



## Original Article

# Unconventional combination of left atrial appendage device occlusion in patients with atrial fibrillation who needed concomitant catheter interventions for underlying structural heart disease

Palaparti Raghuram, Sreeja Pavithran, Kothandam Sivakumar\*

Department of Pediatric Cardiology, Madras Medical Mission, Chennai, India

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## ABSTRACT

**Objectives:** Left atrial appendage occlusion (LAAO) in non-valvular atrial fibrillation (AF) reduces cardioembolic strokes. Despite increased risk, trials exclude valvular AF in structural heart diseases where clots extend beyond appendage.

**Methods:** Patients with AF and relative risks for oral anticoagulation (OAC) needing structural interventions underwent concomitant LAAO. After six months of OAC, aspirin was continued. Transesophageal echocardiogram was done three monthly till one year and yearly thereafter. The patient demographics, procedural details, post-procedural follow-up were analyzed.

**Results:** Nine patients aged  $51.5 \pm 6.3$  years with AF underwent LAAO concomitantly with balloon mitral valvotomy in four patients, atrial septal defect device closure in four and periprosthetic mitral leak closure in one patient. Six patients had heart failure, four had prior embolic events, and two had documented LAA thrombus. The mean CHADS<sub>2</sub>VASc score was  $2.44 \pm 0.8$  and mean HASBLED score was  $3.0 \pm 0.8$ . Devices included Amplatzer Cardiac Plug™ in six patients, Lambre™ Lifetech device in two and Watchman™ device in one. All procedures were successful without acute complications. A patient developed pericardial effusion at six months requiring pericardiocentesis. Early device-associated thrombus in one patient resolved after OAC for six months. No embolic events occurred on follow-up.

**Conclusion:** On a detailed literature search, this largest LAAO experience in structural heart diseases indicates its utility. OAC for six months followed by aspirin seems to prevent thrombus formation in these patients. The only incidence of early thrombus formation indicates immunity from clot formation after device endothelialisation. Larger multicenter trials combining LAAO with structural interventions in valvular AF are warranted in developing nations.

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## 1. Introduction

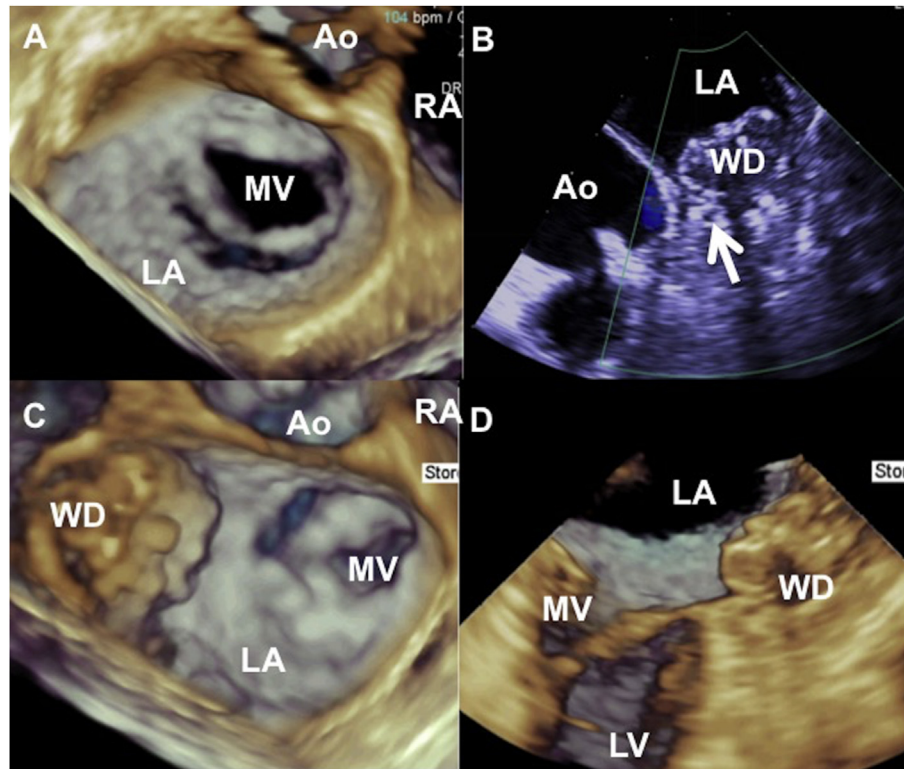
The annual risk of cardioembolic stroke in untreated patients with Atrial fibrillation (AF) and structural heart diseases is 5%.<sup>1</sup> Rhythm or rate control strategy do not mitigate the risk of stroke.<sup>2</sup> Oral anticoagulation (OAC) has its demerits and some patients are not eligible for long-term anticoagulation. As clots in non-valvular AF originate in left atrial appendage (LAA), its closure offers a solution.<sup>3</sup> Despite higher embolic risks in valvular AF, trials exclude them as clots might extend beyond LAA.<sup>4</sup> Being a common problem, LAA occlusion (LAAO) in structural heart disease deserves a clinical

