

# Left atrial appendage closure for “primary primary” prevention during percutaneous closure of septal defects in patients with large atria but no atrial fibrillation

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## Abstract

**Background:** Percutaneous atrial septal defect (ASD) closure is a routine procedure to prevent right ventricular failure, pulmonary hypertension, or paradoxical embolism. The latter is the typical reason for percutaneous patent foramen ovale (PFO) closure. Atrial enlargement represents a risk for developing atrial fibrillation (AF). Percutaneous left atrial appendage (LAA) closure is emerging as a preventive therapy for patients in AF who suffered from a previous stroke or bleeding (secondary prevention) or patients without previous stroke or bleeding (primary prevention). Percutaneous septal closure, particularly that of large ASDs, may inhibit future percutaneous left atrial access when required for LAA closure. Reported herein is the feasibility and safety of concomitant percutaneous closure of the LAA and a septal shunt, mostly large ASDs, in patients without AF, in the sense of “primary primary” preventive LAA closure. The first “primary” relates to “in anticipation of AF” and potentially also for “for prevention of AF”. The second “primary” relates to “prevention of stroke or bleeding”.

**Methods:** Thirteen consecutive patients, older than 40 years without any clinical or electrocardiographic evidence of AF, underwent percutaneous closure of large ASDs or PFOs in the presence of enlarged atria at the university hospitals of Bern and Zurich between April 2013 and June 2015. They concomitantly received “primary primary” preventive LAA closure after informed consent.

**Results** Mean patient age was  $58 \pm 9$  years (46% male). Procedural success was achieved in all patients and no major adverse events occurred acutely or during the following  $2.0 \pm 0.8$  years. No patient developed AF.

**Conclusions:** Concomitant closure of ASD or PFO in the presence of enlarged atria and LAA for “primary primary” prevention appears feasible and safe but has yet to prove its justification. (Cardiol J 2018; 25, 2: 179–187)

**Key words:** atrial fibrillation, atrial septal defect closure, patent foramen ovale closure, left atrial appendage closure

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## Introduction

Atrial septal defect (ASD) is one of the most frequent congenital heart defects [1]. While the only risk of small ASDs is paradoxical embolism, sequelae of larger ASDs comprise pulmonary hypertension, congestive heart failure, and atrial arrhythmia, in particular atrial fibrillation (AF) [2–5]. Percutaneous ASD closure is the treatment of choice for ASDs to prevent such adverse outcome and to improve exertional dyspnea [6–8]. Percutaneous ASD closure is an overall safe procedure but it carries a potential risk for developing AF by device irritation of the septum [9–11]. Although such new onset AF typically occurs only in the first few weeks after device implantation [9, 12], patients undergoing percutaneous closure of large ASDs are temporarily at a double risk for developing AF, 1) due to septal device irritation and 2) due to the preexisting atrial enlargement. Subsequent reduction of atrial diameters after shunt elimination reduces the risk for AF. A net benefit in that respect can be expected but the overall risk for AF of such patients remains elevated. The situation is similar for patients with a patent foramen ovale (PFO) and enlarged atria.

In AF, left atrial appendage (LAA) closure has emerged as an alternative to medical therapy in the form of chronic oral anticoagulation (COA) for stroke or bleeding prevention. While closure of the LAA comes at the price of 2–7% procedural adverse events, it shows a significant reduction in major bleeding events at a similar stroke rate compared to COA [13–16]. After 4 years of follow-up, closure of the LAA even showed significantly improved survival in randomized comparisons [17, 18].

Closure of the LAA so far has been exclusively performed in patients with documented AF, either for primary prevention (patients with AF without previous embolic ischemic event or bleeding) or secondary prevention (patients with AF with a previous embolic ischemic event or bleeding).

