

Left Atrial Appendage Percutaneous Closure with Watchman Device: Single Centre Experience and a Review of Literature

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Abstract

Background: Left Atrial Appendage (LAA) is the main source of left atrial thrombi causing embolic strokes in patients with Non Valvular Atrial Fibrillation (NVAF). Since many patients carry contraindications to Oral Anticoagulation (OAC), percutaneous devices for closure of LAA have been introduced, to avoid peripheral thromboembolism in absence of OAC.

Methods: From March 2012 to March 2014 we enrolled patients which had permanent and persistent NVAF and high thromboembolic risk with absolute contraindication to OAC. They were subjected to insertion of Boston Scientific Watchman device in LAA under transesophageal and fluoroscopic guide, with continuous heparin administration to maintain constant activated clotting time (ACT) of 300-350 sec and under general anesthesia. Patients were discharged with indication to double antiplatelet therapy with Aspirin and Clopidogrel for 6 months and Aspirin thereafter, avoiding Warfarin at all. Follow-up Transesophageal Echocardiography (TEE) was performed 2 months, six months and 12 months after implantation.

Results: We enrolled 21 patients, aging 49 to 80 yrs. (mean 67.61 ± 8.2), with high thromboembolic risk (CHADS₂Vasc 3.23 ± 1.33), and with different contraindications to OAC, in most cases due to severe bleeding risk and difficulty in keeping stable INR values (HASBLED 3 ± 1.09). The mean size of the device implanted was 24.75 ± 2.56 mm, the mean total procedure time was 67.78 ± 18 min, the mean fluoroscopy time was 16.81 ± 2.53 min. In all cases LAA was successfully occluded at first TEE, performed within 2 months from the procedure, while we noticed a trend towards development of non-pathological leaks in the next control TEEs, with patients always free from embolic events at mean follow-up of 13.09 ± 6.04 months. Moreover, we noticed a trend towards reduction of left atrial spontaneous echo contrast after LAA closure.

Conclusion: Percutaneous LAA closure followed by administration of DAPT appears to be safe and effective at mid-term follow-up in patients with absolute contraindications to OAC. Long term safety and efficacy will be demonstrated with longer follow-up and with more patients enrolled.

Keywords: Fluoroscopic guide; Double antiplatelet therapy; Anticoagulation; MRI scans

Introduction

Atrial fibrillation, which is the most frequent arrhythmia worldwide, has a prevalence that increases with age, varying from 0.1% among adults younger than 55 to 9% in the elderly over 80 years old [1]. Atrial fibrillation is the main cause of peripheral embolism in adult population, with a fivefold increased risk of stroke, responsible for up to 20% of all strokes in patients over 80 years old [2]. Oral anticoagulation therapy (OAC) with Warfarin, other Vitamin K antagonists with chronically-adjusted INR or novel oral anticoagulants are the cornerstone of medical therapy, able to significantly reduce thromboembolic risk [3].

However, it is not without its own risks and complications, since all these drugs dramatically increase bleeding risk, and Warfarin is moreover characterized by multiple food and drug interactions, a narrow therapeutic window, and need of frequent monitoring and dose adjustments [4]. It must also be considered that approximately

45% of patients on OAC with Warfarin have suboptimal therapeutic levels of anticoagulation, resulting in high bleeding risk without protection from thromboembolism [5,6]. Anyway, since more than 90% of atrial thrombi in patients with nonvalvular atrial fibrillation (NVAF) originate from left atrial appendage (LAA) because of low blood flow velocities and blood stasis [7-10]. It is intuitive that occluding LAA may prevent formation of thrombi, thus reducing embolic risk. On this basis, several devices for percutaneous closure of LAA have been developed [11-15]. Watchman device has been studied in prospective controlled clinical trials comparing OAC to device placement, and the latter resulted non-inferior to standard INR-adjusted Warfarin therapy in stroke prevention for patients with NVAF and contraindications to OAC [16,17]. Moreover, a recently published prospective multicenter nonrandomized clinical trial (ASAP) has demonstrated that LAA closure with Watchman device can be safely performed without Warfarin bridge to double antiplatelet therapy, as indicated in the PROTECT AF trial and this may be a reasonable alternative for patients at high risk of stroke but with absolute contraindications to systemic oral anticoagulation. All these evidences have contributed to let percutaneous LAA occlusion become

a widely used technique and extend its clinical indications across Europe [16-18,22,37-41]. Therefore we report the initial experience of our Centre in percutaneous closure of LAA with Watchman device in very high bleeding risk patients, in whom Warfarin was absolutely contraindicated and consequently it wasn't administrated.

