Heart, Lung and Circulation (2019) **28,** 1683–1688
1443-9506/04/$36.00
https://doi.org/10.1016/j.hlc.2018.08.022

ORIGINAL ARTICLE

Device-Related Thrombus After Left Atrial Appendage Occlusion With the Amulet Device☆

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Received 8 March 2018; received in revised form 25 June 2018; accepted 30 August 2018; online published-ahead-of-print 27 September 2018

Background Left atrial appendage occlusion (LAAO) is increasingly used for stroke prevention in patients with atrial fibrillation who are considered unsuitable for a lifelong oral anticoagulant regimen. Recently, a single-centre study reported device-related thrombus formation in 16.7% of patients treated with the second-generation Amulet device (St. Jude Medical, St. Paul, MN, USA), presenting a potential major safety concern. As ''real-world'' data on device-related thrombus formation following LAAO with the Amulet occluder are scarce, we aimed to evaluate this outcome in a retrospective registry.

Methods Clinical and tranosesophageal echocardiography data after LAAO with the Amulet in consecutive patients from three centres were collated.

Results Among 38 patients (mean age 75.8 years), mean (standard deviation) CHA_2DS_2-VASc and HAS-BLED scores were 4.4 (1.2) and 3.4 (0.9), respectively. All patients underwent successful device placement without procedure-related adverse events. The antithrombotic regimen at discharge consisted of dual antiplatelet therapy (DAPT) in 27 patients (71.1%), single antiplatelet therapy in 10 patients (26.3%), and no antithrombotic therapy in one patient (2.6%). Device-related thrombus was observed in one patient (2.6%) despite DAPT regimen. The outcome of this patient was uncomplicated after adjustment of oral anticoagulant therapy. No patients presented with a thromboembolic event following LAAO during a mean (standard deviation) follow-up of 15 (5) months.

Conclusions In this retrospective study, device-related thrombus formation with the second-generation Amulet device was rare and occurred at a rate similar to that of the previous device. Importantly, no patient experienced a

☆All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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device-related thromboembolic event during follow-up. Larger real-life studies are required to confirm the safety profile of this increasingly used device.

Keywords Left atrial appendage occlusion • Stroke prevention • Atrial fibrillation • Device-related thrombus formation

Introduction

The concept of percutaneous left atrial appendage occlusion (LAAO) for stroke prevention in patients with atrial fibrillation (AF) was derived from several observational studies reporting that, in patients with non-valvular AF, 90% of left atrial thrombi are located in the left atrial appendage (LAA) [1]. LAAO is non-inferior to medical treatment with warfarin for the prevention of a combined outcome of stroke, systemic embolism and death in patients with non-valvular AF [2–6]. In the 2016 European Society of Cardiology guidelines for the management of AF, LAAO received a IIb level of recommendation in patients in whom long-term anticoagulant treatment was contraindicated [7]. LAAO is also recommended by some authors when electrical isolation of the LAA occurs during extensive ablation for non-paroxysmal AF [8,9]. The number of LAAO procedures is, therefore, increasing rapidly in such patients [10,11].

The first-generation Amplatzer Cardiac Plug (ACP) and the second-generation Amplatzer Amulet occluder (both from St. Jude Medical, St. Paul, MN, USA) are nitinol plugs widely used for LAAO [12]. However, data on the ''real-world'' performance of these two devices, particularly the recently released Amulet device, are scarce. The Amulet was developed to provide better occlusion of the LAA—thus presumably being more effective than the previous generation—as well as limiting device-related thrombogenesis [13]. However, in preliminary experience from Sedaghat et al. [14], there was an unexpectedly high rate of device-related thrombus (DRT) (16.7%)—despite the use of dual antiplatelet therapy (DAPT) in most patients—resulting in stroke in one patient (4.2%). If these findings are confirmed in other studies, this would raise a major concern for the safety of LAAO with the Amulet prosthesis. We therefore conducted a retrospective review of patients who underwent LAAO with the Amulet prosthesis in our three institutions, aiming to determine the rates of DRT, optimal device placement and residual periprosthetic leak.

