treatment. Notwithstanding the need for future studies and further progress, recent advancements associated with the introduction of LAAC and NOAC-based methods provide today's health care professional with an unparalleled suite of potential therapies that considerably improve the outcome of patients with AF.

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