Methods

From March 2012 to March 2014 all patients undergoing LAA percutaneous closure with Watchman device at our Centre were enrolled and prospectively studied. All patients of our series had permanent or persistent NVAF, high thromboembolic risk, defined as CHA2DS2Vasc score higher than 1, and carried at least one contraindication to OAC, defined as severe hemorrhagic complications during OAC therapy, history of spontaneous major bleeding, high bleeding risk according to HASBLED score, or recurrence of thromboembolic events despite Warfarin therapy. All patients received a Transthoracic (TTE) and Transesophageal Echocardiography (TEE) before the procedure, in order to exclude the presence of LAA thrombosis, and to define morphological and dimensional characteristics of LAA. According to the PROTECT-AF trial [16] and current guidelines [42] patients were excluded from the procedure in case of presence of intracardiac thrombus visualized by TEE within 48 h before procedure, in case of any congenital heart disease (including atrial septal defect or septal aneurysms), of moderate to severe valvular disease or presence of a prosthetic valve, and in case of pregnancy. Patients received insertion of Boston Scientific Watchman device in LAA under transesophageal echocardiography and fluoroscopic guide, with continuous heparin administration to maintain constant Activated Clotting Time (ACT) of 300- 350 seconds during the whole procedure and under general anesthesia. The device was implanted through femoral venous access and trans-septal approach using a 3-part delivery system consisting of a trans-septal access sheath, a delivery catheter, and the implantable device. Device size was chosen to be 20% to 30% larger than diameter of LAA orifice to reach a stable positioning of the device. Proper device insertion was confirmed both by angiography and transesophageal echocardiography. All patients were discharged with indication to dual oral antiplatelet therapy (Clopidogrel 75 mg per day for 6 months and Aspirin 100 mg per day indefinitely). Informed consent was obtained from all patients. We checked the safety of the procedure referring to each phase of hospitalization, comprehending occurrence of adverse events related to transesophageal echocardiography, to pharmacological antiplatelet therapy and to the procedure itself, assessing incidence of catheter-related thrombus formation, air embolism, pericardial effusion, device embolization, procedure-related transient ischemic attack or stroke, major bleeding requiring blood transfusion, and vascular lesions at the site of access. Severe pericardial effusion was defined as the presence of haemodynamically significant effusion requiring either pericardiocentesis or surgical drainage. Procedure related transient ischemic attack was defined as acute neurological impairment with onset within 48 hours after the procedure, lasting less than 24 hours and without evidence of cerebral damage at MRI scans, while stroke was defined as a neurological acute impairment more than 24 hours long lasting and with evidence of cerebral ischemia at MRI scans.

According to the PROTECT AF trial long term adverse events were defined as the incidence of ischemic stroke, transient ischemic attack or systemic embolism and death for cardiovascular and embolic causes 2 months, 6 months and 12 months after procedure [16]. Acute

procedural success was defined as stable device placement in LAA without significant peri- device leak (jet-flow detected by transesophageal Doppler echocardiography smaller than 3 ± 2 mm wide). We evaluated long term success and complications through a TEE control and clinical visit performed 2 months, 6 months and 12 months after procedure, to assess formation of peri-device leaks, device dislocations and formation of thrombi on device's surface. Long term success was defined as stable and correct placement and endotelization of the device at the next transesophageal echocardiographic controls. Moreover, we evaluated patients' Quality of Life (QOL) before and after the procedure, using the validated questionnaire SF 12v2, which offers a short, precise, statistically valid tool for health risk assessment and health outcome monitoring. The SF 12v2 is actually a multipurpose short form survey with 12 questions; all selected from the SF 36 Health Survey [19-21]. The questions are combined, scored and weighted to create two scales that provide a complete evaluation of mental and physical function and overall health - related quality of life, resulting in a score ranging from 0 to 100, where a zero score indicates the lowest level of health measured by the scales and 100 indicates the highest level of health. We administered the questionnaire before the procedure and at 6 months follow-up visit to all patients.

