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Amplatzer left atrial appendage closure: access via transseptal puncture versus patent foramen ovale or atrial septal defect

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Running title: LAAC via TSP vs PFO/ASD

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Portrait of the first author

Abstract

Aims: To compare periprocedural and late clinical outcomes of left atrial appendage closure (LAAC) with Amplatzer devices by access through transseptal puncture (TSP) versus a patent foramen ovale (PFO) or an atrial septal defect (ASD).

Methods and results: Between 2009 and 2018, 578 consecutive patients underwent LAAC via TSP or PFO/ASD access in three centers. After a 1:3 propensity score matching, 246 (TSP) vs 246 (PFO/ASD) patients were compared by use of the primary efficacy endpoint of all-cause stroke, systemic embolism and cardiovascular/unexplained death and the primary safety endpoint of major peri-procedural complications and major bleedings at follow-up. Mean age was 75.2±8.7 (TSP) vs 74.4±10.9 (PFO/ASD) years, CHA_2DS_2-VASc score 4.5±1.6 vs 4.3±1.4, and HAS-BLED score 3.3±1.0 vs 3.3±0.9. Device success (97.6% vs 97.8%, p=0.90) was similar. After 2.5±1.4 vs 2.6±1.6 years, clinical efficacy (46/603, 7.6% [TSP] vs 21/233, 9.0% [PFO/ASD], 10.3, hazard ratio (HR), 1.2; 95% confidence interval (CI), 0.69-0.85, p=0.54) and safety (24/603, 4.0% vs 11/233, 4.7%; HR, 1.4; 95% CI, 0.52-3.6, p=0.49) did not differ.

Conclusions: Use of a PFO/ASD access for LAAC with Amplatzer devices offers similar periprocedural and late clinical outcomes as TSP. Simultaneous PFO/ASD closure for an additional protective benefit does not increase risk.

Keywords Atrial fibrillation; Ischaemic Stroke; Bleeding Risk; Transeptal; LAA Closure; PFO Closure

Condensed abstract

Periprocedural and late clinical outcomes of transseptal puncture (TSP) versus patent foramen ovale (PFO) or atrial septal defect (ASD) access for left atrial appendage closure (LAAC) were compared in 246 patients with TSP matched to 91 with PFO/ASD access. After a mean follow-up of 2.5 years, the primary efficacy endpoint all-cause stroke, systemic embolism, and cardiovascular/unexplained death (46/603, 7.6% [TSP] vs 21/233, 9.0% [PFO/ASD], 10.3, HR, 1.2; 95% CI, 0.69-0.85, p=0.54) and the primary safety endpoint of all major periprocedural complications and major bleedings (24/603, 4.0% vs 11/233, 4.7%; HR, 1.4; 95% CI, 0.52-3.6, p=0.49) were similar.

Abbreviations

ACP	Amplatzer Cardiac Plug
ASD	Atrial septal defect
DRT	Device-related thrombus
LA	Left atrium
LAAC	Left atrial appendage closure
OAC	Oral anticoagulation
PFO	Patent foramen ovale
TEE	Transesophageal echocardiography
TIA	Transient ischemic attack
TSP	Transseptal puncture

Introduction

Percutaneous left atrial appendage closure (LAAC) is a validated, non-pharmacological treatment for stroke prevention in patients with non-valvular atrial fibrillation (AF) and contraindications for oral anticoagulation (OAC) [1-5]. Watchman (Boston Scientific, Marlborough, MA, US) and Amplatzer (Abbott, St Paul, MN, US) are the most commonly used systems. The latter's first- and second-generation Amplatzer Cardiac Plug (ACP) and Amulet have shown high device success, an acceptable rate of periprocedural adverse events, and a low annual rate of ischemic events in large multicenter registries [1-3]. A transseptal puncture (TSP) in an infero-posterior portion of the fossa ovalis is generally recommended for optimal implantation results. This approach facilitates coaxial alignment of the delivery sheath to the left atrial appendage (LAA) [4]. To simplify the procedure and potentially avoid TSP related complications in patients with a patent foramen ovale (PFO) or an atrial septal defect (ASD) access to the left atrium (LA) through the PFO/ASD has been practiced in selected centers for over 15 years [6]. In a first retrospective analysis, feasibility and safety of such an approach was reported in 51 patients [6]. The PFO/ASD can be closed at the end of the procedure in a matter of minutes, reloading the gear used for LAAC with a respective occluder. However, left atrial access via PFO/ASD remains shunned by most operators due to the typically more anterior or superior entrance into the LA and therefore more challenging or suboptimal positioning of the delivery sheath. The purpose of the present study was to investigate periprocedural and late clinical outcomes of TSP versus PFO/ASD access for LAAC with Amplatzer devices.