Percutaneous closure of septal defects, particularly large ASDs, hinders future percutaneous transseptal left atrial access although it remains possible at least in the case of smaller ASD [19] or PFO devices [20]. Even if such patients never had AF, their risk for developing AF during follow-up is 2-fold higher after ASD closure than that of the general population [21] and also increased after PFO closure in the presence of enlarged atria.

Herein reported is the first experience with concomitant percutaneous closure of LAA at the time of closure of ASDs or PFOs in the presence

of enlarged atria in patients without history of AF. They were considered at increased risk for later AF, particularly in the initial phase after septal shunt closure due to septal device irritation while atrial dimensions have not yet shrunk after volume un-load. It is referred to in this procedure as “primary primary” preventive LAA closure, i.e., LAA closure for primary prevention (in anticipation of AF or even preventing AF) and for primary prevention of stroke or bleeding, should AF occur.

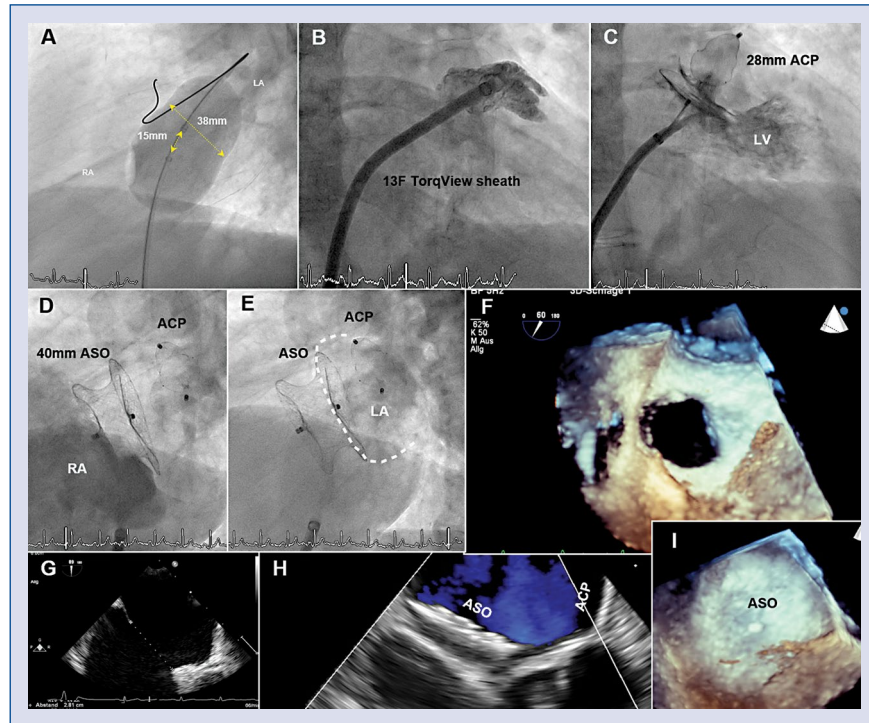
## Methods

### Population

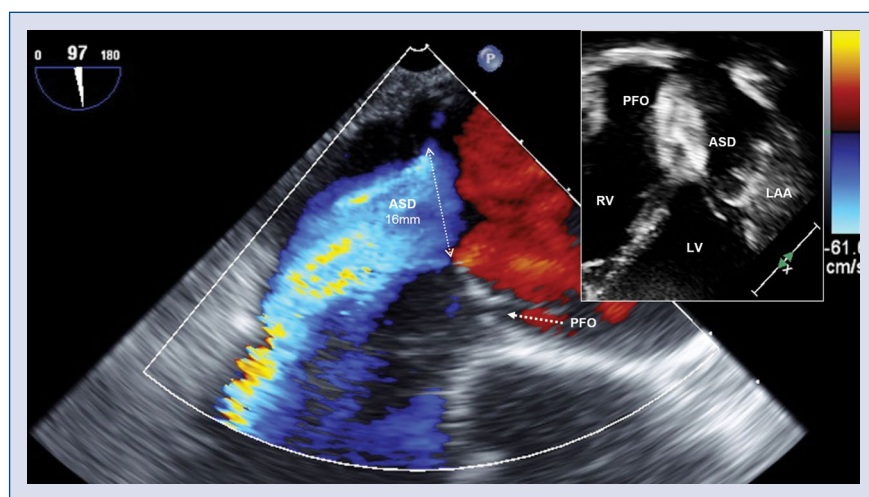
This is a retrospective study of consecutive patients ( $\geq 40$  years) undergoing percutaneous closure of a large ASD ( $\geq 20$  mm) or a PFO with large atria (left atrium [LA]  $\geq 40$  mm, parasternal long axis) and at the same time of the LAA. Patients neither had clinical or electrocardiographic signs of prior AF nor an AF associated