Results

Baseline characteristics of study population are summarized in table 1. A total of 21 patients were enrolled, aging 49 to 80 yrs (67.61 ± 8.2), with high thromboembolic risk (CHADsVasc 3.23 ± 1.33) and with at least one major contraindication to OAC: previous severe hemorrhage without ongoing OAC (5 pts, mean HASBLED score 3.40 ± 0.89 , mainly due to gastrointestinal bleedings), bleeding complications during Warfarin therapy (6 pts, in all cases in patients with HASBLED score ± 3), unstable INRs (8 pts), or recurrence of embolic events despite correct OAC (2 pts). The mean size of device implanted was 24.75 ± 2.56 mm (21-30 mm), mean procedural time was 67.78 ± 18 min (58- 99 min), mean fluoroscopy time 16.81 ± 2.53 min (12-24 min), mean in hospital stay 5.41 ± 2.81 days (Table 2). In one case the procedure was complicated by the formation of a 67 mm long thin thrombus inside the access sheath, detected by TEE after device deployment in LAA. Anyway, it was successfully retracted together with the guide wire without embolic complications, leaving the Watchman device in the correct position in LAA. Moreover, one patient experienced heparin - induced thrombocytopenia, resolved after a few days. Neither other complications nor major bleedings were observed during hospitalization, nor were all the procedures successfully completed. In 20 patients out of 21 LAA was completely occluded at the end of the procedure, while in one case a per device leak of 3 mm was present, in a patient with a small and multilobated appendage (cauliflower morphology), in whom Warfarin was continued after discharge until the next scheduled follow-up TEE. The first follow-up transesophageal echocardiographic control was performed within 2 months after procedure and in 12 out of 21 cases LAA was completely occluded without leaks. On the contrary, 8 patients developed new little leaks smaller than 2 mm: all these nine patients, according to the PROTECT AF trial, were left on DAPT with Aspirin and Clopidogrel, and re-evaluated 6 months after LAA closure. At this latter control, TEE showed persistence of leaks in 9 patients, stable in 7 cases while increased up to 5 mm in two patients. Also in these cases, since leaks diameter was smaller than 5 mm, standard therapy protocol with Aspirin alone was prosecuted. At publication time we performed TEE control after one year from

procedure in 12 patients, and only one showed the persistence of a stable peridevice leak of 3 mm, with a trend towards spontaneous leaks reduction (table 4). As reported in Literature we also documented, in one case, the formation of a device-related thrombus at the 2 months follow-up TEE that disappeared with administration of subcutaneous low- molecular weight heparin (LMWH) at therapeutic dosage for three months and the patient was then switched to standard DAPT therapy. Noteworthy, this patient didn't show peridevice leaks in the previous TEE controls. No stroke, transient ischemic attacks or systemic embolization occurred during the whole follow-up period (6-30 months, mean 13.09 ± 6.04 months). Of notice, we observed a significant reduction in left atrium spontaneous echocontrast after procedure, since it was present in 11 out of 21 patients before LAA closure (in 7 cases light and in 4 cases dense), but it persisted only in three patients at follow-up TEE 6 months after procedure, and in all cases it was very light. At 12 months follow-up TEE spontaneous echo

contrast has disappeared in all patients evaluated (12 at publication time, table 5]. In our series, only one patient died during follow-up, 7 months after the procedure, because of end stage heart failure due to ischemic dilated cardiomyopathy, and the former transesophageal echocardiographic controls didn't show pathologic findings concerning the device implanted. One patient more was lost to follow-up, because eight months after procedure he refused to undergo the scheduled controls (Table 3). Moreover, patients quality of life significantly increased six months after procedure: indeed, the results of SF12v2 questionnaire showed a better mental status, reaching a score of 48.0 ± 8.2 before the procedure vs. 37.7 ± 9.6 after 6 months ($p = 0.010$), basically because of a higher perceived safety derived from the presence of the inserted device. On the other hand, patients' physical performance status didn't significantly change (39.7 ± 6.9 vs 40.5 ± 4.7 , $p= 0.7294$).

Patient's characteristics	Min-max	Mean \pm Standard Deviation /Descriptive variables
Age	49 - 80 yrs	67.61 \pm 8.2
Sex	14 males (66%) 7 females (33%)	
CHADSVasc	1-5	3.23 \pm 1.33
HASBLED	2-5	3 \pm 1.09
Ischemic cardiomyopathy		6
Hypertension		18
Diabetes Mellitus		4
Congestive heart failure (EF < 35%)		1
Prior stroke/TIA		5
Peripheral artery disease		4
Presence of Pacemaker		5
LAA /LA thrombi		0
Follow up	6-30 months	13.09 \pm 6.04 months
Contraindications to Warfarin		
	Unstable INR s	8
	Prior severe bleeding complications during Warfarin	6
	Previous hemorrhage without OAC	5
	Recurrence of embolic events despite Warfarin	2

Table 1: Baseline characteristics of study population.

