Management and outcomes of patients with left atrial appendage thrombus prior to percutaneous closure

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ABSTRACT

Objective Left atrial appendage (LAA) thrombus has heretofore been considered a contraindication to percutaneous LAA closure (LAAC). Data regarding its management are very limited. The aim of this study was to analyse the medical and invasive treatment of patients referred for LAAC in the presence of LAA thrombus.

Methods This multicentre observational registry included 126 consecutive patients referred for LAAC with LAA thrombus on preprocedural imaging. Treatment strategies included intensification of antithrombotic therapy (IAT) or direct LAAC. The primary and secondary endpoints were a composite of bleeding, stroke and death at 18 months, and procedural success, respectively.

Results IAT was the preferred strategy in 57.9% of patients, with total thrombus resolution observed in 60.3% and 75.3% after initial and subsequent IAT, respectively. Bleeding complications and stroke during IAT occurred in 9.6% and 2.9%, respectively, compared with 3.8% bleeding and no embolic events in the direct LAAC group before the procedure. Procedural success was 90.5% (96.2% vs 86.3% in direct LAAC and IAT group, respectively, p=0.072), without cases of in-hospital thromboembolic complications. The primary endpoint occurred in 29.3% and device-related thrombus formation in 12.8%, without significant difference according to treatment strategy. Bleeding complications at 18 months occurred in 22.5% vs 10.5% in the IAT and direct LAAC group, respectively (p=0.102).

Conclusion In the presence of LAA thrombus, IAT was the initial management strategy in half of our cohort, with initial thrombus resolution in 60% of these, but with a relatively high bleeding rate (~10%). Direct LAAC was feasible, with high procedural success and absence of periprocedural embolic complications. However, a high rate of device-related thrombus was detected during follow-up.

INTRODUCTION

Atrial fibrillation is the most common cardiac arrhythmia and a well-established risk factor for thromboembolic complications.1 The presence of left atrial thrombus in patients with non-rheumatic atrial fibrillation is a relatively common finding (17%) during transoesophageal echocardiographic (TEE), cardiac surgery or at autopsy, and the major site of thrombus formation is the left atrial appendage (LAA) in up to ~91%.2 Oral anticoagulation (OAC) is the established treatment for stroke prevention in patients with atrial fibrillation. Transcatheter LAAC closure (LAAC) has emerged as an alternative to OAC, especially in those who are at high risk of major bleeding.3 4 Previously, the presence of LAA thrombus was considered a contraindication to LAAC.

Intensification of antithrombotic therapy (IAT) is the most common strategy when LAA thrombus has been diagnosed. However, increased bleeding risk and incomplete thrombus resolution despite IAT may favour an off-label LAAC, although in the presence of thrombus.5 6 Data from case reports and small case series have suggested the feasibility of LAAC in this context.7 However, no specific data comparing a strategy of IAT versus LAAC in this scenario exist. The aim of this study, therefore, was to describe the chosen management of patients referred for LAAC and found to have LAA thrombus, and to assess the safety and efficacy of the adopted strategy, specifically comparing direct LAAC with IAT.

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METHODS

Study design and patient population

This was a multicentre retrospective registry from 21 centres, including consecutive patients with non-valvular atrial fibrillation referred for LAAC from August 2009 to March 2021 found to have an LAA thrombus on preprocedural imaging. Patients undergoing direct LAAC or deferred LAAC after IAT were included. The indication for LAAC was assessed at each centre. Data were collected in a dedicated database in accordance with the ethics committee of each participating centre. All patients provided informed consent for the procedures.

Baseline clinical characteristics, antithrombotic therapy and indication for LAAC at the time of LAA thrombus diagnosis were recorded. Preprocedural images, either by TEE or CT, were analysed by local physicians with experience in LAAC and cardiac imaging. Thrombus location was defined by its most proximal position within the LAA and divided into five categories (apex, body, neck, ostium and overhanging ostium). Mural thrombus was defined as only one surface exposed to the blood pool, flat and parallel to the endocardial surface, while protruding thrombus had more than one surface exposed and protruded into the LAA cavity. Thrombus of high echogenicity and clear borders was classified as organised thrombus.

Two treatment strategies were adopted in patients with LAA thrombus: deferred LAAC after IAT or direct LAAC. IAT was classified into (1) parenteral anticoagulation (either unfractionated heparin or low molecular weight heparin (LMWH)); (2) addition, change or intensification of OAC, involving direct OAC and vitamin K antagonist (VKA); and (3) addition of antiplatelet therapy. LAAC was performed using either standard deployment techniques or the no-touch technique. The no-touch technique involves the avoidance of contrast injections or the use of only small volume, subselective injections from outside the LAA orifice, avoiding guidewire and catheter manipulation within the LAA by loading the closure device with the delivery sheath in the left superior pulmonary vein (LSPV), and careful retraction of the delivery sheath from the LSPV into the LAA with the device partially unsheathed into its atraumatic ‘ball’ structure.