embolic ischemic or bleeding event. In the patients with prior ischemic events, AF had been excluded by long-term electrocardiogram (ECG). Patients consented to both procedures (ASD closure and LAA closure) separately and also to data collection. The potential benefits and risks of “primary primary” preventive LAA closure was discussed extensively with the patients. The local institutional review boards approved data collection of clinically indicated investigations during follow-up. The procedures were performed at the university hospitals of Bern and Zurich. Demographic and clinical characteristics, including risk for stroke and major bleeding (CHA<sub>2</sub>DS<sub>2</sub>-VASc score, HAS-BLED score), procedural data, and outcome data of in-hospital and follow-up periods were captured from medical records and patient contact.

### Procedure

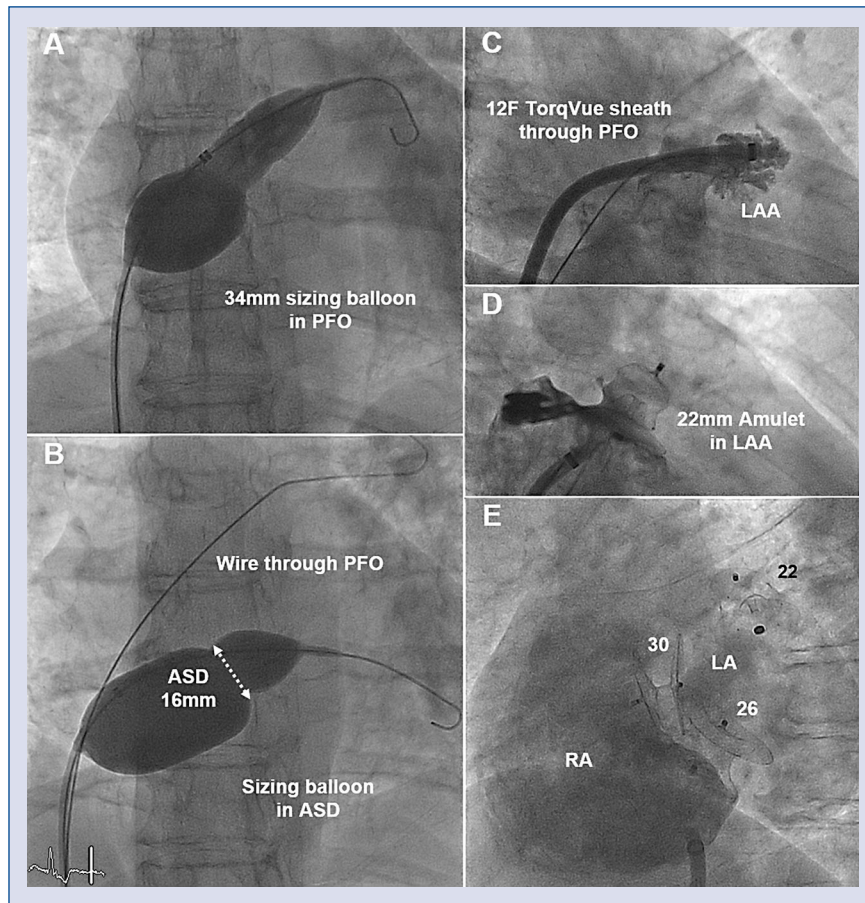
All procedures were performed under fluoroscopy guidance without echocardiography [15, 22, 23]. All patients had had transesophageal echocardiography (TEE) during their workups. Computer tomography was not used. Oral antibiotics (2–3 doses) were given before and after the procedure and all patients received 5000 units of intravenous heparin at the beginning of the procedure. All procedures were done using Amplatzer devices (Amplatzer Cardiac Plug (ACP), Amplatzer Amulet Occluder, Amplatzer Septal Occluder (ASO), Amplatzer Cribriform Occluder, or Amplatzer PFO Occluder, Abbott, St. Paul, MN, USA). Figures 1–4 provide examples. LAA closure