trial of feasibility and safety to prevent thrombus formation within left atrium.

Catheter interventions are increasingly adopted in patients with various structural heart diseases as a preferred alternative to surgery.<sup>5</sup> If these patients have additional AF, LAAO can be combined as a concomitant procedure with these structural interventions thereby simplifying the additional procedural steps associated with LAA closure. Even though LAAO in structural heart diseases is unconventional, a close follow-up of this cohort of patients will throw light on the potential use of this therapy.

\* Corresponding author. Head of Department of Pediatric Cardiology, Institute of Cardio Vascular Diseases, Madras Medical Mission, 4A, Dr J J Nagar, Mogappair, Chennai, 600037, India.

E-mail address: [drkumarsiva@hotmail.com](mailto:drkumarsiva@hotmail.com) (K. Sivakumar).



**Fig. 1.** Mitral stenosis. Left atrial (LA) enface view(A) from three dimensional transesophageal echocardiogram demonstrates adequate mitral valve (MV) opening after balloon valvotomy. Complete seal of the left atrial appendage without any residual color flows with a Watchman device (WD) is shown on two dimensional color Doppler echocardiography(B) and three dimensional enface view(C). A cropped view of the three dimensional echocardiogram(D) shows the entire left ventricular inflow with the device and open mitral valve. (Ao-Aorta; LV-left ventricle; RA-right atrium).

## 2. METHODS

### 2.1. Inclusions and exclusions

Patients who have permanent or paroxysmal AF in association with any structural heart disease amenable for a catheter intervention were included in this study. In mitral interventions, LAAO was performed after balloon mitral valvotomy or bioprosthetic para-valvar leak closure before exiting the septal puncture. In atrial septal defects, LAAO preceded the device closure. Any patient with mechanical valve prosthesis was excluded. Thrombus within the LAA was an exclusion.

### 2.2. Risk stratification

The risk of cardioembolic stroke in patients with valvular AF is predicted by Valvular CHA<sub>2</sub>DS<sub>2</sub>-VASc [Valvular disease, Congestive heart failure, Hypertension, Age  $\geq$ 75 years (doubled score), Diabetes mellitus, prior Stroke or TIA or thromboembolism (doubled score), Vascular disease, Age 65–74 years and Sex] score of 2 or greater.<sup>6</sup> Risk of bleeding with OAC is predicted by a HASBLED [Hypertension, Abnormal liver and renal function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly age over 65 years and Drugs or alcohol intake] score of 2 or greater.<sup>7</sup>

### 2.3. Informed consent

All patients consented after getting informed about (i) alternative option of monitored life-long OAC, (ii) possibilities of thrombus formation outside LAA and (iii) lack of protection in such locations

with LAAO. Institutional ethical committee approved this study after ensuring a meticulous transesophageal echocardiographic surveillance for detection of left atrial thrombus.

