Amplatzer Cardiac Plug for Stroke Prevention in Patients with Atrial Fibrillation and Bigger Left Atrial Appendix Size

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Abstract

Left atrial appendage (LAA) dimensions have been shown as an independent predictor of higher risk for stroke in AF patients. Little data exist on the outcomes after LAA closure in patients with nonvalvular atrial fibrillation (NVAf) who have relatively bigger LAA size. This study aims to evaluate the results associated with LAA closure with the Amplatzer cardiac plug (ACP, AGA, St. Jude Medical, Minneapolis, MN) in bigger LAA size. A total of 25 patients with NVAf underwent LAA closure with the ACP device. All patients received short-term (up to 3 months) dual-antiplatelet therapy (clopidogrel and aspirin) after the procedure and aspirin only thereafter. A transesophageal echocardiography was performed in all patients at the 3- and 6-month follow-ups. No patient was lost to follow-up (≥ 12 months in all patients). The mean age, CHA₂DS₂-VASc score, and HAS-BLED score were 66.2 ± 8.79 years; 3.2 ± 1.46 and 2.4 ± 1.0 , respectively. The average sizes of the LAA landing zone and ostium were 23.08 ± 5.0 and 24.9 ± 4.4 mm, respectively. The procedure was successful in 23 (92%) patients and was canceled in 2 (8%) patients due to huge LAA dimensions. In 56% of the patients “pull and release” technique is needed to appropriately implant the ACP. During a mean follow-up of 12 months, no cases of periprocedural stroke and no mortality were observed. In patients with NVAf at high risk of cardioembolic events and big LAA size, LAA closure using the ACP device is safe and effective.

Keywords

- closure device
- big left atrial appendage

Stroke is the most fearing and debilitating complication of atrial fibrillation (AF). Up to 23% of nonhemorrhagic stroke is associated with AF,¹ and they experienced more severe clinical presentation, more disabled sequelae and more frequent recurrence. Furthermore, stroke patients with AF show more serious cardiac adverse event as well.

Oral anticoagulants, either vitamin K antagonist, direct thrombin inhibitor, or antifactor X drug, have been proven to effectively reduce stroke and systemic embolism in nonvalvular AF patients.^{2–5} However, bleeding risk complication remains a major concern of the anticoagulant side effect.^{6,7}

Currently, left atrial appendage (LAA) closure devices are available as an alternative to anticoagulant therapy. Studies showed that 90% of thrombus formation in nonvalvular AF attributed to LAA.⁸ Recent study showed that bigger LAA size is correlated with cryptogenic stroke. Randomized controlled trial showed that LAA closure resulted in better stroke prevention as compared with vitamin K antagonist.⁹ However, the benefit of LAA closure in subset of patients with a bigger LAA size is not yet clear, which is considered to have a higher risk of stroke.¹⁰ We studied implantation of an LAA closure device, namely, Amplatzer cardiac plug (ACP, AGA, St. Jude Medical, Minneapolis, MN) in bigger LAA size.

Methods

Patients

A total of 25 patients (aged 66.2 ± 8.79 years, 9 are women) with nonvalvular AF participated in this study. Risk of stroke is evaluated by means of CHA₂DS₂VASc score¹¹ and risk of bleeding due to anticoagulant therapy is evaluated by means of HAS-BLED score.¹² Inclusion criteria are nonvalvular AF patient with a CHA₂DS₂VASc score of at least 2, and HAS-BLED score of at least 3. Exclusion criteria are the presence of thrombus in the left atrium, acute decompensated heart failure, and conditions that transseptal puncture contraindicated. All patients are optimally treated based on their clinical characteristics. Overall, 65% of patients are having angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, 55% on beta adrenergic blocker, 30% on calcium channel blocker, 30% on digoxin, and 39% on statin for hypertension, heart failure, dyslipidemia, or upstream therapy of AF. Oral anticoagulants used are new oral anticoagulants (54%) and warfarin (46%). Only 30% of the patients are having long-term amiodarone.

LAA Sizing

Both angiography and transesophageal echocardiography (TEE) are used to measure ostial and landing zone diameters. Angiographic measurement is performed by placing TorqVue 45° just at the mouth of LAA ostium and gives a hand injection of contrast media during right anterior oblique 20 to 30 degrees with cranial angulation of 20-degree view. Transesophageal echocardiography measurements are performed using 45 and 90 to 110-degree views. The largest diameter from any TEE view is used as TEE results. If angiographic measurement results are different from TEE results then we classify it according to their difference. In case if the difference is less than 10 mm then the largest diameters is used as the final LAA diameter. However, if the difference between angiographic and TEE results is more than 10 mm, then the average of those

diameters are concluded as the final diameters. The ACP size selection is 2 to 4 mm above the final LAA landing zone diameter. ►Fig. 1 shows angiographic and TEE measurement of LAA.