**Figure 1.** Simultaneous closure of the left atrial appendage (LAA) and an atrial septal defect (ASD) in a 55-year-old male with exertional dyspnea and a newly detected large ASD secundum but no history of atrial fibrillation. **A.** Overinflated 34 mm Amplatzer sizing balloon in ASD, measuring 38 mm at the waist representing the ASD; **B.** Contrast medium injection into the LAA through a 13 French (F) TorqView sheath in a right anterior oblique projection; **C.** Implantation of a 28 mm Amplatzer Cardiac Plug (ACP) through this sheath; **D.** Implantation of a 40 mm Amplatzer Septal Occluder (ASO) through the same sheath in a left anterior oblique projection. The right atrium (RA) is filled with contrast medium; **E.** Same view during the levophase with the left atrium (LA) delineated (dotted line) by contrast medium; **F.** Three-dimensional (3D) transesophageal echocardiography (TEE) before the procedure depicting the ASD; **G.** Two-dimensional (2D) TEE before the procedure indicating an ASD diameter of 28 mm; **H.** 2D TEE at 11-month follow-up depicting the ASD and LAA occluders; **I.** 3D TEE at 11-month follow-up. The ASO occludes the ASD completely without evidence of thrombus.



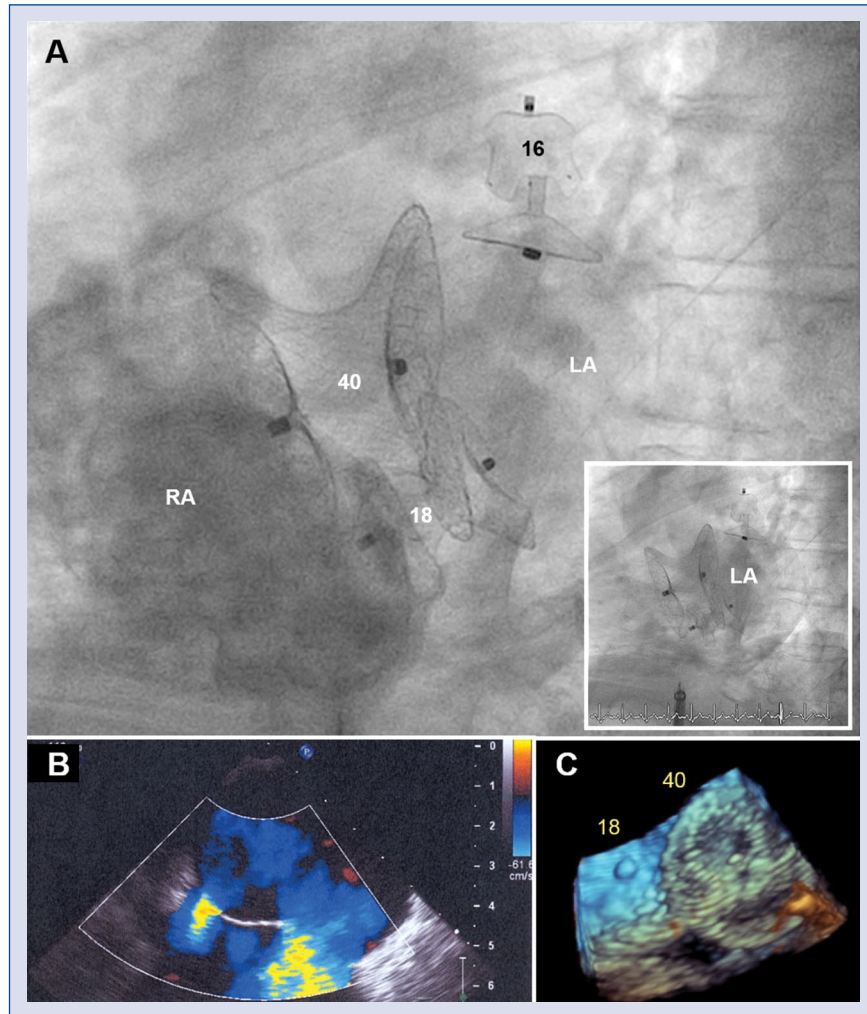
**Figure 2.** Transesophageal echocardiography of a 53-year-old woman with exertional dyspnea and chest pain and a newly detected secundum atrial septal defect (ASD) as well as a patent foramen ovale (PFO) but no history of atrial fibrillation. The coronary arteries were normal on the incidental angiogram. The insert shows the result after simultaneous device closure of ASD (26 mm Amplatzer Septal Occluder), PFO (30 mm Amplatzer Cribriform Occluder), and left atrial appendage (LAA, 22 mm Amplatzer Amulet) Occluder; LV — left ventricle; RV — right ventricle.