### 2.4. Clinical parameters

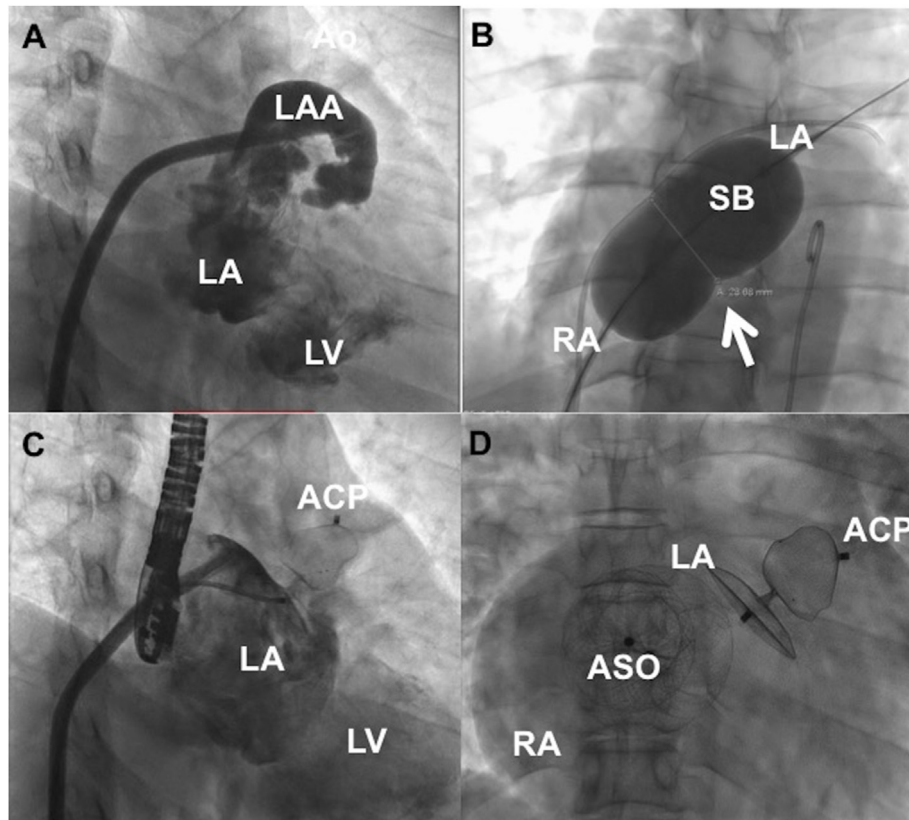
A history of occurrence, timing and number of thromboembolic events, previous OAC usage and their side effects, labile prothrombin time values, antiarrhythmic drugs, symptoms suggestive of heart failure and NYHA functional class, medications for heart failure and other comorbidities was obtained. Any previous echocardiographic documentation of LAA thrombus was also recorded.

### 2.5. Preprocedural echocardiogram

A transesophageal echocardiography assessed the suitability for a catheter intervention to treat the structural lesion. Imaging of LAA focused on size of the ostium, landing zone, depth, side lobes (if any), clots (if any) and spectral Doppler velocities in paroxysmal AF. These parameters guided the choice of the device and its size.

### 2.6. Procedural details

The procedure was routinely performed on local anesthesia with minimal conscious sedation. Heparinisation was done after vascular access in patients with atrial septal defects and after septal puncture in mitral interventions to maintain activated clotting time above 250 s. Transeptal puncture was made in a region marginally posterior and inferior to the conventional region of oval fossa guided by fluoroscopy.<sup>8</sup> After achieving optimal hemodynamics on balloon mitral valvotomy or mitral para-valvar leak device closure,



**Fig. 2.** Atrial septal defect device closure. Left atrial (LA) angiogram(A) through a large atrial septal defect shows a convoluted appendage (LAA). The defect measured 28 mm with a sizing balloon (SB) on a stop-flow technique. Left atrial pressure measured with another catheter did not show increase during balloon sizing. (B) Appendage was occluded(C) with an Amplatzer cardiac plug (ACP) and the atrial septal defect was occluded(D) with an Amplatzer septal occluder (ASO). (LV-left ventricle; RA-right atrium).

angiograms of the LAA were performed in right anterior oblique cranial and caudal projections to measure the depth and landing zone diameters. In patients with atrial septal defects, steps of septal puncture were circumvented. Left atrial pressures were optimized to 10–12 mmHg with intravenous fluids prior to the angiograms. A brief transesophageal echocardiogram guided LAAO.