Methods

PATIENT POPULATION

A total of 578 consecutive patients underwent LAAC with the first-generation ACP and the second-generation Amplatzer Amulet between 2009 and 2015 at Coburg hospital, Germany, and Bern and Zurich university hospitals, Switzerland. Indications for LAAC were based on current guidelines and expert recommendations [4,7]. Exclusion criteria included active infection, reasons for OAC other than AF, and pregnancy. All patients gave written informed consent. Data were captured in a dedicated database according to the respective regulations of the responsible ethic committee´s. Late clinical outcomes were collected from follow-up visits, telephone calls and hospitalizations. All adverse events underwent adjudication by a clinical event committee of two independent physicians, and in case of disagreement, by a third referee.

LAAC PROCEDURE AND FOLLOW-UP

LAAC with Amplatzer occluders was previously described in detail [8]. Transesophageal echocardiography (TEE) guidance was performed depending on operator routine. Most devices were implanted conventionally via TSP, preferably in the infero-posterior portion of the fossa ovalis. In case of a known PFO/ASD, access to the LA was attained through them by some operators [6]. Most such cases were performed without TEE guidance and in their majority, PFO/ASD closure was performed at the end of the procedure. After deployment of the occluder in the LAA, the delivery sheath was kept in the LA. A properly sized Amplatzer PFO/ASD occluder (Abbott, St Paul, MN, US) was attached to the LAAC pusher cable and deployed to the PFO/ASD (**Figure 1**). Postprocedural antithrombotic therapy consisted of dual antiplatelet regimen with aspirin and clopidogrel for 1-6 months [8]. A follow-up TEE was performed in a time frame from 6 weeks to 4 months post LAAC.

DEFINITIONS AND CLINICAL ENDPOINTS

Demographic, clinical, and procedural characteristics, as well as adverse events and endpoints were assessed according to the current recommendations of the European Heart Rhythm Association (EHRA) and the Associations of Percutaneous Coronary Interventions (EAPCI) [4], the Bleeding Academic Research Consortium (BARC) [9], the Valve Academic Research Consortium criteria (VARC-2) [10], and the 2017 Cardiovascular and Stroke Endpoint Definitions for Clinical Trials [11]. Device success was defined as correct deployment of the occluder. Major periprocedural complications included death, any stroke, major bleeding, device embolization, major access vessel complication, need for cardiovascular surgery or cardiopulmonary resuscitation, cardiac tamponade, and other relevant complications leading to prolonged hospital stay. The primary efficacy endpoint was a composite of all-cause stroke, systemic embolism, and cardiovascular/unexplained death. The primary safety endpoint was a composite of major periprocedural complications and major bleeding events at follow-up.

STATISTICAL ANALYSES

Continuous variables are presented as mean±standard deviation (SD). Those were compared using the unpaired t-test. Categorical variables were presented as frequency and percentage and were compared using the Chi-square test. The Kaplan-Meier method was used for graphical assessment of time dependent events. For comparison of event curves, the log-rank (Mantel-Cox) test was used. For determination of hazard ratio, the Mantel-Haenszel method was applied. Analyses were performed using Prism, Version 7.0 (GraphPad, La Jolla, CA, USA).

A propensity score matching was performed using the R software [12]. With a caliper value of 0.05 and ratio of 3:1, there were no significant differences in the covariables among the two groups using a univariate logistic regression.

Results

STUDY POPULATION

Of 578 consecutive patients who underwent LAAC with Amplatzer devices, 462 interventions were performed via TSP access and 116 via PFO/ASD. After the 3:1 propensity score matching, a cohort of 246 patients with TSP and 91 patients with PFO/ASD access remained and showed good comparability with similar baseline characteristics (**Table 1)**. This analysis comprises a total of 836 patient-years with a mean follow-up of 2.5 ± 1.4 years (TSP) and 2.6 ± 1.6 years (PFO/ASD).

PROCEDURAL CHARACTERISTICS AND TEE FOLLOW-UP

Procedural characteristics and TEE follow-up are summarized in **Table 2**. In the PFO/ASD group, 54 of 83 (65.1%) patients received a simultaneous PFO closure, and 8 of 8 (100.0%) patients a simultaneous ASD closure. This resulted in higher amounts of contrast volume in the PFO/ASD group (158.1±87.9 [TSP] vs 191.1±79.3 ml [PFO/ASD], p=0.0021), but did not significantly prolong fluoroscopy time (14.3±9.1 vs 17.0±13.0 min, p=0.64). Overall device success was high and similar for both groups (240/246, 97.6% vs 89/91, 97.8%, p=0.90). The device contour in fluoroscopy, which reflects the degree of under- or oversizing, was determined in 138/246 (56.1%) [TSP] and 60/91 (56.9%) [PFO/ASD] patients, respectively and no difference between the groups was observed. A “tire-shape” indicates optimal compression of the lobe, and was documented in 72/138 (33.2%) [TSP] vs 27/60 (31.4%) [PFO/ASD], p=0.35, individuals. The “square-shaped” lobe, which is a sign of undersizing, occurred in 28/138 (12.9%) vs 13/60 (15.1%), p=0.83 of patients. Oversizing or deep implantation is indicated by a “strawberry” compression of the lobe. It was seen in 38/138 (17.5%) vs 20/60 (23.3%), p=0.41, cases.