Procedure of ACP Implantation

The procedure of ACP implantation has been published elsewhere.¹³ In brief, the procedure is comprised of: (1) TEE-guided transseptal puncture, which targeted more inferior part of fossa ovalis, (2) LAA angiography to measure landing zone and ostial diameter, (3) step by step ACP release in LAA. Of note that device release should be started at distal part LAA with slowly unsheathing the device till the ball shape is formed, then keep it unsheathed but hold the proximal part of delivery system softly to let the device move slightly proximal inside LAA when the strawberry shape is formed. Then hold the delivery system tightly while continuing unsheathing and keep the device in the landing zone when the lobe is completely opened. Once the lobe is positioned at the landing zone, release the disk by means of simultaneous unsheathing and light pushing of device. If the superior edge of the ostium is far enough from the landing zone special technique (pull and release technique) is needed to reposition the disk to cover the superior edge (►Fig. 2). The appropriate position of ACP in LAA and absence of residual flow jet is confirmed by TEE before the device is unscrewed from the delivery system (►Fig. 3).

Follow-Up

Follow up period was 12 months. Transthoracic echocardiography study performs immediately, and TEE at 3 months and 6 months after ACP implantation. Outpatient based clinical observations are performed every month. Dual antiplatelets (clopidogrel 75 mg once daily [OD] and aspirin 80 mg OD) were administered for 3 months followed up by aspirin 80 mg OD for life. Anticoagulant is administered only if evidence of thrombus appears in echocardiography study during the follow-up period.

Fig. 1 Ostial and landing zone measurement by TEE and angiogram (RAO cranial). Ostial and landing zone diameters are shown by solid and interrupted white line. Cx, left circumflex artery; RAO, right anterior oblique; TEE, transesophageal echocardiogram.

Fig. 2 Step by step procedure of ACP implantation. RAO 30 with 20 degrees cranial angulation view is working view (A), distal tip of delivery sheath located at distal part of LAA (B), unsheathing till ball shape is formed at distal part of LAA (C), continue unsheathing and keep the device at distal part of LAA till strawberry shape is formed (D), more unsheathing with a soft push on device to avoid device jump out when the full lobe shape is formed. Note that tire shape of the lobe indicates appropriate size device (E). Gently push the device while continuing unsheathing will release the disc (F). Contrast injection shows disc position inside landing zone (G), pull and release technique to reposition the disc. First pull the disc slowly out of the ostium and release it (H), contrast injection shows the disc appropriately cover the whole ostium (I), after ACP position is confirmed at a good position then unscrew to release the whole device (J). ACP, amplatzer cardiac plug; LAA, left atrial appendage; RAO, right anterior oblique.

Results

Of 25 eligible patients, majority (56%) are having long-standing persistent AF. Based on CHA₂DS₂-VASc score subjects are at a high risk for stroke. Overall, 23 patients were successfully implanted ACP. Two cases were canceled for ACP implantation due to huge LAA size which did not fit to the available ACP size. The clinical characteristics are presented in ►Table 1.

An average size of echocardiography and angiographic measurement of LAA landing zone and ostium are 23.08 ± 5.03 and 24.9 ± 4.41 , respectively. LAA ostial diameter measured by

angiography is similar to that measured by TEE, but landing zone diameter is significantly different between angiography and TEE measurement (24.6 ± 5.1 vs. 21.6 ± 4.57 , respectively with p value of 0.033). The average implanted ACP size is 26.96 ± 3.296 mm. There was no device replacement due to under- or oversizing. The LAA measurement data are presented in ►Table 2.

In 56% of the 23 implanted patients upper disc positioned slipped in the LAA which did not cover the whole ostium. Special technique the so-called “pull and release technique” to reposition the disc to appropriate position is needed. The

Fig. 3 Transesophageal echocardiography examination of patient 15. Measurement of landing zone and ostium mainly performed in approximately 45-degree view (A). Unsheathe the device at distal part of LAA till ball shape is formed. At this stage, moving the device to a desired position is safe (B). Full release of the lobe at the landing zone with appropriate compression at the device edge—for a good anchoring (C). Full release of the disc. Of note the disc superior edge position inside the landing zone (D). Pull and release technique. Slowly pull the disc out of ostium (don't worry with the lobe position if its anchoring is good) (E). Release the disc then it will cover the whole ostium from superior edge to inferior edge. Color Doppler shows no leakage jet into LAA (F).