Material and Methods

Study Design

This study included consecutive patients with non-valvular AF who underwent LAAO with the Amulet device due to contraindication to long-term oral anticoagulants, in three centres (Aix-Marseille University, Nord Hospital; Aix-Marseille University, Timone Hospital; and European Hospital of Marseille) during March 2015 to December 2016. Clinical, procedural and imaging data were retrospectively examined. All operators who participated in this study had previously performed at least 15 LAAO procedures with the ACP device. M.P. and F.F. had performed 25 and 15 LAAO procedures with the ACP device respectively. S.A. is a clinical proctor for St. Jude Medical and had performed over 50 LAAO procedures with the ACP. S.A. has also a significant experience with the Watchman device with involvement in over 40 procedures (BostonScientific, Natick, MA, USA).

This study complied with the Declaration of Helsinki. The research protocol was approved by the Research Ethical Committee of Aix-Marseille University. All patients gave informed consent to undergo the procedure.

LAAO Procedure

Preprocedural LAA imaging to evaluate LAA anatomy and dimensions was optional, performed at the discretion of the operator. The technique of LAAO device implantation has been described elsewhere [12]. The procedure was performed under general anaesthesia with transoesophageal echocardiography (TEE) and fluoroscopy guidance. Left atrial access was obtained through a transseptal puncture, at the inferior and posterior part of the fossa. After exchange from the transseptal sheath to the dedicated delivery sheath, a 100-IU/kg bolus of unfractionated heparin was administered, targeting an activated clotting time of 250–300 seconds. Two-dimensional TEE using several views from 0° to 135° and real time three-dimensional TEE views were used for both detailed LAA assessment and device positioning. Device deployment was performed under both TEE and fluoroscopy guidance. Before delivery, device stability was evaluated according to the following criteria: compression of the lobe of the device; lobe orientation in the axis of the landing zone; concave disc shape, separated from the lobe; distal position of the lobe to the circumflex coronary artery; and stability to a gentle 60-second tug test [13]. All patients underwent post-procedural transthoracic echocardiography to assess the device position and exclude pericardial effusion before hospital discharge. In line with the manufacturer's instructions, antithrombotic therapy consisted of DAPT (aspirin 75 mg plus clopidogrel 75 mg daily) for at least 6 weeks unless contraindicated.

Definitions

According to expert consensus, technical success was defined as exclusion of the LAA without residual leak >5 mm on colour Doppler TEE without device-related complications [15]. Procedural success was defined as technical success without procedure-related complications [15].

Amulet device placement was considered optimal when the disk of the occluder covered the LAA rim [16] (Figure 1). All efforts were made to achieve optimal placement of the Amulet, including gentle counterclockwise rotation during the tug test. In all other cases, if the Amulet disk failed to "catch" the pulmonary vein (PV) ridge, due to the need of a deeper placement within the LAA, a funnel-shape LAA or poor LAA orientation, the Amulet placement was considered suboptimal.

Follow-Up

All patients underwent two dimensional (2D) and real time 3D TEE under controlled sedation with midazolam to evaluate the Amulet position and the presence of a DRT and/or peri-device leak 6–12 weeks after device placement. Full 2D screening in several views from 0° to 135° and real time 3D views were performed to detect DRT. If the TEE did not show abnormalities (thrombus or peri-device leak >5 mm), clopidogrel treatment was stopped and lifelong monotherapy with aspirin 75 mg once a day was continued thereafter.

Statistical Methods

Owing to the small number of patients, a full statistical analysis was not undertaken. Values are presented as means (standard deviations [SDs]) or numbers (percentages).

Results

Patient Characteristics

Thirty-eight (38) patients, predominantly men (76.3%), with a mean (SD) age of 75.8 (7.7) years (range 63–89 years) were included in this analysis (Table 1). Mean (SD) CHA_2DS_2-VASc score was 4.4 (1.2) and 14 patients (36.8%) had previous stroke, transient ischaemic attack or systemic embolism. Mean (SD) HAS-BLED score was 3.4 (0.9) (range 2–5). Atrial fibrillation was paroxysmal in 23 patients (60.5%). Hypertension was the most frequent associated comorbidity, found in 33 patients (86.8%). Nine (9) patients (23.7%) presented with left ventricular ejection fraction ≤40%.