Major periprocedural complications (11/246, 4.5% [TSP] vs 4/91, 4.4% [PFO/ASD], p=0.98) did not differ. The most common complication was cardiac tamponade (7/246, 2.8% vs 4/91, 4.4%, p=0.48). Three device embolizations occurred in the TSP group (1.2%) and no device embolization was observed in the PFO/ASD group.

TEE at follow-up was available in 153 of 246 patients (62.2%) [TSP] and in 67 of 91 (73.6%) [PFO/ASD], p=0.050). Due to the lack of a controlled design, patient frailty and logistic reasons, the TEE follow-up rate is incomplete. The rate of DRT was similar (8/246 (4.4%) [TSP] vs 3/91 (4.1%) [PFO/ASD], p=0.98). In the TSP group, one patient with DRT suffered a transient ischemic attack (TIA), and one patient each a non-disabling ischemic stroke and a disabling ischemic stroke. In the PFO/ASD group, DRT were not associated with thrombo-embolic events during follow-up. The rates of major peri-device leaks (3/246 (1.2%) vs 0/91, p=0.29) were low and did not differ. Major peri-device leaks were not associated with ischemic events at follow-up. In concomitant PFO and ASD closure, TTE/TEE follow-up was performed in 48/54 (88.9%) and 6/8 (75.0%) cases, respectively. A residual shunt after PFO and ASD closure was detected in 7/48 (2.1%) and 1/6 (16.7%) patients. Residual shunts after PFO closure were considered as clinically non-relevant and patients were treated with antiplatelet therapy. None of the patients was switched to (N)OAC. No ischemic event was documented at follow-up. One patient with residual shunt after ASD-closure underwent re-intervention with implantation of a second ASD-occluder. A residual shunt after TSP was detected in 19/182 (10.4%) of the patients, in whom TTE or TEE was performed at follow-up. 3 of those 19 patients (15.8%) suffered from two disabling strokes and one TIA, of which one disabling stroke and one TIA occurred in the presence of a DRT.

CLINICAL OUTCOMES

Late clinical outcome is shown in **Table 3**. All events are reported per 100 patient-years. The cumulative incidence of the primary endpoints is depicted in **Figure 2**. Kaplan-Meier curves of its components are shown in **Figure 3**. Antithrombotic therapy at follow-up was similar for both groups and consisted predominantly of aspirin. At follow-up, the number of anticoagulated patients had increased (17/246 (6.9%) [TSP] vs 9/91 (9.9%) [PFO/ASD]) (4/246 [1.6%] vs 2/91 [2.2%]). Reasons for initiation of (N)OAC during follow-up were stroke/TIA/thromboembolism (3/17 (17.6%) [TSP] vs 2/9 (22.2%) [PFO/ASD]), DRT, dense smoke in the LA (1/17 [5.9%] vs 3/9 [33.3%]), peri-device leak, ≥ 5 mm (2/17 [11.8%] vs 0/9 [0.0%]), pulmonary embolism or deep venous thrombosis (5/17 [29.4%] vs 2/9 [22.2%]), OAC mistakenly given by general practitioners (1/17 [5.9%] vs 1/9 [11.1%]) and unknown reasons (5/17 [29.4%] vs 1/9 [11.1%]).

The primary efficacy endpoint of all-cause stroke, systemic embolism, and cardiovascular/unexplained death was comparable for both groups (46/603, 7.6% [TSP] vs 21/233, 9.0% [PFO/ASD], 10.3, hazard ratio (HR), 1.2; 95% confidence interval (CI), 0.69-0.85, p=0.54). None of the components of the primary efficacy endpoint were different between the two groups. All-cause stroke occurred in 16/603, 2.7% in the TSP vs 4/233, 1.7% in the PFO/ASD group (HR, 0.65; 95% CI, 0.25-1.73, p=0.39). Cardiovascular and unexplained death were documented for the TSP group in 42/60, 7.0% vs 18/233, 7.7% in the ASD/PFO group (HR, 1.12; 95% CI, 0.63-1.97, p=0.70). Also, the primary safety endpoint of major peri-procedural complications and major bleeding events occurred with a comparable frequency in the TSP and PFO/ASD group (24/603, 4.0% vs 11/23, 4.7%; HR, 1.31; 95% CI, 0.50-3.40, p=0.49). Likewise, the rate of major bleedings was similar in both groups (14/603, 2.3% vs 7/233, 3.0%; HR, 1.31; 95% CI, 0.50-3.40, p=0.58).

Discussion

In the present study, we compared periprocedural and late clinical outcomes of LAAC through a TSP versus through a PFO or an ASD. Device success was high in both groups and similar rates of major periprocedural complications were documented. In the long-term, left atrial access through a PFO or an ASD provided similar efficacy with regard to all-cause stroke, systemic embolism, and cardiovascular/unexplained death compared to the TSP access. In terms of safety, the rate of major bleeding events was also similar.