**Figure 3.** Simultaneous closure of patent foramen ovale (PFO), atrial septal defect (ASD), and left atrial appendage (LAA) in patient of Figure 2; **A.** Sizing balloon in PFO; **B.** Sizing balloon in ASD, wire through PFO; **C.** Contrast medium injection into LAA through 12 French (F) TorqVue sheath in a right anterior oblique projection; **D.** LAA occluded (with 22 mm Amplatzer Amulet Occluder); **E.** Final result: LAA occluded with 22 mm Amplatzer Amulet Occluder (22), then PFO occluded with 30 mm Amplatzer Cribriform Occluder (30), and finally ASD occluded with 26 mm Amplatzer Septal Occluder (26). Left anterior oblique projection; LA — left atrium; RA — right atrium.

was performed before septal closure. After crossing the septal defect from the right femoral vein, a 0.035" Backup wire (Boston Scientific, Natick, MA, USA) was placed in the LA. A 34 mm Amplatzer sizing balloon was placed across ASDs and inflated to aid eyeball sizing of the defect. The balloon was removed. Over the Backup wire, the 14 French (F) 45° × 45° Amplatzer TorqVue delivery sheath was introduced. The LAA was engaged in a right anterior oblique (RAO) view and contrast injections were performed in RAO caudal and cranial views. Sizing was done by eyeballing the outer diameter of the delivery sheath (12 F: 4.5 mm, 13 F: 5.0 mm, and 14 F: 5.5 mm) served as reference. About 20–50% oversizing was the rule [15]. Stability of the device was assessed by a tug test and by angiographic imaging with contrast medium injections in 2 views showing the device in profile without

overlap of the 2 device components. After release of the LAA occluder, the TorqVue sheath was left in the LA and the appropriately sized septal occluder (aiming for at least 30% oversizing in ASDs) was attached to the same delivery cable and introduced through the sheath. In case of ASDs, the left atrial disc was fully and the right atrial disc partially deployed in the LA. This technique forces the ASO to self-center in the defect. The pulling of the right disc trough, the defect was observed based on the migrating of the lower device indentation in a left anterior oblique (LAO) projection before the right atrial disc was fully deployed. Correct device position was confirmed by LAO contrast medium injections and a robust wiggle of the device. The sheath was removed and the puncture site was manually compressed by the patient unless a simultaneous arterial puncture mandated compression



