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Safety and feasibility of interventional left atrial appendage closure without contrast agent

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KEYWORDS

- atrial fibrillation
- imaging modalities
- left atrial appendage
- prior stroke or transient ischaemic attack
- renal insufficiency
- transoesophageal echocardiogram

Abstract

Aims: Interventional left atrial appendage closure (LAAC) is routinely performed under both echocardiographic and angiographic guiding. However, adverse outcomes, e.g., kidney injury and cerebral embolism, might be associated with injections of contrast agent into the LAA. Therefore, this prospective registry investigated the safety and feasibility of LAAC without the support of angiographic images as the default approach.

Methods and results: This single-centre registry included a total of 46 non-selected, consecutive patients. In the first 25 patients (54%), LAAC with the Amulet device was performed routinely with LAA angiography prior to implantation and after release of the device. The following 21 patients (46%) were treated without the use of contrast agent. The combination of successful implantation and lack of procedural complications was regarded as the primary endpoint. Procedure time, number of recapture manoeuvres, change of device size, compression, leakage, dose area product and late thrombosis on the device were investigated as secondary endpoints. Besides the longer fluoroscopy time and duration of the procedure in the group using angiography, no significant differences could be found. Major complications occurred equally often in both cohorts.

Conclusions: Interventional LAAC with the Amulet device can be performed safely without the use of contrast agent. This approach might help to enhance the use of LAAC in patients at high risk of contrast-induced nephropathy and procedural stroke.

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Abbreviations

AF	atrial fibrillation
CKD	chronic kidney disease
CT	computed tomography
LAA	left atrial appendage
LAAC	left atrial appendage closure
NOAC	novel oral anticoagulants
OAC	oral anticoagulation
LCx	left circumflex coronary artery
TOE	transoesophageal echocardiography
TSP	transseptal puncture

Introduction

Atrial fibrillation is the underlying cause of 15-20% of all strokes, with more than 90% of these resulting from thromboembolic events originating in the left atrial appendage (LAA)[1]. Oral anticoagulation (OAC) has been shown to be very effective in preventing these thromboembolic events[2-4]. However, a significant number of patients at risk for embolic stroke are not treated properly with OAC for various reasons including poor compliance or high risk of bleeding events[5,6]. Two large randomised controlled trials (PROTECT AF, PREVAIL) and data from several registries have shown that left atrial appendage closure (LAAC) is an equivalent, effective and safe concept in terms of stroke prevention in atrial fibrillation[7-13]. The results of a recent international questionnaire displayed a high level of confidence in LAAC amongst interventional cardiologists surveyed. The majority believed the procedure to be as effective as OAC in terms of stroke prevention and safer in terms of bleeding risk[14].

In daily clinical practice, the majority of patients treated with LAAC have a relative or absolute contraindication to OAC, such as previous major bleeding or a high bleeding risk[13]. Another important subgroup is patients with chronic kidney disease (CKD) who are unsuitable for the novel oral anticoagulants (NOAC) and at the same time carry an elevated risk of stroke[15] and bleeding events[16,17]. This situation leads to a clinical dilemma and makes LAAC a viable option for stroke prevention in this particular subgroup. However, the use of contrast agent for angiography and/or cardiac computed tomography (CT) prior to or during LAAC poses the risk of contrast-induced nephropathy[18], which might hinder the referral of these patients for LAAC and thereby leave them with a high risk of thromboembolic or bleeding events. For this special subgroup of patients, it is desirable to avoid the use of contrast agent during LAAC, as well as to abandon the CT scan prior to the procedure.

In this study we investigated the hypothesis that LAAC without angiography of the LAA and CT imaging is feasible and safe.

Methods

PATIENT POPULATION

The analysed data originate from a single-centre cohort study containing patients who underwent percutaneous LAAC, performed using the AMPLATZER™ Amulet™ Left Atrial Appendage Occluder (St. Jude Medical, St. Paul, MN, USA) between December 2014 and January 2016. Procedure and device were approved, clinically indicated and followed the Declaration of Helsinki guidelines. Patients gave their written consent. Data evaluation was authorised by the ethics committee (Ethik-Kommission der Ärztekammer Hamburg, Bearb.-Nr: WF-32/16).