Procedural Characteristic	Mean \pm Standard deviation
Size of device implanted	24.75 \pm 2.56 mm

Procedural time	67.78 ± 18 min
Fluoroscopy time	16.81 ± 2.53 min
In hospital stay	5.41 ± 2.81 days

Table 2: Procedural characteristics in study population.

Adverse events and complications observed	Number of cases during hospitalization (n =21)	Number of cases at 2 months follow-up(n =21)	Number of cases at 6 months follow-up(n =21)	Number of cases at 12 months follow-up (n =12)
Death for cardiac cause	0	0	0	1
Death for embolic cause	0	0	0	0
TEE- related injury	0	0	0	0
Medical therapy-related adverse events	1	0	0	0
Catheter-related thrombus formation	1	0	0	0
Device- related thrombus formation	0	1	0	0
Air embolism	0	0	0	0
Pericardial effusion	Severe requiring pericardiocentesis: 0/21 Small not requiring any therapeutic intervention: 1/21	0	0	0
Device embolization	0	0	0	0
Procedure-related and long term TIA	0	0	0	0
Procedure-related and long term stroke	0	0	0	0
Procedure-related and long term major bleeding	0	0	0	0
Procedure-related and long term vessel injuries	0	0	0	0

Table 3: Adverse events and complications observed.

Peri-device leaks	After procedure (n =21)	Number of cases at 2 months follow-up (n =21)	Number of cases at 6 months follow-up (n =21)	Number of cases at 12 months follow-up (n=12)
< 1 mm width	0	0	0	0
2-3 mm width	1	8	6	1

> 3 mm width	0	1	3	0
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Table 4: Evolution of peri-device leaks after procedure.

Left atrium spontaneous echocontrast	Before procedure (n =21)	Six months after procedure (n =21)	12 months after procedure (n=12)
Light	7	3	0
Dense	4	0	0

Table 5: Spontaneous echocontrast in left atrium before and after procedure.

Discussion

Atrial fibrillation is the most common cardiac arrhythmia, its prevalence increases with age 1, and it is associated with high thromboembolic risk, being responsible for up to 20% of all ischemic strokes [17,18]. OAC allows reducing thromboembolic risk 3, but it's usually subjected to lots of limitations, as multiple food and drug interactions, a narrow therapeutic window, need of frequent monitoring and dose adjustments, and possible severe bleeding complications. For these reasons up to 50% of patients with atrial fibrillation do not receive OAC, either for relative or absolute contraindications or for patients or physician's perceived risk of iatrogenic complications [24,25]. It must be also considered that approximately 45% of patients on OAC have suboptimal therapeutic levels of anticoagulation, resulting in low time in therapeutic range that causes high bleeding risk without protection from thromboembolism [5,6]. On the contrary, it is known that both Aspirin alone and double antiplatelet therapy have lower efficacy than Warfarin for ischemic stroke and peripheral embolism prevention, but are associated with a significantly high risk of bleeding [26,27,28]. Anyway, it is well known that in patients with NVAF the origin of thrombi embolizing in peripheral arteries is allocated in LAA in more than 90% of cases 7, since reduced blood flow velocities lead to blood stasis and thrombus formation [29,30]. On this basis, several devices for percutaneous closure of LAA have been developed. The Watchman system consists of a parachute-shaped device with a self-expanding frame structure covered with a permeable polyester membrane on the atrial side, and with midperimeter fixation barbs to secure it in the LAA. This device was compared to chronic adjusted-dose warfarin therapy in patients with NVAF in the Watchman Left Atrial Appendage System for Embolic Protection in Patients With Atrial Fibrillation (PROTECT AF) trial [12,16], a prospective multicenter randomized non-inferiority trial on 707 patients with NVAF and CHADS2 score >1, followed up for 5 years. This trial evaluated a composite primary end point for efficacy considering the occurrence of stroke (ischemic or hemorrhagic), cardiovascular or unexplained death, or systemic embolism that met the non-inferiority end point. Moreover, a continuous access registry provided further safety and efficacy data, including patients in the device arm of the PROTECT AF trial (542 patients) and 460 patients enrolled in the Continued Access Protocol (CAP) registry, and showed also significant decline in the rate of procedure-related complications with increasing operators' experience [13]. A long term follow-up of PROTECT AF trial [31] has recently been published, demonstrating that after 1588 patient-years of follow-up (mean 2.3 ± 1.1 years), the primary efficacy event rates still