The Amplatzer devices feature a two-part plug-and-disc system with closure of the LAA according to the "pacifier" principle. To provide a full coverage of the LAA orifice without leaving a peri-device leak as potential space for tissue filling and DRT, optimal deployment of the Amplatzer system is strived for. This assumedly is facilitated by a recommended access to the LA via a TSP in the infero-posterior portion of the fossa ovalis, directly opposite the LAA. Not to use a PFO tunnel is based on the concern that they are located too cranio-anteriorly for proper coaxial LAA intubation with the delivery sheath (**Figure 4**). Nevertheless, a previous study has demonstrated technical feasibility of LAAC with Amplatzer devices via a PFO/ASD [6]. The present study confirms those early findings of feasibility for the PFO/ASD access with the same rate of implantation attempts and need for repositioning of the device as in case of TSP. Concomitant PFO/ASD closure resulted in higher amounts of contrast volume, but did not prolong fluoroscopy time. An additional amount of 33 ml contrast volume was used for final right atrial angiographic check of the implantation result after ASD- or PFO closure.

Procedural major complications were mainly constituted by cardiac tamponade. Most recent studies reported low rates of cardiac tamponade with 1.24%[1], 1.2%[2], 1.02%[13] and 0.2%[14]. The relatively high rate of cardiac tamponade in the present study may be attributable to the low rate of periprocedural TEE guidance (TSP vs PFO/ASD: 39.8% vs 28.6%, p = 0.06), especially

in the early phase of recruiting, and reflects the learning curve of the operators. Nowadays, TEE guiding is strongly recommended to avoid such complications. Hypothetically, passage of a PFO or ASD simplifies LA access and avoids potential complications of TSP like perforation of the left atrial free wall or the aortic root. However, in our study a higher number of cardiac tamponade (4 [4.4%]) was documented in the PFO/ASD group. In 2 of 4 patients, multiple implantation attempts were needed for proper deployment of the device, which may have been related to a more challenging positioning of the delivery sheath and the occluder in these cases. From that one can conclude that the PFO/ASD access may be demanding and is rather an option for advanced operators.

The rate of device embolization in the TSP group (1.2%) was slightly higher than documented in other registries with 0.76%[1], 0.1%[2], 0.24%[13] and 0.20%[14]. It is most likely a chance finding and reflects the learning curves. Nonetheless, overall adverse event rates are in line with the large multicenter registries for the ACP (5.0%)[1] and for the Amulet (3.2%)[2].

TEE at follow-up revealed a low rate of major peri-device leaks, which is comparable to those reported in the ACP [1] and Amulet [2] multicenter trials (1.9% and 1.6%). Also, the rate of DRT was comparable for the TSP and PFO/ASD access. In current registries the incidence of DRT varies notably, which may be attributable to a missing consensus on the definition of DRT, different sample sizes of those series and reporting bias related to inconsistency in TEE follow-up [1, 2, 15].

Implantation results for the TSP and PFO/ASD access led to similar late clinical outcomes. The rate of all-cause stroke, TIA, and systemic embolism is comparable with other Amplatzer registries (2.3% for the ACP [1], 2.9% for the Amulet [3]). In the PFO/ASD group, the rate of stroke and TIA was numerically lower. This may be attributable to combined PFO/ASD closure in this group, yet the present study was not powered to detect such differences. A meta-analysis

of six randomized trials, including 3,560 patients with a mean follow-up of 4.6 (2.0-5.9) years yielding about 25,000 patient-years confirmed that stroke risk was significantly lower after transcatheter PFO closure than under antithrombotic therapy alone [16]. Despite an elderly patient cohort, major bleeding events during follow-up were rare and did not differ between the groups. The 5-year follow-up of the PROTECT-AF and PREVAIL studies reported a major bleeding rate of 1.7% [5]. Of note, these populations were eligible for oral anticoagulation, significantly younger, and at lower risks for stroke and bleedings. Consequently, our data show higher rates of all cause and cardiovascular death in comparison to the above-mentioned trials.

Limitations

Although data were prospectively collected, this study has several limitations attributable to its non-randomized, observational, and retrospective design. It was not powered to detect differences in thromboembolic and bleeding events, as well as cardiovascular mortality. Despite adequate matching of the two groups, unmeasured confounders likely persist. TEE guidance was performed depending on operator´s routine and preferences and varied between the three centers. Also, TEE follow-up was not available for all patients and was not assessed in a standardized manner by a core lab. This may have led to an underreporting of DRT and peri-device leaks for both groups.

Conclusion

In patients undergoing left atrial appendage closure with Amplatzer systems, the use of a PFO or ASD for LA access is equally feasible and safe and offers similar late clinical outcomes in comparison to a TSP. Additional PFO or ASD closure does not increase risk and may yield further protection against systemic embolism.