Clinical, procedural and outcome variables were collected for 46 patients. Indications for LAAC were at the implanting physician's discretion and followed the current European Society of Cardiology (ESC) and local institutional guidelines[19-21], including absolute or relative contraindications to OAC or excessive risk of both bleeding and thromboembolic events.

In this study, 25 consecutive patients were treated with the use of angiography compared to 21 consecutive patients who were treated afterwards without the use of contrast agent. The change of imaging strategy from dual mode to single mode was chosen arbitrarily after an internal review of the study protocol in April 2015.

The primary endpoint was the combination of successful implantation and the lack of procedural complications (mortality, stroke/TIA/peripheral embolism, systemic embolism, pericardial effusion/tamponade, bleeding, access-related complications, or any device-related complication). Secondary endpoints were procedure time, number of recapture manoeuvres, change of device size, compression, leakage, dose area product, late thrombosis on the device and device embolism in the first three months.

CHARACTERISTICS OF THE OCCLUSION DEVICE

We focused on the AMPLATZER Amulet Left Atrial Appendage Occluder because it appeared to be a safely implantable and less traumatic device for our pilot study. It is a transcatheter self-expanding device with two flexible components, the proximal disc and the distal lobe, connected by a central waist. This device is made out of nitinol mesh with Dacron patches sewn into the lobe and disc. It is available in eight sizes (16, 18, 20, 22, 25, 28, 31 or 34 mm corpus diameter; 7.5 or 10 mm length). The diameter of the proximal disc is 6 to 7 mm larger than the lobe diameter. Depending on the device size, the Amulet lobe has 12, 16 or 20 stabilising wires to anchor in the LAA. It is installed to a delivery catheter and can be recaptured after positioning. The delivery catheter tip is blunt. The catheter also allows injection of contrast agent into the LAA and proximal to the device in order to facilitate accurate placement and angiographic assessment of leakage[22].

PROCEDURE

All procedures were performed under conscious sedation by two operators with two- and three-dimensional transoesophageal echocardiography (TOE) (iE33 and EPIQ 7 ultrasound system; Philips Healthcare, Andover, MA, USA) and in 25 cases additionally with angiographic guidance **(Figure 1)**. CT data were not collected in either group. After transseptal puncture (TSP) under TOE guidance, the patients received intravenous heparin in order to maintain an activated clotting time >250 seconds.

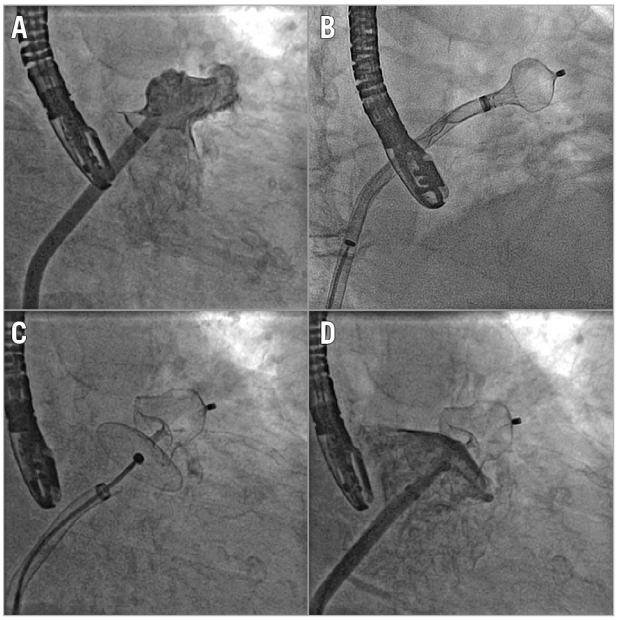

Figure 1. *Fluoroscopic and angiographic imaging. A) Contrast agent application for the presentation of LAA morphology. B) Positioning the partly extended Amulet device in the landing zone. C) Full expansion of the device. D) Injection of contrast agent shows effective LAA occlusion. LAA: left atrial appendage*

As recommended in the expert consensus approach described by Tzikas et al[23], the sheath was introduced into the LAA under echocardiographic and fluoroscopic guidance. In the first 25 cases contrast medium was injected through the sheath, which was positioned at the level of the LAA ostium and angiographic pictures were recorded typically in a right anterior oblique (RAO) 30°/cranial 20° and an RAO 30°/caudal 20° view. Fluoroscopy was used in all cases.