### 2.7. Amplatzer cardiac plug

The size of the device was chosen 3–6 mm more than the landing zone measured 10 mm distal to the ostium. Achieving good separation between the lobe and disk, concave shaped disk sealing the ostium of the LAA completely, two thirds of the lobe distal to the left circumflex artery on transesophageal echocardiogram implied a satisfactory deployment.<sup>9</sup>

### 2.8. Lambre device

The size of the implant would be 4–8 mm larger than the measured LAA orifice. The distal umbrella was released into the LAA by pushing out the device from the delivery sheath. Subsequently, the sheath was withdrawn to expose the proximal cover, allowing it to expand in the left atrium and seal the LAA ostium.<sup>10</sup> A gentle tug test was performed to ensure device stability.

### 2.9. Watchman device

The Watchman device was advanced in the sheath until the marker of the device catheter matched the most distal marker on the access sheath. Retracting the sheath deployed the device (Fig. 1,

Video 1). To avoid embolism of the Watchman Device, four release PASS criteria were evaluated before release: Position, Anchor, Size and Seal.<sup>1</sup>

Supplementary video related to this article can be found at <https://doi.org/10.1016/j.ihj.2020.07.019>

### 2.10. Atrial septal defect closure

In patients with secundum atrial septal defects, once stable position of the LAA occluder is achieved, an appropriate long sheath was advanced into the left upper pulmonary vein (Fig. 2, Video 2). Atrial septal occluder devices were deployed guided by fluoroscopy and echocardiography. In patients with elevated left ventricular end-diastolic pressures beyond 25 mmHg, a fenestrated atrial septal defect occluder (FASD, Occlutech, Helsingborg, Sweden) was chosen to provide a 6–8 mm fenestration within the device.<sup>11</sup>

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### 2.11. Post-procedural follow-up

OAC was initiated after procedure to maintain an international normalized ratio of 2.0–3.0. Low dose aspirin at 75–150 mg was also given daily. Routine pre-discharge echocardiogram assessed stability of the LAA device and outcome of the structural intervention. Follow-up transesophageal echocardiogram was done at three monthly intervals till one year and yearly thereafter. The OAC was discontinued after six months if there was no evidence of thrombus on the device.

**Table 1**  
Patient clinical characteristics.

Age/ Sex	Diagnosis	Concurrent procedure	LV EF	PAH	RV function	CHADSVASc score	HASBLED score	Previous LAA thrombus	Previous thrombo embolism	LAA ostium/ landing zone (mm)	Device make and size (mm)	Device resizing	Fluoroscopy (minutes)	Follow-up (month)
1 66/ M	Mitral PVL	PVL closure with 8 mm VSDO	60% Mild		Normal	2	3	No	No	22/24	ACP 28	No	23.5	42
2 52/F	RHD MS	Inoue BMV, 25 mm	48% No		Normal	3	4	Yes	Cerebral embolism	18/17	Lambre 18/20	No	9.0	33
3 43/F	RHD MS	Inoue BMV 24 mm	47% Moderate		Mild	3	4	No	No	24/22	Watchman 27	Upsized	14.1	22
4 47/F	RHD MS	Inoue BMV, 25 mm	63% Mild		Normal	2	3	Yes	Peripheral and cerebral embolism	30/28	Lambre 32/36	No	10.5	39
5 37/ M	RHD MS	Inoue BMV, 26 mm	60% Mild		Normal	2	2	No	No	23/22	ACP 26	No	17.4	65
6 50/ M	23 mm ASD	30 mm Occlutech ASD occluder	63% No		Normal	3	3	No	Cerebral embolism	19/18	ACP 20	Downsized	27.4	16
7 67/F	36 mm ASD, Heart failure	40 mm Occlutech Fenestrated ASD occluder	58% Moderate		Moderate	4	4	No	No	23/22	ACP 26	No	27.5	14
8 57/F	29 mm ASD	34 mm Amplatzer septal occluder	62% Mild		Normal	2	2	No	No	22/20	ACP 24	No	14.4	39
9 45/F	32 mm ASD	36 mm Amplatzer septal occluder	56% Mild		Normal	1	2	No	No	29/27	ACP 30	No	58.3	28