Impact on daily practice

LAAC is an established treatment option for stroke prevention in patients with AF as an alternative to OAC. While TSP is the standard access to the LA for LAAC with Amplatzer devices, technical feasibility of LAAC through a PFO/ASD has been shown for Amplatzer devices. However, PFO/ASD access may be demanding and therefore is rather an option for advanced operators.

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Figure Legends

Figure 1. (A) access to the left atrium through a PFO, (B) implantation of a ACP, (C) left atrial angiography after LAAC, (D) right atrial angiography after PFO occlusion, (E) 3-D TEE after 5 months.

Figure 2. Cumulative incidence of primary endpoints in % per 100 patient-years.

Figure 3. Kaplan-Meier curves of clinical events up to 48 months. (A) primary efficacy endpoint, (B) primary safety endpoint, (C) all-cause stroke and transient ischemic attack, (D) all-cause stroke (without transient ischemic attack), (E) major, life- threatening and fatal bleeding, and (F) cardiovascular and unexplained death.

Figure 4. Schematic illustration of TSP versus PFO access in the bicaval view (A) and short axis view (B) in TEE.

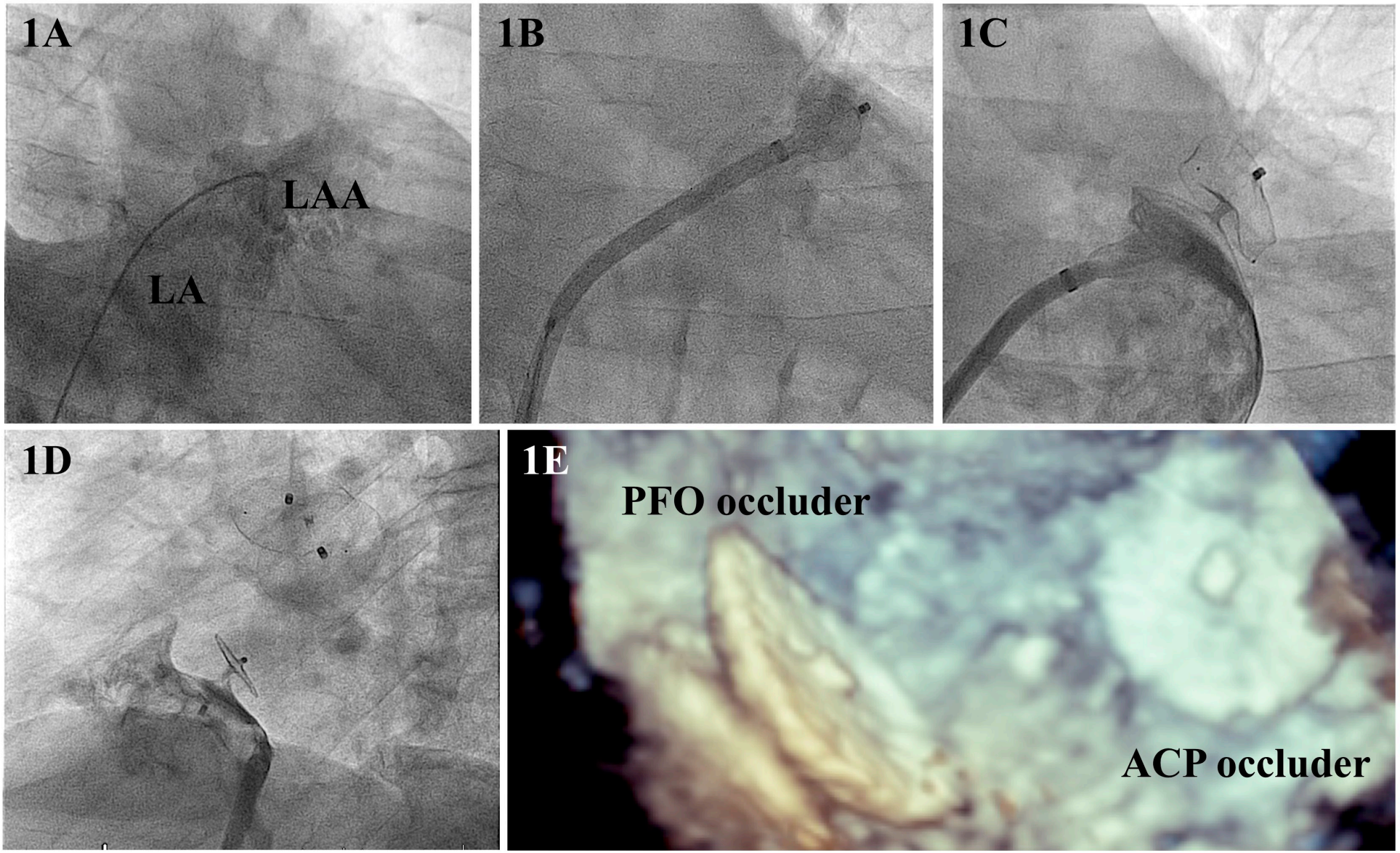
Table 1. Baseline characteristics			
	LAAC via TSP (n = 246)	**LAAC via PFO/ASD** (n = 91)	**p-Value**
DEMOGRAPHICS & CLINICAL FEATURES			
Age at time of LAAC (yrs)	75.2 ± 8.7	74.4 ± 10.9	0.50
Body mass index (kg/m²)	27.5 ± 5.4	27.6 ± 5.1	0.92
Female gender	80 (32.5)	29 (31.9)	0.91
Arterial hypertension	215 (87.4)	79 (86.8)	0.89
Diabetes mellitus	69 (28.0)	25 (27.5)	0.92
Coronary artery disease	130 (52.8)	45 (49.5)	0.58
Prior PCI/CAGB	120 (48.8)	39 (42.9)	0.33
Left ventricular ejection fraction (%)	55.0 ± 12.4	55.4 ± 10.3	0.80
GFR (ml/min)	67.6 ± 24.5	68.3 ± 27.0	0.81
Prior stroke/TIA	79 (32.1)	28 (30.8)	0.81
CHA_2DS_2-VASc score	4.5 ± 1.6	4.3 ± 1.4	0.47
HAS-BLED score	3.2 ± 1.0	3.0 ± 1.0	0.27
ANTI-THROMBOTIC MEDICAL THERAPY PRIOR TO LAAC			
Any oral anticoagulation	142 (57.7)	60 (65.9)	0.17
Vitamin K antagonists	114 (46.3)	44 (48.4)	0.74
Non-vitamin K antagonists	29 (11.8)	17 (18.7)	0.10
Aspirin	118 (48.0)	37 (40.7)	0.23
Platelet inhibitors other than aspirin	52 (21.1)	18 (19.8)	0.79