In TOE the LAA landing zone was evaluated in multiple planes (mainly 0°, 45°, 90°, 135°) 10 mm distal to the left circumflex coronary artery (LCx), as this usually predicts the actual landing zone best suited for the Amulet device. Maximum and minimum diameters were recorded, measured edge to edge. The device size was chosen to be 3 to 5 mm larger than the mean diameter of the LAA landing zone. Additional angiographic measurements in the first cohort were comparable with the TOE measurements and did not influence the selection of device size.

A stable implantation was achieved when: a) the compression of the device lobe was sufficient, b) the axis of the device lobe was in line with the axis of the LAA neck, c) the disc was concavely shaped and affixed to the atrial wall, d) separation between the device lobe and disc was visible, e) two thirds of the device lobe was positioned distal to the LCx in the LAA, and f) the disc met manual stability criteria (pull and tug) **(Figure 2)**. In the angiographic group, contrast agent was injected through the sheath to confirm the correct device positioning and the effective LAA occlusion. After meeting these criteria, the device was released **(Figure 3)**. Standard post-procedural treatment included dual platelet inhibition (aspirin and clopidogrel) until control TOE after three months. Other treatment strategies were determined individually based on a higher risk of embolism.

FOLLOW-UP

All patients were scheduled for follow-up TOE and assessment of clinical endpoints three months after implantation. In the absence of device-related thrombi or peri-device leakages, patients were switched to aspirin monotherapy.

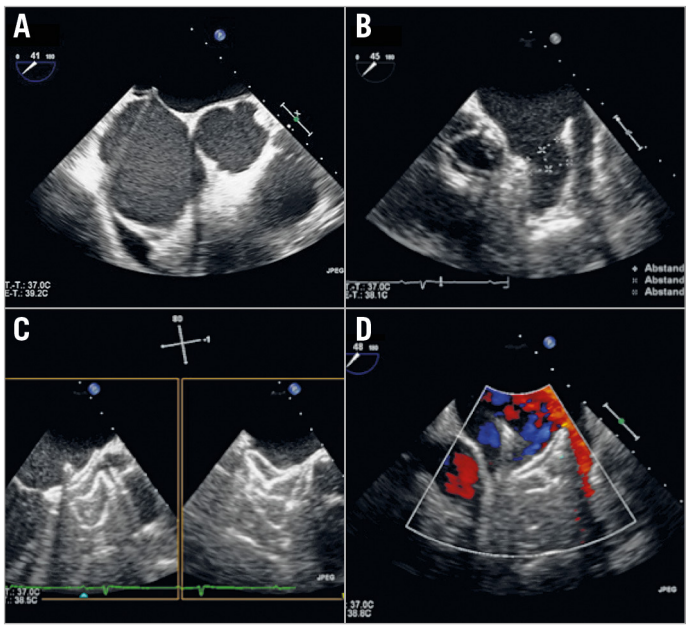

Figure 2. *Transoesophageal imaging. A) Puncture needle tenting the interatrial septum in the fossa ovalis. B) Measuring landing zone diameter 10 mm distal to the LCx. C) Biplane view of implanted Amulet device. D) Colour Doppler signal showing missing flow in the LAA. LAA: left atrial appendage; LCx: left circumflex coronary artery*

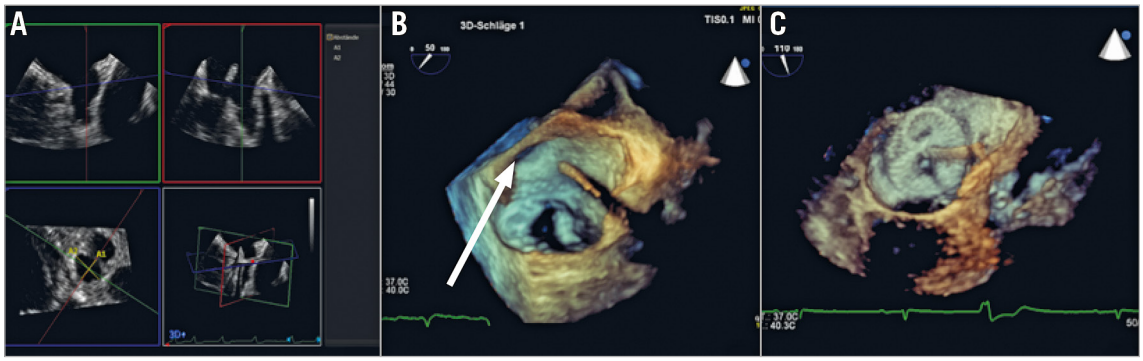

Figure 3. *3D transoesophageal imaging. A) Measurements of the landing zone diameter. B) Sheath aimed perpendicular to the LAA ostium (white arrow) after transseptal puncture. C) Successfully implanted Amulet device before release from the delivery catheter. LAA: left atrial appendage*