**Figure 4.** Simultaneous closure of the left atrial appendage (LAA) and a newly detected double atrial septal defect (ASD) in a 64-year-old male with dyspnea but no atrial fibrillation. All devices were implanted through the same 14 French TorqVue sheath; **A.** 40 mm Amplatzer Septal Occluder (ASO, 40), 18 mm ASO (18), and 16 mm Amplatzer Amulet Occluder (16) depicted in a left anterior oblique projection. The right atrium (RA) and in the insert the left atrium (LA) are filled with contrast medium; **B.** Double ASD in a transesophageal echocardiography (TEE) before the intervention; **C.** Double ASD in a three-dimensional TEE 4 months after the intervention with the two ASOs in place.

by a medical person. Before discharge the same or the following day, transthoracic echocardiography was performed to assure the correct position of the devices and to exclude pericardial effusion. There were no recommendations for physical restrictions of any sort.

Post interventional antithrombotic regimen comprised clopidogrel 75 mg for 1–3 months and acetylsalicylic acid 100 mg for 5–6 months. Control TEE was recommended after 3–6 months to assess for device thrombi and residual shunts or leaks.

### Outcome

The composite endpoint was defined according to Valve Academic Research Consortium (VARC)-2

criteria [24]. The primary safety endpoint was defined as death related to closure of the LAA, procedure-related ischemic stroke, hemorrhagic stroke, cardiac tamponade, need for urgent surgery (e.g., due to embolization of the device, repair of procedure-related injury, or bleeding) and major or life-threatening bleeding (according to VARC-2 criteria). The primary efficacy endpoint was defined as stroke (non-disabling, disabling, ischemic, or hemorrhagic), systemic embolization, or cardiovascular or unexplained death. New-onset of AF was looked for clinically and by (24-h) ECG. Clinical follow-up data were obtained reviewing medical records and by contacting patients.

**Table 1.** Baseline characteristics (n = 13).

<b>Characteristics</b>	
Age [years]	58.2 ± 9.1
Body mass index [kg/m <sup>2</sup> ]	27.0 ± 4.4
Women	7 (54%)
CHADS <sub>2</sub> score	1.2 ± 1.3
CHA <sub>2</sub> DS <sub>2</sub> -VASc score	1.92 ± 1.7
HAS-BLED score	0.85 ± 1.1
<b>Atrial rhythm (including history)</b>	
Atrial fibrillation (paroxysmal or permanent)	0 (0%)
Atrial flutter	0 (0%)
<b>Clinical features</b>	
Prior ischemic stroke	3 (23%)
Coronary artery disease	0 (0%)
Valvular heart disease	0 (0%)
Renal function (mean eGFR, in mL/min/1.73 m <sup>2</sup> )	97 ± 24
<b>Anti-thrombotic therapy prior to laac</b>	
Acetylsalicylic acid	3 (23%)
Platelet inhibitors other than acetylsalicylic acid	0 (0%)
Chronic oral anticoagulation	0 (0%)
<b>Echocardiographic data</b>	
Systolic left ventricular ejection fraction [%]	65 ± 2
Left atrial diameter (PLAX echo, mm)	42 ± 5

Values are number (%) or mean ± standard deviation; eGFR — estimated glomerular filtration rate; PLAX — parasternal long axis

**Table 2.** Intervention (n = 13).

<b>Procedural characteristics</b>	
Fluoroscopy time [min]	16 ± 8
Amplatzer Cardiac Plug	6 (20 ± 3, 16–24 mm)
Amplatzer Amulet Occluder	7 (21 ± 4, 16–25 mm)
Amplatzer Septal Occluder	10 (34 ± 6, 24–40 mm)
Amplatzer Cribriform Occluder	1 (30 mm)
Amplatzer PFO Occluder	2 (25 mm)
Implantation attempts	1.0 ± 0.0
<b>Concomittant procedures</b>	
Coronary angiography	12 (92%)
<b>Periprocedural success and adverse events</b>	
Procedural success	13 (100%)
Combined safety endpoint*	0 (0%)