The procedure, therefore, is performed without engaging the LAA with the delivery sheath. This technique is feasible with the Amplatz cardiac plug and Amulet (Abbott Laboratories), LAmbre (Lifetech Scientific), Ultrasel (Cardia) and Watchman FLX (Boston Scientific), but not with Watchman (Boston Scientific) device. Embolic protection devices (EPD) were used at the operator’s discretion.

Device success was defined as deployment of the occluder in the correct position. Procedural success was defined as exclusion of the LAA without device-related complications, leak > 5 mm or procedural-related complications (including stroke, systemic embolism, transient ischaemic attack, pericardial effusion and bleeding). Clinical follow-up was performed according to each centre’s standard of care, and data regarding vital status, bleeding and thromboembolic complications and device-related thrombosis (DRT) were collected at last follow-up.

The primary endpoint was a composite of major adverse events, including death, bleeding and stroke at 18-month follow-up. The secondary endpoint was procedural success rate. This research was done without patient involvement. Patients were not invited to comment on the study design and were not consulted to develop patient relevant outcomes or interpret the results.

Statistical analysis

Categorical variables were summarised as n (percentage) and compared using χ² test or Fisher’s exact test as appropriate. Continuous variables were summarised as mean (SD) or median (IQR; 25th–75th percentile) and compared using two-sided Student’s t-test or Mann-Whitney U test according to their distribution. Assessment of normality for continuous data was performed using the Shapiro-Wilk test. Survival analyses were performed using Kaplan-Meier survival function. Time zero was considered to be the first diagnosis of LAA thrombus during work-up for LAAC. Survival comparisons were performed using log-rank test. P values less than 0.05 were considered statistically significant. All data were analysed using Stata V.14.

RESULTS

From 3222 patients undergoing LAAC in 21 institutions, 126 (3.9%) patients with LAA thrombus on preprocedural imaging were included. The indication for LAAC and baseline antithrombotic treatment are presented in online supplemental figure 1. Thrombus location and dimensions by TEE (85.7%) or CT (14.3%) are presented in figure 1 and table 1.

Therapeutic strategy: IAT or direct LAAC

Patient flow according to therapeutic approach, thrombus resolution and use of EPD is shown in figure 2. Seventy-three patients (57.9%) underwent IAT followed by deferred LAAC, while 53 (42.1%) underwent direct LAAC. Patients undergoing direct LAAC were older, with a higher prevalence of diabetes and higher bleeding risk (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs/alcohol concomitantly (HAS-BLED) score: 3.6±1.4 vs 3.0±1.4, p=0.014) (table 1). LAA apical thrombus was more frequent in patients undergoing direct LAAC (54.2% vs 78.7%, p=0.006) and mobile thrombus was more common in the IAT group (51.5% vs 23.9%, p=0.003) (figure 1).

Among patients undergoing IAT, total thrombus resolution was achieved in 60.3% (n=44/73) after 57 days (IQR: 25th–75th percentile) and compared using two-sided Student’s t-test or Mann-Whitney U test according to their distribution. P values less than 0.05 were considered statistically significant. All data were analysed using Stata V.14.

Among the 53 patients allocated to direct LAAC, total thrombus resolution was achieved in 60.3% (n=44/73) after 57 days (IQR: 25th–75th percentile) and compared using two-sided Student’s t-test or Mann-Whitney U test according to their distribution. P values less than 0.05 were considered statistically significant. All data were analysed using Stata V.14.

Arrhythmias and sudden death

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LAAC and in-hospital outcomes

Procedural details according to treatment strategy are summarised in table 2. The most commonly used device was the Amplatzer cardiac plug or Amulet (74.4%), particularly in the group undergoing direct LAAC (83.0% vs 69.9%, p=0.091). No-touch technique and EPD were more frequently used in the direct LAAC group (64.2% vs 20.6%, p<0.001; and 34.0% vs 17.8%, p=0.038, respectively). Embolic material was present in the EPD filters in 19.4% of cases, all of whom had identifiable LAA thrombus during the procedure.

In-hospital outcomes and medical therapy at discharge are presented in table 3. In the overall cohort, device and procedural success were achieved in 98.4% and 90.5%, respectively. Two unsuccessful deployments occurred in the IAT group due to complex LAA anatomy. Procedural success was 86.3% in the IAT group and 96.2% in the direct LAAC group (p=0.072). This difference was mainly driven by a lower rate of bleeding, particularly pericardial effusion, and higher rate of complete LAA occlusion in the direct LAAC group. There were no cases of intraprocedural stroke, systemic embolism or death. One patient in the IAT group had a transient ischaemic attack (0.8%) on the day of the procedure. Approximately half (49.6%) were discharged on DAPT. There was no statistical difference between groups in terms of in-hospital outcomes and the choice of medical therapy at discharge. Clinical characteristics, procedural aspects and in-hospital complications according to the presence of thrombus at the time of LAAC procedure are shown in online supplemental tables 1–3.