DATA ANALYSIS

Statistical analysis was conducted using SigmaPlot 11.0 (Systat Software, Inc., San Jose, CA, USA). The results were expressed as mean±standard deviation (SD) for normally distributed data. Event rates were displayed as percentages. Continuous variables that were not normally distributed were expressed as medians. Comparisons between groups were performed using unpaired t-tests or Mann-Whitney rank-sum tests for continuous variables, and chi² or Fisher's exact tests for categorical variables. Results were defined to be statistically significant at a p-value <0.05.

Results

A total of 46 patients with non-valvular atrial fibrillation, CHA_2DS_2-VASc score ≥2 and relative or absolute contraindications to OAC therapy who were treated with the Amulet device between December 2014 and January 2016 were included in the registry. The baseline characteristics are displayed in **Table 1**. Apart from age, there was no significant difference in the two analysed groups.

The device was successfully implanted in all patients **(Table 2)**. The diameter of the LAA landing zone did not vary between the groups and median device size was 25 mm for both groups. The amount of contrast agent (Imeron® 350; Bracco Imaging S.p.A., Milan, Italy) used in the angiography cohort was 76 (±50) ml. The procedure time was measured from TSP to the end of the procedure and showed a significant difference between groups (37.6±16.6 min vs. 27.6±9.2 min; p=0.044). In addition, fluoroscopy time was significantly longer in the first cohort (12.3±6.1 vs. 7.9±2.9 min; p=0.018). The dose area product did not vary between the cohorts (3,504±2,661 cGy/cm² vs. 2,338±2,009 cGy/cm²) **(Figure 4)**.

Table 1. Baseline characteristics (n=46).

		LAAC with contrast agent (n=25)	LAAC without contrast agent (n=21)	Significance (*p*-value)
Age, years		74.0±7.3 (median: 77)	79.0±3.4 (median: 79)	0.009
Sex	Female	8 (32.0%)	5 (23.8%)	0.278
Atrial fibrillation	Paroxysmal	10 (40.0%)	9 (42.9%)	0.536
	Persistent	10 (40.0%)	5 (23.8%)	
	Permanent	5 (20.0%)	7 (33.3%)	
Sinus rhythm (at time of implantation)		13 (52.0%)	13 (61.9%)	0.513
CHA_2DS_2-VASc score		4 (median)	5 (median)	0.441
Prior stroke (incl. TIA/ICB)		8 (32.0%)	6 (28.6%)	
HAS-BLED score		4 (median)	4 (median)	0.588
Indication	Prior bleeding	13 (52.0%)	9 (42.9%)	0.549
	High risk	12 (48.0%)	12 (57.1%)	0.991

ICB: intracranial bleeding; LAAC: left atrial appendage closure; TIA: transient ischaemic attack

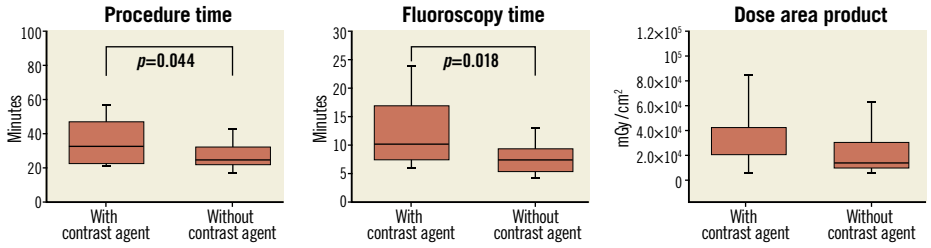

Figure 4. *Comparison of procedure time, fluoroscopy time and dose area product between the groups with and without using contrast agent.*

Table 2. Procedure details (n=46).