\*Composite of death, stroke, clinically relevant pericardial effusion, VARC-2 life-threatening or major bleeding, VARC-2 major access vessel complication, device embolization, VARC-2 severe kidney injury, or bailout surgery. Values are number (%) or mean ± standard deviation; PFO — patent foramen ovale; VARC — Valve Academic Research Consortium

## Statistical analysis

Data are expressed as mean and standard deviation for continuous variables and as number and percentage for categorical variables. Analysis was performed using a standard statistical software program (SPSS, version 23; IBM, Armonk, NY, USA).

## Results

### Baseline characteristics

Thirteen patients were included between April 2013 and June 2015. Patients were 58 ± 9 years old (54% women). Baseline characteristics are described in Table 1. No patient had any history of AF. Three patients had a previous history of ischemic cerebrovascular events. The total procedural fluoroscopy time was 16 ± 8 min (Table 2).

### Device success

In all patients ASD or PFO and LAA closures were successful. In 1 patient, 2 ASDs and in 1 patient, a PFO in addition to an ASD were present and closed with 2 separate devices (Figs. 2, 3). No periprocedural complications occurred (Table 2).

### Clinical follow-up

Length of hospital stay was 1 night in 9 patients and the remaining 4 patients were discharged the same day. TEE follow-up was available after 6.7 ± 2.0 months in 10 patients. No device-related complications occurred (Table 3). One patient needed a re-intervention because of 2 residual ASD shunts at follow up. Re-intervention was successfully performed under fluoroscopy only using a 25 mm and a 18 mm PFO Occluder at 6 months after initial procedure. At clinical follow-up of 2.0 ± 0.8 years, no adverse events had occurred, no patient had reached a primary safety or efficacy endpoint, and at latest contact 91% of patients were on no anticoagulant or antiplatelet medication and 9% still acetylsalicylic acid (Table 4). The patients were asked for clinical symptoms of AF and all postinterventional ECGs were screened for AF. No patient had developed AF.

## Discussion

Atrial fibrillation is the most common sustained cardiac arrhythmia [25] and is associated with substantial mortality and morbidity, particularly due to stroke [26]. ASD closure is advocated for prevention of stroke (paradoxical or secondary to AF) or heart failure due to volume overload. PFO closure is used for prevention of paradoxical

**Table 3.** Postprocedural data and follow-up transesophageal echocardiography (TEE).

<b>Post procedure in-hospital (n = 13)</b>	
Hospital stay [days]	0.8 ± 0.4
Same day discharge	4 (31%)
Pericardial effusion	0 (0%)
<b>Antithrombotic therapy (n = 13)</b>	
Acetylsalicylic acid	12 (92%)
Platelet inhibitors other than acetylsalicylic acid	12 (92%)
Dual antiplatelet therapy	12 (92%)
Vitamin K antagonists	0 (0%)
Non vitamin K dependant oral anticoagulants	0 (0%)
<b>TEE (n = 10)</b>	
Duration from intervention [months]	6.7 ± 2.0
All devices in correct position	10 (100%)
Late pericardial effusion	0 (0%)
Late device embolization	0 (0%)
Device thrombus (any)	0 (0%)
Procedural success at TEE follow-up	8 (100%)
Shunt or leak > 5 mm	1 (10%)
Shunt or leak < 5 mm	2 (20%)

Values are number (%) or mean ± standard deviation.