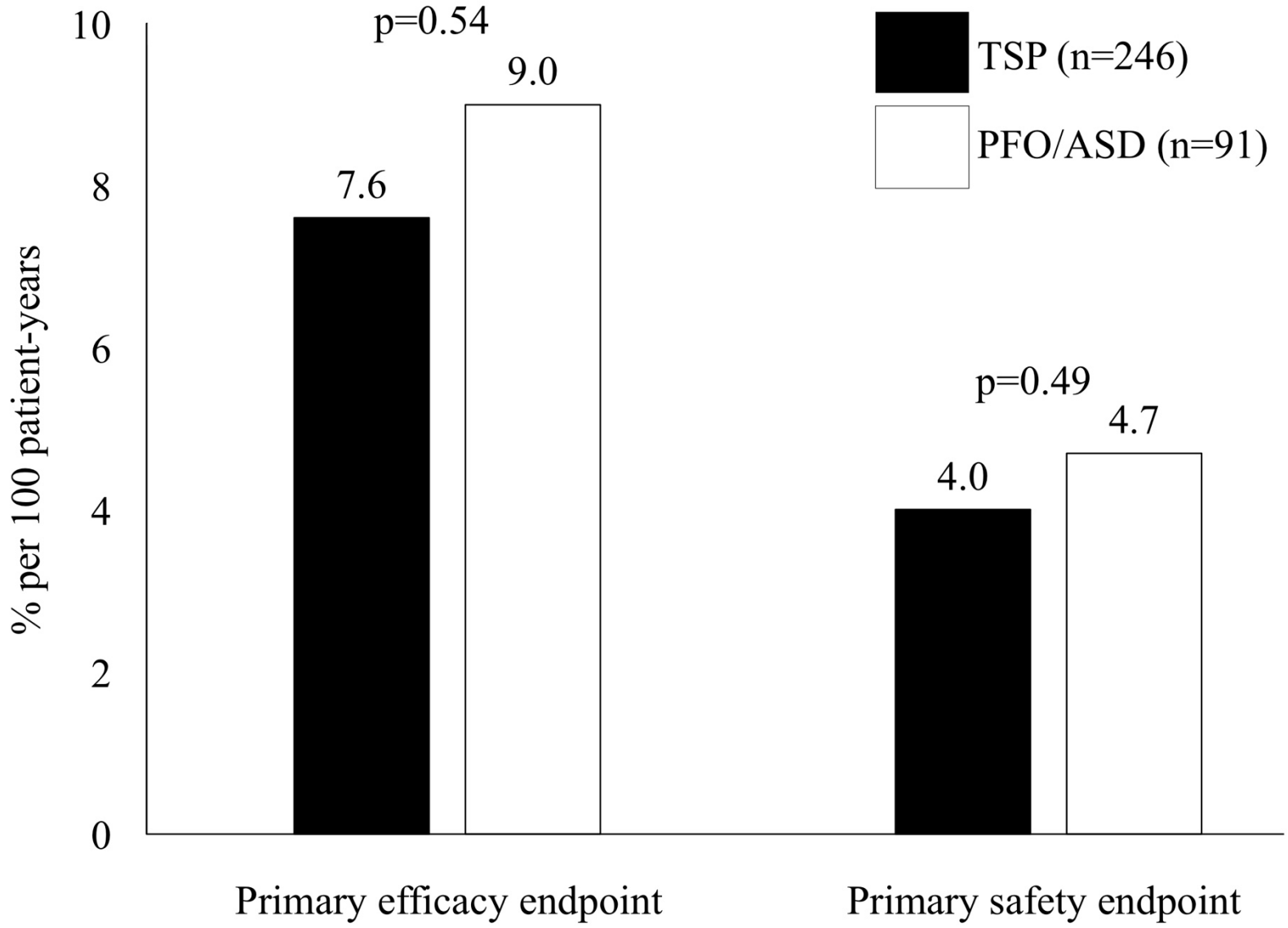
Table 2. Procedural characteristics

	LAAC via TSP (n = 246)	LAAC via PFO/ASD (n = 91)	p-Value
Amplatzer cardiac plug	149 (60.6)	62 (68.1)	0.20
Amplatzer Amulet	97 (39.4)	29 (31.9)	0.20
Device success	240 (97.6)	89 (97.8)	0.90
Residual gap	25 (10.2)	12 (13.2)	0.43
Implantation attempts	1.1 ± 0.4	1.1 ± 0.4	0.99
Need for repositioning of the device	22 (8.9)	12 (13.2)	0.25
No device implanted	1 (0.5)	1 (1.1)	0.46
Local anesthesia	225 (91.5)	91 (100.0)	0.0040
TEE guidance	98 (39.8)	26 (28.6)	0.060
Access via PFO	0	83 (91.2)	
Access via ASD	0	8 (8.8)	
Combined PFO closure	2 (0.8)	54 (65.1)	< 0.0001
Combined ASD closure	0 (0.0)	8 (100)	< 0.0001
Fluoroscopy time (min)	14.3 ± 9.1	17.0 ± 13.0	0.64
Contrast media (ml)	158.1 ± 87.9	191.1 ± 79.3	0.0021
PERI-PROCEDURAL COMPLICATIONS			
Peri-procedural complication	11 (4.5)	4 (4.4)	0.98
Death	1 (0.4)	0 (0.0)	0.54
Stroke	0 (0.0)	0 (0.0)	1.0
Cardiac tamponade	7 (2.8)	4 (4.4)	0.48
Major bleeding	8 (3.3)	4 (4.4)	0.62
Major access vessel complication	0 (0.0)	0 (0.0)	1.0
Need for bailout surgery	5 (2.0)	0 (0.0)	0.17
Device embolization	3 (1.2)	0 (0.0)	0.29
Severe kidney injury	2 (0.8)	0 (0.0)	0.39
Need for cardio-pulmonary resuscitation	3 (1.2)	0 (0.0)	0.29
TEE FOLLOW - UP			
TEE performed	153 (62.2)	67 (73.6)	0.050
Thrombus on device	8 (4.4)	3 (4.1)	0.98
Peri - device leak, ≥ 5 mm	3 (1.2)	0 (0.0)	0.29