		LAAC with contrast agent (n=25)	LAAC without contrast agent (n=21)	Significance (*p*-value)
Size of device (mm)		23.7±4.3 (median: 25)	25.5±4.0 (median: 25)	0.142
Landing zone diameter* (mm)		20.1±4.1	21.0±5.0	0.570
Compression (%)		17.0	17.6	0.718
Dose of heparin (IU)		9,166.7 ±2,823.3	9,000.0 ±2,052.0	0.674
Successful implantation (n)		25 (100.0%)	21 (100.0%)	
Recapture (n)		14 (56.0%)	6 (28.6%)	0.066
Change of device size (n)		5 (20.0%)	2 (9.5%)	0.339
Procedure time** (min)		37.6±16.6	27.7±9.2	0.044
Amount of contrast agent (Imeron 350) (ml)		76.2±49.7	0	<0.001
Fluoroscopy time (min)		12.3±6.1	7.9±2.9	0.018
Dose area product (cGy/cm^2)		3,503.5 ±2,660.5	2,337.2 ±2,008.8	0.081
Complications (n)	Total	2 (8.0%)	2 (9.3%)	0.874
	Mortality	0	0	
	Stroke/TIA/peripheral embolism	0	0	
	Coronary air embolism	1	0	
	Systemic embolism	0	0	
	Pericardial effusion/tamponade	0	1	
	Bleeding	1	1	
	Device-related complications	0	0	
Discharge medication	DAPT	23	19	
	Warfarin	1	1	
	NOAC	1	1	

*Landing zone diameter was measured in 4 planes (0°, 45°, 90°, 135°) and mean value was calculated. **Procedure time was measured in transoesophageal echocardiography from transseptal puncture to the end of the procedure. DAPT: dual antiplatelet therapy; LAAC: left atrial appendage closure; NOAC: novel oral anticoagulants; TIA: transient ischaemic attack

In the angiography group, recapturing of the device was necessary in 14 patients (56%), in the other group in six patients (28%). Change of device size was necessary in five (20%) versus two (9%) patients.

With respect to the primary outcome, no significant difference between the two cohorts could be found. Implantation was successful in all patients and procedural complications occurred equally often, in two patients in each group (8.0 vs. 9.3%; p=0.874).

In the contrast agent cohort, one complication was an air embolism into the right coronary artery, which led to temporary atrioventricular block III° and was managed by single-shot injection of epinephrine (0.4 mg) and atropine (1 mg). Another patient developed a relevant haematoma at the puncture site (BARC type 2).

In the group without contrast agent, one patient had a procedural pericardial tamponade which was successfully managed by pericardiocentesis. There was no repositioning of the device during the procedure. Furthermore, one patient developed post-procedural haematemesis (BARC type 3a), most likely caused by a laceration trauma from the TOE probe which was positioned in mid-oesophagus during the complete procedure. In this case, gastrointestinal bleeding was also the indication for LAAC. Endoscopy showed long-segment oesophageal ulcerations. After a fasting period, high-dose proton pump inhibitor therapy and transfusion of three packed red blood cells, healing was achieved.

The majority of patients were discharged on dual platelet inhibition (aspirin and clopidogrel). One patient in each group was still treated with warfarin and one patient in each group received NOAC because of excessive risk of embolism. Follow-up data, including TOE imaging at three months after the procedure, were available for 38 out of 46 patients (83%) and are presented in **Table 3**. Two patients in the angiography group showed cardiovascular events such as bleeding under dual platelet inhibition as did one patient in the group not using contrast agent. Neither stroke nor device embolism was documented in either cohort. Late thrombus formation on the device was documented for one patient from each group. Both patients received oral anticoagulation for at least 12 weeks. A remaining insignificant gap (<5 mm) was documented in four patients in the angiography group and in three patients in the contrast-free group. Here the medication was continued longer with aspirin and clopidogrel. All other patients were switched to aspirin monotherapy indefinitely.

Table 3. Follow-up data (n=38).

	LAAC with contrast agent (n=21)	LAAC without contrast agent (n=17)
Lost to follow-up	4	4
Thrombus	1	1
Device embolism	0	0
Gap	4	3
Stroke/TIA	0	0
Bleeding	2	1

DAPT: dual antiplatelet therapy; LAAC: left atrial appendage closure; NOAC: novel oral anticoagulants; TIA: transient ischaemic attack

Discussion

This observational pilot study demonstrates that the additional use of contrast agent might not be obligatory in LAA occlusion. In our cohort, with 21 patients, the procedure was safe and feasible using fluoroscopic and echocardiographic guidance only. Furthermore, our objective is to address the simplification of LAAC by encouraging implanting physicians not only to

consider contrast-free implantation in certain patients but also to forego preprocedural CT imaging.