met the criteria for non-inferiority to standard Warfarin therapy. Moreover, the recent PREVAIL trial has confirmed that procedure complications occurring after Watchman LAA occlusion are infrequent, that Watchman LAA occlusion is non-inferior to chronic Warfarin for the prevention of stroke and systemic embolism starting 1 week after randomization, and that the primary efficacy endpoint of early and late events was similar [17]. It must be noticed that all the previously mentioned studies were designed with administration of Warfarin for the first 45 days after device implantation, in order to guarantee complete device endothelialization, since Watchman device is made of nitinol covered with a polyethylene membrane allowing blood flow through the device. Anyway, Reddy et al. [18] showed in March 2013 that LAA percutaneous closure with Watchman device is safe even followed by administration of DAPT without Warfarin Bridge, with a rate of ischemic stroke, hemorrhagic stroke, systemic embolism and cardiovascular/unexplained death similar to the standard PROTECT-AF protocol comprehending OAC. Our data are consistent with this study, since we didn't observe any complication during follow-up, even avoiding Warfarin at all. Anyway, one of the most frequent events observed in patients after LAA percutaneous obliteration, both followed by Warfarin Bridge or with direct DAPT therapy, was an incomplete LAA occlusion, responsible of residual blood flow between LAA and left atrium cavity. The anatomical variability of the LAA, its wide range of ostial diameters and lengths, and the morphology of its ostium that is elliptical rather than round can actually lead to incomplete obliteration. This eventuality may create a sort of pouch with stagnant blood, that increases probability of thrombus formation and lowers the procedure's efficacy in stroke prevention [32,33]. The PROTECT AF trial design defined "LAA closure" as any seal with leaks smaller than 3 mm 2 mm. Viles Gonzalez et al. reported a post-hoc analysis of the Watchman implantation cohort in the PROTECT AF trial to study the incidence and natural history of peri-device flow, and to determine its functional impact on clinical outcomes [34]. This analysis didn't show significant correlation between residual flow around the LAA closure device up to 5 mm wide and clinical outcome, both in patients that continued OAC and in patients in whom Warfarin was stopped 45 days after procedure despite incomplete LAA closure. Moreover, a recent publication by Bail et al. monitored incidence and evolution of incomplete occlusion of the LAA during and after placement of the WATCHMAN device on 58 patients, showing that it is relatively common and that intraprocedural gaps are more likely to persist over 12 months and to become larger over time than the gaps found at follow-up echocardiography [35]. In our series of patients a complete occlusion of LAA was achieved in 12 out of 21 cases and in the other

patients peridevice leaks were smaller than 5 mm so, according to the ASAP study all patients carried on the standard DAPT therapy protocol [18]. Only in one patient we observed the formation of a thrombus on the device and, of notice, the patient didn't show pathological findings at the previous TEE. We didn't observe any complication among patients with peri-device leaks. Interestingly, we also found a significant decrease in left atrium spontaneous echo contrast after the procedure irrespective from LA enlargement, present in all patients of our series (mean left atrial volume 65, 3 ml ± 5, 4 ml), and from the presence of leaks. This observation, to be confirmed in larger and longer trials, may provide further evidence that in nonvalvular atrial fibrillation the origin of thrombi is allocated in LAA, that an open passage of blood with low flow velocities is responsible of thrombus formation and embolization, and that the reduction of spontaneous echocontrast in left atrium after LAA occlusion might be a marker of procedure success. Moreover, according to the previous Literature we observed an improvement in patients' quality of life, since the presence of the device reassured patients to be protected from stroke [36].

Study Limitations

This clinical experience carries up several limitations, as the number of patients is very small and their thromboembolic and bleeding risks are very high, then this could overestimate the beneficial effects of this therapeutic protocol. At last, it is noteworthy to remember that also double antiplatelet therapy and even Aspirin alone can cause a bleeding risk that must be carefully evaluated in such fragile patients.

Conclusion

LAA percutaneous closure with Watchman device appears to be safe and effective at mid-term follow-up in patients with nonvalvular atrial fibrillation and absolute contraindications to Warfarin. Administration of DAPT after procedure avoiding Warfarin at all, even in case of presence of peri- device leaks smaller than 5 mm has shown a favorable outcome. Moreover, we observed significant decrease in left atrium spontaneous echocontrast after LAA percutaneous obliteration, a parameter that could suggest the success of the procedure if confirmed by larger and longer observation.

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