Table 1 Subject characteristics

Characteristics	Value
Age (y)	66.2 ± 8.79
Type of atrial fibrillation, n (%)	
Paroxysmal	0 (0)
Persistent	3 (12)
Long-standing persistent	14 (56)
Permanent	8 (32)
CHA ₂ DS ₂ -VASc score	3.2 ± 1.46
HAS-BLED score	2.4 ± 1.0
HAS-BLED score ≥ 3, n (%)	11 (44)

Table 2 Procedural data

Variable	Value
LAA measured by TEE	
LAA orifice diameter (mm)	24.96 ± 4.65
LAA landing zone (mm)	21.58 ± 4.57
LAA Measured by fluoroscopy	
LAA orifice diameter (mm)	24.94 ± 4.26
LAA landing zone (mm)	24.59 ± 5.10
Devices and procedures	
Patients selected, n (%)	25(100)
Patients implanted, n (%)	23 (92)
Implantation success, n (%)	23 (100)
ACP size (mm)	26.96 ± 3.29
Device replacement, n (%)	0 (0)

Abbreviations: ACP, amplatzer cardiac plug; LAA, left atrial appendage; TEE, transesophageal echocardiogram.

technique consists of three steps: (1) pull the TorqVue 45° approximately 1.5 cm away from LAA ostium, (2) pull the disc slowly till it forms strawberry shape outside the ostium without change in lobe position, (3) release the disc to cover the ostium. Ostial diameter of the patients who need “pull and release” technique is significantly larger from those who doesn't need the technique (→ **Table 3**).

Table 3 Characteristics of patients who underwent “pull and release” technique

Diameters	With pull and release technique (n = 13)	Without pull and release technique (n = 10)	p Value
Ostial	25.9 ± 2.32	23.1 ± 5.98	0.032
Landing zone	22.8 ± 3.67	22.2 ± 5.79	0.696
ACP size	27.5 ± 2.47	26.2 ± 4.16	0.346

Abbreviation: ACP, amplatzer cardiac plug.

Table 4 Complications

Complications	n (%)	Time detected
Mild pericardial effusion	1 (4.3)	Periprocedural
Tamponade	1 (4.3)	Periprocedural
Inguinal hematoma	0 (0)	Periprocedural
Femoral artery pseudoaneurysm	0 (0)	Periprocedural
Device thrombus	2 (8.6)	At 3 mo

Complication rates were noted in two subjects. One patient experienced cardiac tamponade 24 hours after the implantation that need pericardiocentesis. Unfortunately, during pericardiocentesis the operator accidentally punctured right ventricle resulting in small tear that needed surgical correction. Surgery report showed no active bleeding from LAA closure site. Another complication is mild pericardial effusion that no intervention needed. Types of complication are presented in → **Table 4**.

During follow-up, two patients experience device-related thrombosis at 3 months TEE follow-up and one patient experienced mild stroke 6 months after implantation. In all complicated patients, ACP positions were appropriate without evidence of cull de sac or gap. Those patients had high-stroke risk as they have CHA₂DS₂VASc score of 3. The patients comprised of two permanent and long-standing persistent AF. Of the two patients who experienced device-related thrombus, one patient was treated with warfarin and another one treated with dabigatran 150 mg twice a day. TEE reexamination 3 months after anticoagulant therapy revealed no thrombus in both patients. The stroke patient completely recovered without sequelae, no thrombus and ACP position is appropriate on TEE examination. Then, they continue on aspirin therapy for life. Ventricle rate is well controlled by β blocker, nondihydropyridine calcium channel blocker, and digoxin as a single drug or combination. In overall, Kaplan–Meier survival analysis showed cumulative survival proportion of 88% (standard error of 0.65) (→ **Fig. 4**).

Fig. 4 Kaplan–Meier analysis for stroke and systemic thromboemboli-free survival. Device-related thrombus is included as event.

Discussion

This long-term observational study showed that ACP implantation in bigger LAA size is safe and effective. The successful implantation was achieved in 92% of the patients, and canceled in 2 patients (8%) due to huge LAA size. Cardiac tamponade that need surgical correction occurred in one patient (6%). One patient experienced mild stroke during study period.