The reason for LAAO was serious bleeding without curable cause in 33 patients (86.8%). A total of 15 patients (39.5%) presented with previous intracranial bleeding. In three patients (7.9%), LAAO was mandated due to ischaemic stroke occurring despite an adequate oral anticoagulant therapy regimen. In the remaining two patients, LAAO was performed due to the need for prolonged triple therapy following coronary artery stenting. The antithrombotic regimen at discharge consisted of DAPT in 27 patients (71.1%), single antiplatelet therapy in 10 patients (26.3%), and no antithrombotic therapy in one patient (2.6%).

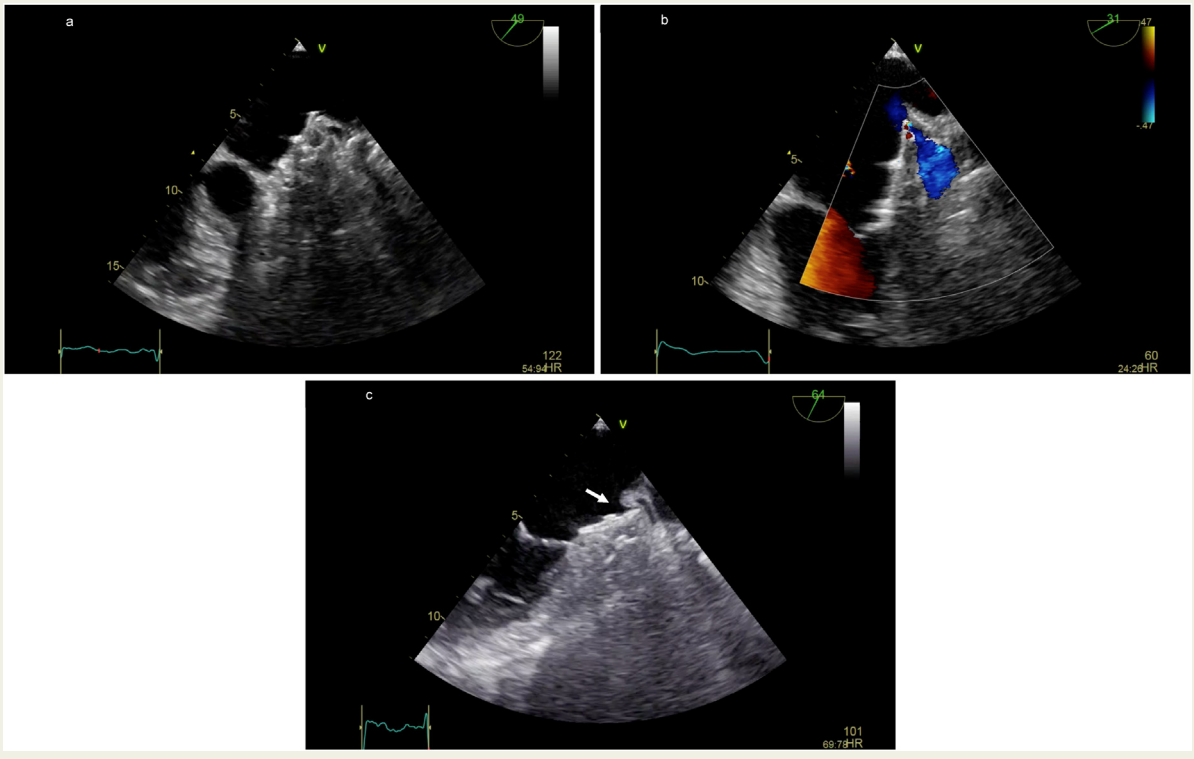

Figure 1 TEE follow-up imaging after LAAO with the Amulet showing optimal device placement (a), optimal device placement with residual peri-device leak <3 mm (b), and suboptimal device placement resulting in an artificially created cul-de-sac (white arrow) between the ridge of the left superior pulmonary vein and the disc of the Amulet failing to cover the rim (c).
Abbreviations: LAAO, left atrial appendage occlusion; TEE, transesophageal echocardiography.