Several studies have found evidence that echocardiography in addition to angiography is a suitable imaging procedure for percutaneous LAAC[24-26]. Furthermore, it has been shown that LAAC in general is a safe procedure with an acceptable incidence of periinterventional complications. Despite the lack of randomised trials, registries have shown that Amulet devices have a favourable early outcome[27-29].

Our data displayed a total complication rate of 8.7% (periprocedural and post-procedural) without a significant difference between the investigated groups. The only complication described, which might have resulted from imaging quality, was the pericardial tamponade. There is a risk of LAA injury while performing LAA angiography due to the sheath. However, this complication occurred in the group without angiographic guidance and showed no statistical significance.

A device-related complication, thrombus formation, is a well-described incident after LAAC with the Amulet device. Two patients (5.3%) out of our 38 follow-up patients revealed this adverse event, which is in line with prior published experiences from large-scale series[30,31]. As both patients had a successful device implantation with good positioning of the plate, the imaging modalities during the procedure did not have any influence on this complication. The thrombus dissolved completely in both cases after OAC treatment. Device embolism[32,33] did not occur in either group.

From a general perspective, a lack of increase in complications or other clinically relevant events might have been caused by the learning curve of the operators refining this implantation technique. As operators get more expertise, recapturing and changing the device size becomes less frequent, potentially lowering complication rates. However, the overall learning curve was rather flat because the operators had implanted over 100 devices before starting this study.

LAAC can dramatically lower the rate of thromboembolic events or major bleedings, which is especially important for patients with chronic kidney disease, who have a much higher risk at baseline. While a study by Kefer and al[12] did not show any significant difference in the procedural safety of LAAC (using the AMPLATZER™ Cardiac Plug; St. Jude Medical) for patients with or without prior renal impairment, it is likely that patients with critical renal function were not taken into account for the procedure. A contrast-free implantation approach might help more patients to be considered for this form of embolic protection.

In our opinion, LAAC without additional angiographic guidance should be performed for all patients who have relevant or absolute contraindications to contrast agent use and have sufficient echocardiographic imaging quality. However, angiographic assessment of LAA size and anatomy is still the gold standard and should be part of the standard approach in all suitable patients. In patients with complicated LAA anatomy, i.e., multiple lobes or poor echocardiographic imaging quality, angiography is still necessary and helpful.

Limitations

The main limitation of this study is the small number of patients which results in a low statistical power. However, this investigation was able to demonstrate that the contrast-free approach may enrich the opportunities of implantation techniques available to the implanting physicians treating patients with chronic kidney disease. Thus, it should only be performed by experienced operators.

As the main priority of this study was to demonstrate feasibility of this new technique, future studies with a greater patient collective and strict inspection of renal function parameters in a randomised fashion need to prove the benefit of our approach on kidney function.

A distinct advantage of angiography-free guidance is the absence of nephrotoxic effects associated with contrast agent. In addition, omitting injections into the LAA might reduce cerebral embolism based on spontaneous echo contrast, sludge and thrombus formation in the LAA[34]. The study of Rillig et al shows that the number of LAA angiographies during LAAC is associated with the incidence and number of acute brain lesions[35]. Our series was too small to draw conclusions on clinical endpoints such as periprocedural stroke. Therefore, it remains hypothetical whether neurocognitive deficits could be reduced by angiography-free guidance.

Conclusions

This observational pilot study demonstrates the safety and feasibility of interventional LAAC without the support of angiographic imaging of the LAA. However, future research with larger population groups is needed to underscore these findings and increase the statistical power.

Impact on daily practice

Patients with chronic kidney disease are frequently found in routine clinical practice. As these patients are often unsuitable for NOAC therapy but have an elevated risk of stroke and bleeding events, LAAC is an alternative. Because of relative or absolute contraindications to contrast agent, we suggest performing LAAC only with fluoroscopic and echocardiographic guidance.

Conflict of interest statement

F. Meincke and A. Ghanem received honoraria as proctors from St. Jude Medical. The other authors have no conflicts of interest to declare.

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