Similar results was achieved by Streb et al¹⁴ in Poland who had more than 95% success in 22 nonvalvular AF patients with CHA₂DS₂VASc score of 2 and HAS-BLED score of 3 that implanted ACP. Also, a serious complication occurred in 1 patient in their series. Other series with 52 patients aged 74 ± 8 years and median CHADS₂ score of 3 achieved success rate of 98.1%. Procedure-related complications were device embolization (1.9%) and pericardial effusion (1.9%), with no cases of periprocedural stroke. During a mean follow-up of 20 ± 5 months, the rates of death, stroke, systemic embolism, pericardial effusion, and major bleeding were 5.8, 1.9, 0, 1.9, and 1.9%, respectively. The presence of mild peridevice leak was observed in 16.2% of the patients at the 6-month follow-up as evaluated by TEE. There were no cases of device-related thrombosis.¹⁵

Surprisingly, for average Indonesian body size, their LAA sizes are bigger than expected. An average ACP size in our series is 26.96 ± 3.296 mm which is even bigger than that of western people. Recently, a single-center ACP implantation of 100 cases in Western country reported that average LAA size was 20.8 ± 3.19 mm by fluoroscopy at landing zone with average ACP size of 24.36 ± 3.27 mm,¹⁶ and in other series showed an average LAA size of 20.7 ± 2.7 mm by fluoroscopy in the orifice area.¹⁷ In Asian population, Lam et al reported their initial ACP implantation and found that the mean implanted ACP size is 23.6 ± 3.1 mm.¹³ There is no clear explanation on why the LAA size of our series is bigger than previous reported data. We assumed subject characteristics of only persistent or permanent AF patients with large left atrial dimension (46.0 ± 0.76 mm) attributed to LAA size. Those types of patients usually have large left atrium dimension as shown in our data with enlarge left atrium dimension (46.0 ± 7.64 mm).

The importance to close bigger LAA is weighed by its potential higher stroke risk. Some studies showed that LAA is significantly enlarged in more than half of patients with cryptogenic stroke/transient ischemic attack,¹⁸ and may contribute to the pathogenesis of stroke. The facts of relatively bigger LAA size in our population need special attention from medical practitioner dealing with AF. Postprocedural dual antiplatelet (clopidogrel 75 mg OD and aspirin 80 mg OD) administration for 3 months and only aspirin 80 mg OD afterwards consequences of total 13% thromboembolic events comprise of two device-related thrombus and one stroke event. The device-related thrombosis was managed well with readministration of vitamin K antagonist for 3 months. Using a similar regimen of dual antiplatelet post-LAA closure, Faustino et al reported 4.5% device-related thrombosis 1 month after implantation of ACP.¹⁷ However,

none of those patients with device-related thrombosis experienced stroke or systemic thromboemboli. In a major trial of LAA closure, PROTECT AF, warfarin was administrated for at least 45 days to avoid excessive thrombus formation on the device until device endothelialization supervened then followed with dual antiplatelet therapy for 6 months and aspirin for lifetime.¹⁹ TEE evaluation of device-related thrombus should routinely be performed at 3 months after implantation of LAA closure. Blessing et al comparing 28 patients received aspirin plus one among vitamin K antagonist, a novel anticoagulant, or low-molecular-weight heparin in full anticoagulant doses with 26 patients received double antiplatelet (aspirin and clopidogrel) during the first 4 weeks after successful LAA closure device implantation. During 1 month observation they found that double antiplatelet therapy was associated with a higher incidence of device-related thrombosis and unexplained death without differences in bleeding rate.²⁰ On the contrary, Schlundt et al gave a short-term dual antiplatelet therapy (100 mg of aspirin and 75 mg clopidogrel per day) for 6 weeks, followed by a monotherapy with 100 mg of aspirin per day after Watchman (Boston Scientific, Maple Grove, MN) implantation. During 12 months follow up they found none of the patients got either an ischemic or hemorrhagic stroke or a systemic embolism and no device-attached thrombus.²¹ Lack of data warrant clinical trial with sufficient sample size to have definite answer on whether direct dual antiplatelet or anticoagulant precedes dual antiplatelet as appropriate treatment after ACP implantation. However, lesson learnt from our subjects with bigger LAA size, anticoagulant preceding antiplatelet therapy seems more appropriate to prevent device-related thrombus and stroke event.

Limitation

The need of pull and release technique is not yet determined in subject with normal LAA size due to lack of control group.

Conclusion

ACP implantation is safe and effective for big LAA size closure. New technique of "pull and release" is useful to completely cover ostium of particular LAA types.

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