Table 1 Baseline patient characteristics.

	All patients (n = 38)
Age, years, mean (SD)	75.8 (7.7)
Men, n (%)	29 (76.3)
Paroxysmal AF, n (%)	23 (60.5)
LVEF ≤40%, n (%)	9 (23.7)
Creatinine >200 μmol/l, n (%)	4 (10.5)
Prior myocardial infarction, n (%)	21 (55.3)
Prior severe bleeding, n (%)	33 (86.8)
History of LAA thrombus, n (%)	3 (7.9)
CHA_2DS_2-VASc score, mean (SD)	4.4 (1.2)
Congestive heart failure, n (%)	9 (23.7)
Hypertension, n (%)	33 (86.8)
Age ≥ 75 years, n (%)	20 (52.6)
Diabetes, n (%)	17 (44.7)
Stroke, n (%)	14 (36.8)
Vascular disease, n (%)	22 (57.9)
Age 65–74 years, n (%)	15 (39.5)
Sex category female, n (%)	9 (23.7)
HAS-BLED score on oral anticoagulant therapy, mean (SD)	3.4 (0.9)

Abbreviations: AF: atrial fibrillation; HAS-BLED: Hypertension, Abnormal renal and liver function, Stroke, Bleeding, Labile international normalized ratios, Elderly, Drugs or alcohol; LAD: left atrial appendage; LVEF: left ventricular ejection fraction; SD: standard deviation.

LAAO Procedure

Technical and procedural successes were achieved in all patients. Optimal device placement according to the expert consensus was achieved in 26 patients (68.4%). No major periprocedural adverse events occurred. Groin haematoma at access site >6 cm not requiring surgical intervention, representing minor bleeding according to the Munich consensus document (Bleeding Academic Research Consortium type 2), was observed in three patients (7.9%) [15].

TEE Follow-Up

All but one patient underwent TEE a mean (SD) of 55 (21) days after device implantation. In the remaining patient, a cardiac computed tomography scan was performed and this excluded DRT and showed optimal device placement. Device-related thrombus was found in one patient (2.6%) at TEE. The patient was 70 years old and had permanent AF. The LAAO indication was stroke occurring despite an adequate oral anticoagulant regimen (dabigatran 150 mg twice daily). The CHA_2DS_2-VASc score was 4 in this patient. Despite optimal device placement and DAPT, a thrombus was diagnosed during the systematic TEE 90 days after the procedure. A lifelong oral anticoagulant regimen was resumed thereafter and a TEE 4 weeks later did not reveal residual DRT. Residual leaks >3 mm but <5 mm were reported in five patients (13.2%). Transoesophageal echocardiography follow-up data are summarised in Table 2. No patient experienced stroke within the period from the implantation procedure to the TEE following device placement. No procedure-related death was observed. No patients presented with a thromboembolic event following LAAO during a mean (standard deviation) follow-up of 15 (5) months.

Discussion

In our three-centre study, thrombus formation following LAAO with the Amulet device was infrequent (2.6%). In addition, no patient experienced stroke during the procedure or the 15-month follow-up period.

With the first-generation ACP, the reported rate of DRT varied from 0% to 4% in most studies, with very infrequent overall periprocedural thromboembolic events related to DRT [5,13,17–19]. However, in a study from Plicht et al. [16], an unexpectedly high rate of Amplatzer Cardiac Plug (ACP) related thrombus (17.6%) despite DAPT raised serious safety concerns with this prosthesis. Transoesophageal echocardiography highlighted the role of the central screw of the device as the origin of thrombus formation in these patients.

Left atrial appendage occlusion is increasingly being used for stroke prevention in patients with AF who are considered unsuitable for lifelong oral antithrombotic treatment; or as an alternative to oral anticoagulant treatment in the US [7]. The Amulet device is one of the most frequently used devices. The Amulet device was designed to better exclude the LAA while limiting device-related thombogenesis. In particular, the proximal female screw on the disc has been recessed [12,13]. However, the first report regarding its clinical use, by Sedaghat et al. [14], was concerning due to a very high rate of DRT (16.7%). This value is higher than the 11.0% rate of DRT observed in a retrospective registry during LAA imaging in 101 patients after LAAO with the first- and second-generation nitinol plug [20]. In our multicentre registry, the rate of DRT following LAAO with the Amulet was very low (2.6%), while thromboembolic risk profile of the patients included in the current report was

Table 2 Transoesophageal echocardiography follow-up.