**Table 4.** Clinical follow-up (n = 13).

<b>Long-term clinical follow-up</b>	13 (100%)
Duration from procedure [years]	2.0 ± 0.8
<b>Antithrombotic therapy</b>	
Acetylsalicylic acid	1 (9%)
Other platelet inhibitors	0 (0%)
Dual antiplatelet therapy	0 (0%)
Vitamin K antagonists	0 (0%)
Non vitamin K dependant oral anticoagulants	0 (0%)
<b>Clinical outcome</b>	
All-cause death	0 (0%)
All-cause stroke	0 (0%)
All-cause transient ischemic attack	0 (0%)
Myocardial infarction	0 (0%)
Systemic embolism	0 (0%)
Venous thrombosis/ /pulmonary embolism	0 (0%)
Fatal, lifethreatening, or major bleeding	0 (0%)
Hospitalization	0 (0%)
Primary safety endpoint	0 (0%)
Primary efficacy endpoint	0 (0%)

Values are number (%) or mean ± standard deviation.

stroke. LAA closure is indicated for prevention of stroke or bleeding in patients with AF [13–18].

The present study reports the feasibility and safety of “primary primary” preventive LAA closure during percutaneous ASD or PFO closure in patients with enlarged atria but no AF. It proved technically successful and safe but efficacy of our approach cannot be determined. No patient developed AF and therefore the potential of preventing embolic ischemia or bleeding because of the obviated need for oral anticoagulation remains unknown.

A large nationwide study of Nyboe et al. [21] included 1168 patients with ASD who were followed-up over a long-term period. The risk of developing AF was up to 10-fold in comparison to the general population. In case of conservative management, the stroke risk was 2.6-fold. In case of ASD closure, the stroke risk was reduced to 2-fold. This can be due to both, the elimination of paradoxical embolism and the reduction of atrial sizes. Yet, the risk of AF-associated stroke remains elevated [21].

Atrial fibrillation with the need for COA is expected to occur with a certain frequency in patients at some point in time after septal defect closure while they were still in sinus rhythm [9, 27]. Age > 40 years is a well-known risk factor for AF after ASD closure [28]. Moreover, ASD closure devices can trigger new-onset AF in the early phase. In the later phase they may reduce the risk of AF as the atria shrink after elimination of the shunt [10, 11]. Large devices in the interatrial septum may render percutaneous LAA closure intricate or downright impossible.

Chronic oral anticoagulation has been proven to effectively prevent thromboembolic strokes but there is a risk of serious bleeding which deters many patients from taking this therapy [29]. Therefore, alternative treatment options for stroke prevention in patients with AF with increased stroke risk are needed. Closure of the LAA has emerged as promising [13, 30].

Left atrial appendage closure in the sense of “primary primary” prevention has the potential to avoid future strokes in case new-onset AF goes undetected on top of the potential to avoid major bleeding in case a patient requires COA for AF during follow-up. However as is inherent to every preventive intervention, the risk and cost of the combined and partially preventive intervention may become unjustified, in case AF never develops during follow-up. This concern is alleviated by the safety of such an approach which is apparent from these data.

### Limitations of the study

The study has several limitations. It is a retrospective study and not a randomized trial and therefore selection bias is evident. The sample size is small. Furthermore, none of these patients developed AF during the relatively short observation period. More patients and longer follow-up are required to derive a clinically important message.

### Conclusions

This study demonstrates feasibility of “primary primary” preventive LAA closure during percutaneous closure of large ASDs or PFOs with atrial enlargement in patients without AF. In this series no adverse safety events occurred. The idea is to prepare such patients for the likely event of later AF. ASD closure alone with a large septal device renders it difficult if not impossible to later perform a transseptal puncture for LAA closure.

**Conflict of interest:** S. Gloekler — grant from the Swiss Heart Foundation; F. Maisano — consultant for Abbott, Edwards, and Medtronic, and cofounder and shareholder of 4Tech Cardio and receiver of royalties from Edwards; B. Meier — speaker fees of Abbott; F. Nietispach — consultant for Abbott, Edwards, and Medtronic, and shareholder of Edwards.

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