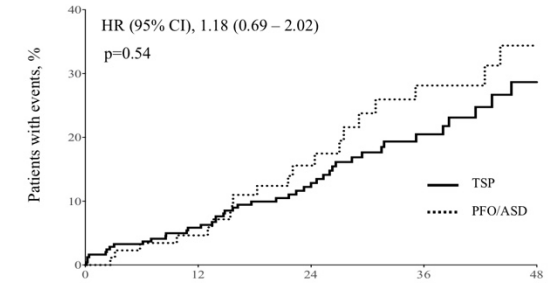
Table 3. Late clinical outcomes

	LAAC via TSP (n = 246) (603 patient-years)		LAAC via PFO/ASD (n = 91) (233 patient-years)		p-Value
Age at follow-up (yrs)	78.1 ± 8.7		77.4 ± 10.7		0.52
Time from study inclusion to follow-up in yrs	2.5 ± 1.4		2.6 ± 1.6		0.55
CLINICAL OUTCOMES					
	Events/Patient-Years	Observed Rate	Events/Patient-Years	Observed Rate	
Primary efficacy endpoint	46/603	7.6 (5.8-10.0)	21/233	9.0 (6.0 - 13.4)	0.54
Primary safety endpoint	24/603	4.0 (2.7-5.9)	11/233	4.7 (2.7 - 8.3)	0.49
Cardiovascular/unexplained death	42/603	7.0 (5.2 - 9.3)	18/233	7.7 (4.9 - 11.9)	0.70
Stroke and TIA	16/603	2.7 (1.6 - 4.3)	4/233	1.7 (0.7 - 4.3)	0.39
Stroke without TIA	14/603	2.3 (1.4 - 3.9)	3/233	1.3 (0.4 - 3.7)	0.18
Disabling stroke	8/603	1.3 (0.7 - 2.6)	2/233	0.9 (0.1 - 3.1)	0.61
Non-disabling stroke	6/603	2.4 (0.5 - 2.2)	1/233	0.4 (0.1 - 2.4)	0.47
Ischemic stroke	14/603	2.3 (1.4 - 3.9)	3/233	1.3 (0.4 - 3.7)	0.37
Hemorrhagic stroke	1/603	0.2 (0.0 - 0.9)	0/233	0.0	0.54
TIA	2/603	0.3 (0.1 - 1.2)	1/233	0.4 (0.1 - 2.4)	0.80
Systemic embolism	1/603	0.2 (0.0 - 0.9)	1/233	0.4 (0.1 - 2.4)	0.46
Major bleeding	14/603	2.3 (1.4 - 3.9)	7/233	3.0 (1.5 - 6.1)	0.58
ANTI-THROMBOTIC THERAPY AT TIME OF FOLLOW-UP					
Any oral anticoagulation	17 (6.9)		9 (9.9)		0.36
Vitamin K antagonists	6 (2.4)		4 (4.4)		0.35
Non-vitamin K antagonists	11 (4.5)		4 (4.4)		0.98
Aspirin	149 (60.6)		48 (52.7)		0.20
Platelet inhibitors other than aspirin	25 (10.2)		13 (14.3)		0.29



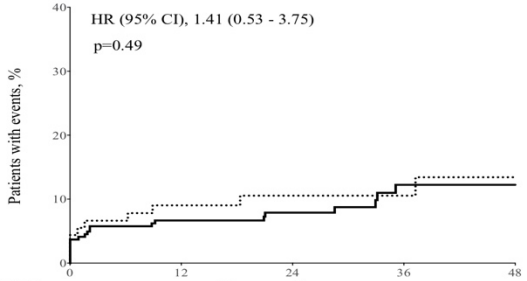


3A Primary efficacy endpoint



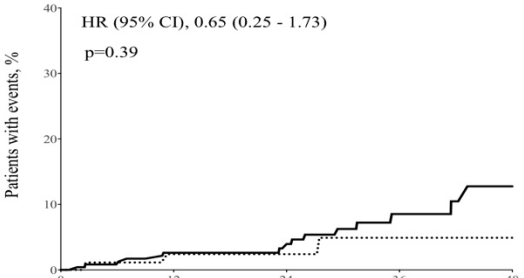
No. at risk					
TSP	246	213	143	67	32
PFO/ASD	91	76	47	33	16

3B Primary safety endpoint



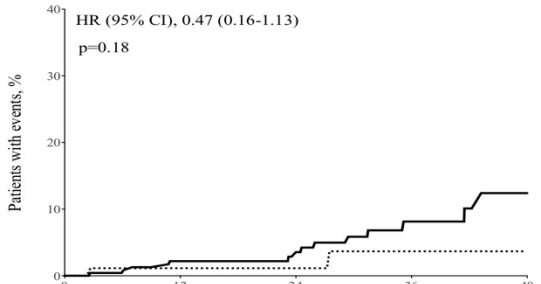
No. at risk					
TSP	246	204	135	67	33
PFO/ASD	91	71	47	33	15

3C All-cause stroke and transient ischemic attack



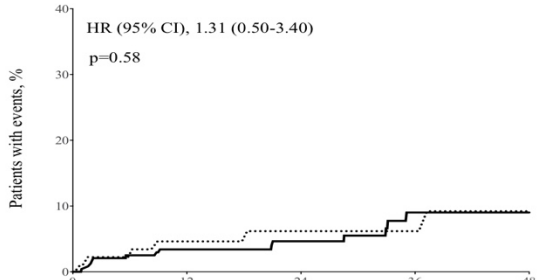
No. at risk					
TSP	246	212	143	67	32
PFO/ASD	91	75	47	34	16

3D All-cause stroke (without transient ischemic attack)



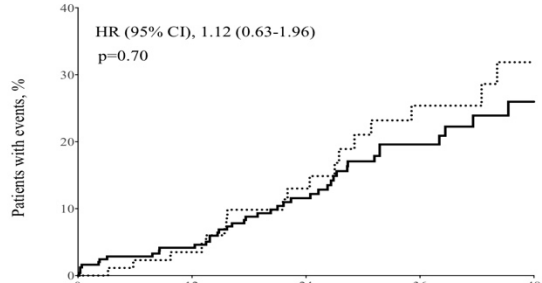
No. at risk					
TSP	344	213	143	67	32
PFO/ASD	219	76	48	34	16

3E Major, life-threatening and fatal bleeding



No. at risk					
TSP	246	210	140	68	34
PFO/ASD	91	74	48	33	15

3F Cardiovascular and unexplained death



No. at risk					
TSP	246	214	143	67	32
PFO/ASD	91	77	49	34	16