ACP-Amplatzer cardiac plug; ASD-secondum atrial septal defect; BMV-balloon mitral valvotomy; CHADSVASc, HASBLED-Acronyms (see text); EF-ejection fraction; LAA-left atrial appendage; LV-left ventricle; MS-mitral stenosis; PVL-paravalvular leak; RHD-rheumatic heart disease; RV-right ventricle; VSDO-muscular ventricular septal defect occluder.

### 3. Results

Nine patients (five females) aged  $51.5 \pm 6.3$  years underwent structural interventions and LAAO in a single institution between July 2014 and October 2018 (Table 1). Six patients had heart failure despite medications, three patients had previous embolic stroke, one had previous peripheral embolism. Two patients had previous documented LAA thrombus. All except one patient had permanent AF lasting more than one year. The other risk factors included hypertension in one patient, past history of bleeding in two patients, labile prothrombin time in two, liver disease in one and advanced renal disease in two patients. The mean CHADSVASc score of our cohort was  $2.44 \pm 0.86$  and mean HASBLED score was  $3.0 \pm 0.88$ .

#### 3.1. LAA occlusion

Amplatzer cardiac plug was used in 6 patients, LAmbré™ Life-tech device in 2 patients and Watchman device in 1 patient. Procedural success was 100% without complications in all the patients where there was an intention to deploy a device to occlude the LAA. There were no patients where LAAO was not performed due to non-availability of appropriate sized device or inability to deploy the device within the LAA. Three patients needed either up or down sizing of the devices.

#### 3.2. Atrial septal defect closure

Four patients with secundum atrial septal defects aged  $54.75 \pm 8.1$  years underwent device closure along with LAAO. The mean defect size was  $30 \pm 4.6$  mm. One patient with ventricular dysfunction had fenestrated device closure was done with FASD 40/8 device (Fig. 3, Video 3). Amplatzer cardiac plug was used in all the 4 patients. Two patients were successfully electrically cardioverted and others remained in permanent AF.

Supplementary video related to this article can be found at <https://doi.org/10.1016/j.ihj.2020.07.019>

#### 3.3. Rheumatic mitral stenosis

Four patients with severe mitral stenosis aged  $49 \pm 8.6$  years presented with mitral stenosis. Two patients had renal failure, one had peripheral embolism, one had cerebrovascular accident, one had a prior balloon mitral valvotomy 7 years earlier. The valve area improved to more than  $1.5\text{sq.cm}$  and the mean transmitral gradient reduced to less than  $5\text{ mmHg}$  in all patients. LAAO was done with Amplatzer cardiac plug in one patient, LAmbré device in two and Watchman device in one patient.