	All patients (n = 37)*
Days from device implantation	55 (21)
Optimal device placement, n (%)	26 (68.4)
Device migration, n (%)	0
Device-related thrombus, n (%)	1 (2.6)
Peridevice leakage >3 mm, n (%)	5 (13.2)
Peridevice leakage >5 mm, n (%)	0
Pericardial effusion, n (%)	0

*1 patient refused to undergo transoesophageal echocardiography follow-up.

similar to those included in the Sedaghat et al. study [12]. Our results are in line with those of Gloekler et al. [21], who performed a head-to-head comparison of the two generations of Amplatzer LAA occluders. Despite DAPT, Gloekler et al. [21] reported thrombus formation in 2/50 patients (4.0%) treated with the Amulet. Similarly, in initial experience from Freixa et al. [13], among 24 patients effectively treated with the Amulet, one patient (4.2%) who was not correctly receiving DAPT presented with DRT on systematic TEE. The rate of DRT was 1.5% in the 673/1088 patients with TEE follow-up from the largest prospective registry on outcomes after LAAO with the Amulet occluder [22].

The difference in the rate of thrombosis observed between our study and that of Sedaghat et al. [14] may be related to procedural factors. In contrast to Plicht et al. [16], all thrombi observed by Sedaghat et al. [14] were located in an artificially created cul-de-sac between the ridge of the left superior pulmonary vein and the disc of the Amulet failing to cover the rim. In most of the patients, Sedaghat et al. [14] did not achieve optimal device placement, which is likely to be responsible for thrombus formation. In fact, they reported that this artificially created cul-de-sac, the so-called ''neo-appendage'' [14], was created in as many as 14 of the 24 patients in their study (58.3%). The rate of DRT formation reached 28.5% among the 14 patients without optimal device placement. Conversely, no patient with optimal device placement presented with DRT [14]. We, therefore, hypothesised that suboptimal Amulet device placement may create local conditions for device-related thrombogenesis [23]. Failure to cover the rim of the LAA with the disc of the ACP or Amulet devices is a common finding. With the ACP, such neo-appendage creation was observed in 21/34 patients (61.8%) in the study by Plicht et al. [16]. However, the rate of neo-appendage creation with the Amulet in our experience was much lower (31.6%). Optimal device choice and placement should, therefore, aim to cover the rim of the LAA and achieve complete LAA sealing. In the case of failure, careful post-procedural management including oral anticoagulant therapy—if possible—and repeated LAA imaging to enable early DRT detection may be proposed until full device endothelialisation.

According to manufacturer recommendations, DAPT is required after LAAO with the Amulet device. At discharge, DAPT seems to have both good safety and efficacy profiles for DRT prevention [15,20,24]. In our study, DAPT regimen was prescribed in 71.1% of our patients which is significantly higher than the 23.4% and 54.3% rates reported in larger studies on the Amulet device [20,22].

Finally, LAAO is associated with a steady learning curve. Our significant experience with the technique of LAAO might also explain our satisfactory outcomes.

This observational study has the limitations inherent to its retrospective design and to the small number of patients included. However, the main limitation was that we did not conduct a direct comparison between the first- and second-generation LAA occluders. Otherwise, we did not perform late (6-12 months) LAA imaging to detect DRT occurrence after cessation of the DAPT.

Conclusions

In this multicentre study, the rate of DRT after LAAO with the Amulet device was low and similar to those from the largest registries. Importantly, none of the 38 patients experienced stroke during the procedure or the 15-month follow-up period. Larger ''real-world'' studies are required to confirm the safety profile of this increasingly used device.

Acknowledgements

Language editing support was provided by Jenny Lloyd (MedLink Healthcare Communications Limited) and was funded by the authors.

Sources of Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of Interest

Dr. Sébastien Armero is proctor for St. Jude Medical.

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