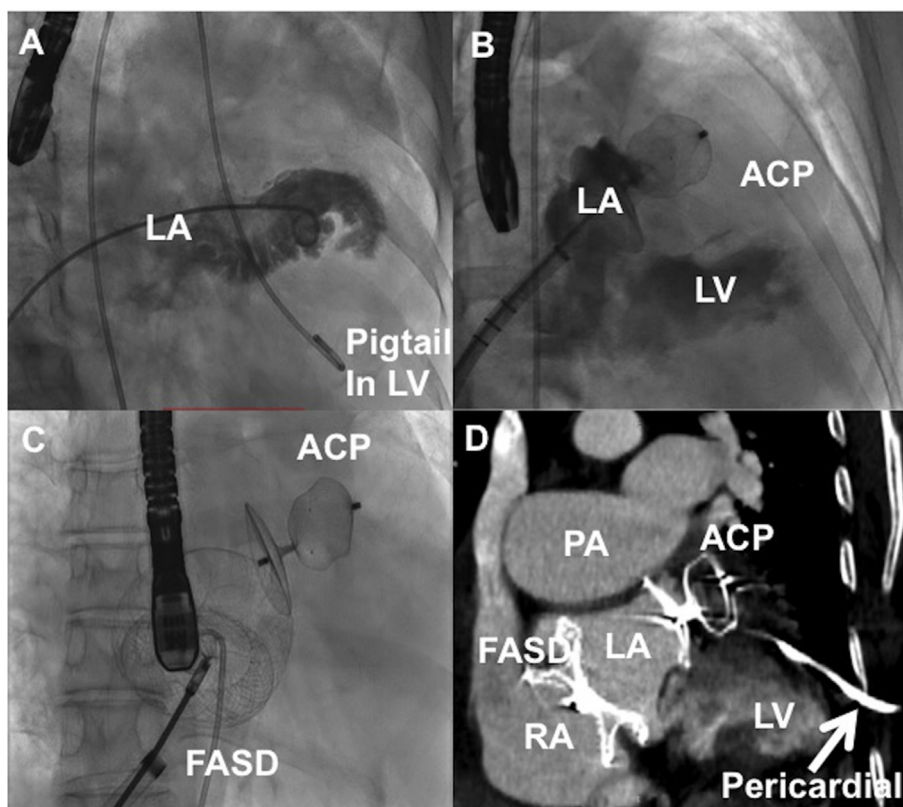
#### 3.4. Mitral periprosthetic leak

A 63-year-old patient with a 8 mm mitral bioprosthetic para-valvular leak had transapical closure with a 8 mm Amplatzer muscular ventricular septal occluder device. The LAA was occluded with Amplatzer cardiac plug. Finally the percutaneous transapical access was closed with a duct occluder device (Fig. 4, Video 4).

Supplementary video related to this article can be found at <https://doi.org/10.1016/j.ihj.2020.07.019>

#### 3.5. Follow-up

The median follow-up duration was 2.8 years, ranged 1.2–5.5 years. No patients were lost to follow-up. One patient with mitral stenosis with advanced renal failure, recurrent hemoptysis, labile prothrombin time was identified to have a small thrombus on the surface of the device at one-month follow-up. Increased OAC dose



**Fig. 3.** Fenestrated Atrial septal defect device closure. Left atrial (LA) pigtail angiogram in an elderly female with secundum atrial septal defect delineates (A) a long lobulated atrial appendage, which was closed (B) by an Amplatzer cardiac plug (ACP). Occlutech fenestrated occluder device (FASD) closed the atrial septal defect (C) due to elevated left ventricular end-diastolic pressures. When a recurrence of atrial fibrillation and heart failure after six months led to occurrence of pericardial effusion drained by a percutaneous pericardiocentesis through left intercostal space below the apex (shown as arrow), a computed tomogram (D) excluded erosion as a reason for the effusion. (PA-Pulmonary artery; LV-left ventricle; RA-right atrium).

resulted in dissolution of the thrombus at six-month follow-up. There was no further thrombus on a 22-month follow-up. One patient aged 60 years with paroxysmal AF, heart failure, ventricular dysfunction treated with fenestrated 40 mm atrial septal defect occluder device had a paroxysm of fast AF with recurrence of heart failure and moderate serous pericardial effusion. She was treated with pericardiocentesis. Contrast computed tomography excluded possibility of device erosion (Fig. 3). She remained stable at 14 months of follow-up. There was no delayed detection of thrombus in the nine patients. At the time of last follow-up, two patients were in sinus rhythm and others in permanent AF.

#### 4. Discussion

##### 4.1. Valvar AF

Valvar AF in the setting of mitral stenosis carries a much higher risk of LAA thrombus and embolic events compared to non valvar AF and the thrombus sometimes extends beyond the LAA.<sup>12,13</sup> Surgical LAA closure with concurrent valvular surgery has shown varied results.<sup>14,15</sup> The lack of demonstrable improvement in outcome on combining surgical LAA exclusion with valve surgery can be explained by (i) additional surgical time adding to the morbidity, (ii) pro-coagulant state after cardiopulmonary bypass and (iii) incomplete exclusion during surgical stapling.<sup>16,17</sup> So patients with AF undergoing cardiac surgery are only given a Class IIB recommendation for LAA exclusion.<sup>18</sup>

Catheter interventions on mitral valve have evolved over the years to achieve results comparable to surgery. Contrary to surgery,

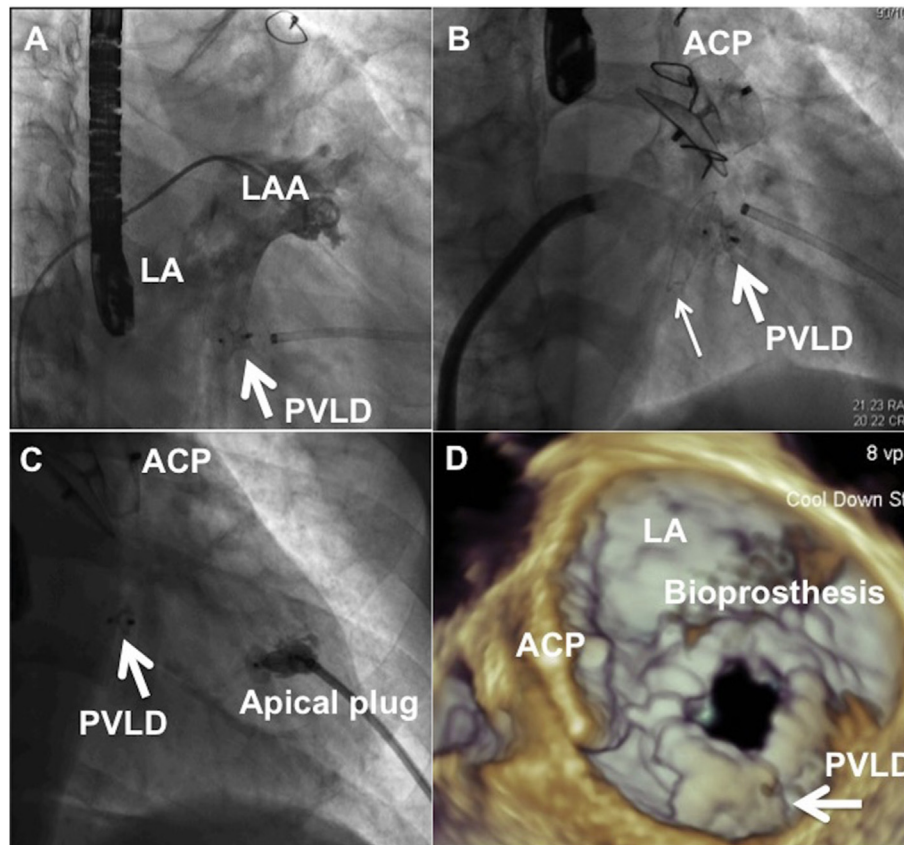
transcatheter LAAO may take very minimal additional time and is often complete. In our cohort, the additional fluoroscopic time was less than 15 min for LAAO. Concurrent LAAO has been shown on isolated single reports to be a safe and feasible strategy when combined with balloon valvotomy or Mitraclip (Abbott, Plymouth, MN) repairs.<sup>19–22</sup> Our cohort of five patients with rheumatic mitral valve disease is the only largest study available in literature currently.

##### 4.2. Superiority of LAAO on long-term follow-up

Early studies with LAAO showed non-inferiority to OAC in the first years of follow-up. The lack of proof of superiority was due to 5–8% of periprocedural complications.<sup>3</sup> When the follow-up continued beyond five years, complete endothelialisation of the device prevented further thrombus formation resulting in superiority of LAAO compared to OAC.<sup>22,23</sup> A similar longer meticulous follow-up is indicated in patients with structural heart diseases following LAAO to see the utility of this strategy in valvar AF, where the risk of thrombus is higher than in non valvar AF.

##### 4.3. Justification for an invasive strategy

Eight of the nine patients had a CHADsvASc higher than 2.0 indicating a higher propensity for thromboembolism necessitating chronic OAC.<sup>6</sup> The only patient with a score of 1.0 had recurrent paroxysms of AF, increasing her risk. The HASBLED score of  $3.0 \pm 0.88$  justified a strategy to avoid chronic OAC.<sup>7</sup> The choice between the three different occluders used in the study varied



**Fig. 4.** Mitral periprostheses leak. Following closure of a paravalvar leak around a mitral bioprosthesis using a muscular ventricular septal occluder (PVLD) through a percutaneous transapical access(A), left atrial appendage (LAA) injection defined its dimensions. The appendage was occluded with an Amplatzer cardiac plug (ACP). (B) The apical puncture was closed with a vascular plug (Apical plug). (C) Six months later, three dimensional transesophageal left atrial (LA) enface view(D) shows both the devices in stable position.

dependent on the time of regulatory approval of each device, product sizes more than 30 mm and availability. Even though the small patient numbers did not permit a comparison between the devices, the principal aim was to test LAAO in patients with structural heart diseases.

#### 4.4. Choice of OAC and duration of therapy

The nine patients could not receive Non-Vitamin K antagonist OAC due to various reasons including non-affordability, intolerance or unacceptability in mitral valve diseases. Recommendations for aspirin therapy for six months following device closure of secundum atrial septal defects using nitinol septal occluders is based on endothelialisation of the device within the period.<sup>5</sup> Small nitinol occluder devices get endothelialized early in animal studies.<sup>29</sup> As the largest device used in our study had a disc diameter of 36 mm comparable to a left atrial disc of a small 12 mm atrial septal occluder, we assumed a complete endothelialisation of the device at six months and switched them to aspirin therapy. All patients had serial transesophageal echocardiography on follow-up that excluded thrombus formation on the device.

#### 4.5. Atrial septal defects with AF

Atrial septal defects in elderly are frequently associated with atrial arrhythmia and they carry a higher risk of cardioembolic stroke.<sup>24</sup> Sporadic reports have established the safety and feasibility of LAAO along with device closure of atrial septal defect in few patients, but in these studies, the two procedures were done either

simultaneously or sequentially in two sittings.<sup>25,26</sup> Our report is the largest in literature to perform both interventions simultaneously in single sitting. This strategy prevented device related thrombus, embolism and major bleeding in our study as well as other studies.<sup>26</sup> Attempts are made to prophylactically close the LAA in patients undergoing atrial septal defect closures even without any past history of AF in anticipation of future occurrence of an arrhythmia in older age.<sup>27,28</sup>

#### 4.6. Limitations

Even though our study had more number of patients compared to previous isolated reports of LAAO in structural heart diseases, the study cohort was small. It could be argued that valvar AF might develop thrombus outside LAA and a longer follow-up would throw more light. Recurrence of mitral stenosis following balloon valvotomy and degeneration of mitral bioprosthesis could alter hemodynamics in future that could impact clot formation. In spite of these arguments, a total endothelialization of device could effectively close off the LAA thereby taking away the prime originator of thrombus in these patients, leading to reduced incidence of strokes. A longer and larger multicenter study is warranted to test this hypothesis.

#### 5. Conclusions

On a detailed literature search, our series of nine patients is the largest study to report LAAO as a concurrent procedure during structural interventions. While justifying primary LAA closure

compared to OAC in valvar AF is highly contentious, closing LAA concurrently in patients who need mitral or interatrial septal interventions adds very little to the procedural complexity. The lack of appearance of thrombus on the device surface or in other parts of the left atrium on follow-up possibly indicates a reduction of thrombogenicity after endothelialisation of the device, despite withdrawal of OAC after six months and continuing low dose aspirin therapy. A larger multicenter study with longer periods of follow-up could show the safety of the approach. Considering the burden of structural heart disease with AF, LAA closure may serve as a superior tool to OAC on a longer follow-up as endothelialisation of the device gets complete.

## 6. Impact on daily practice

When left atrial appendage occlusion is combined with other structural cardiac interventions in patients with atrial fibrillation, the additional procedure may prevent thrombus formation originating from the appendage. If this strategy proves to prevent cardioembolism and thrombus formation on longer periods of follow-up, a large number of patients with structural heart disease and valvar atrial fibrillation may be benefited by this concomitant procedure.

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None.

### Declaration of competing interest

All authors have none to declare.

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