Clinical and imaging follow-up

Follow-up post-LAAC was available in 124 patients (98.4%). The median time of follow-up was 22.1 months (IQR: 13.2–40.5). The primary endpoint of major adverse events at 18 months occurred in 29.3% (95% CI 21.7% to 38.8%) in the overall cohort, 31.5% (95% CI 21.7% to 44.4%) in those with IAT and 26.1% (95% CI 15.7% to 41.6%) of those undergoing direct LAAC (p=0.365; figure 4A). Bleeding complications occurred in 17.4% (95% CI 11.6% to 25.8%) at 18-month follow-up: 22.5% (95% CI 14.1% to 34.7%) in the IAT group and 10.5% (95% CI 4.5% to 23.6%) in the direct LAAC group (p=0.102; figure 4B).

Six patients suffered a stroke during follow-up. Two presented during IAT and prior to LAAC. Four presented after LAAC: two in the IAT group (2.6- and 2.9-month follow-up) and two in the direct LAAC group (10.8- and 12.7-month follow-up (figure 4C). Eighteen-month all-cause mortality was 11.6% (95% CI 6.7% to 19.7%), 9.0% (95% CI 3.8% to 20.7%) in the IAT group and 15.4% (95% CI 7.6% to 29.7%) in the direct LAAC cohort (p=0.260). Follow-up imaging was performed in 102 (80.9%) patients (90 by TEE, 11 by CT and 1 by both) within a median time of 2.9 months (IQR: 1.9–9.1). Thirteen patients (12.8%) had DRT, without difference between strategies (13.6% and 11.6% in the IAT and direct LAAC group, respectively, p=0.999). A trend towards a lower rate of DRT was observed in patients with OAC at discharge (4%), compared with those without OAC (14.7%, p=0.155).

DISCUSSION

The present study is the first multicentre registry to analyse both medical and interventional management and outcomes in patients referred for percutaneous LAAC and found to have LAA thrombus. The main findings were the following: (1) although ~62% were taking OAC at baseline, the initial management in over half of patients was IAT (58%), with direct LAAC being employed in 42%; (2) first IAT (predominantly parenteral anticoagulation) resulted in complete LAA thrombus resolution in 60%, with subsequent further IAT increasing this to 75%; (3) patients undergoing direct LAAC more frequently had apical and immobile LAA thrombi with high procedural success rate (96%), no increased procedural complications and no periprocedural...
embolic events; (4) the primary endpoint of major adverse events at 18 months was 29.3%, with no difference between strategies and DRT occurring in 12.8%; and (5) bleeding complications tended to be higher in the IAT group compared with the direct LAAC group despite a lower estimated bleeding risk.

Medical management of LAA thrombus

The prevalence of LAA thrombus is relatively frequent in non-anticoagulated (9%–22%) and anticoagulated (up to 8.3%) patients with atrial fibrillation. A number of clinical (as incorporated into the congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke, vascular disease, age 65–74 years, sex category (CHA2DS2VASC scoring system), anatomical (left atrial size) and functional (spontaneous echo contrast and LAA exit velocity) factors have been associated with LAA thrombus. Multilobed LAAs have been shown to have a higher risk of thrombus. Cauliflower LAA morphology, which is associated with lower velocity and shear strain rate within the LAA, is associated with a higher risk of stroke, while chicken-wing morphology and a shorter distance from LAA ostium to the first bend have been shown to have a lower risk of stroke. This association may be due to differences in fluid dynamics within the LAA, conferring a greater risk of thrombus formation. In patients referred for ablation of atrial fibrillation and

Table 1  Baseline characteristics and preprocedural imaging findings according to treatment strategy

|                                                                 | Overall cohort N=126 | Intensification of antithrombotic therapy n=73 | Direct LAAC n=53 | Difference (95% CI) | P value |
|----------------------------------------------------------------|----------------------|-----------------------------------------------|------------------|--------------------|---------|
| **Clinical baseline characteristics**                           |                      |                                               |                  |                    |         |
| Age, years*                                                   | 72.5 (10.4)          | 70.9 (11.0)                                  | 74.7 (9.1)       | −3.8 (−7.5 to −0.1) | 0.042   |
| Male sex, n (%)                                               | 78 (61.9)            | 49 (67.1)                                    | 29 (54.7)        | 12.4 (−4.8 to 29.6) | 0.157   |
| Body mass index, kg/m²*                                       | 26.8 (4.3)           | 27.2 (4.1)                                   | 26.3 (4.5)       | 1.0 (−0.8 to 2.7)  | 0.276   |
| Diabetes, n (%)                                               | 43 (34.1)            | 18 (24.7)                                    | 25 (47.2)        | −22.5 (−39.2 to 5.8) | 0.009   |
| Previous stroke, n (%)                                        | 50 (38.0)            | 34 (46.6)                                    | 16 (30.2)        | 16.4 (−0.5 to 33.2) | 0.063   |
| Prior peripheral embolisation, n (%)                          | 8 (6.4)              | 5 (6.9)                                      | 3 (5.7)          | 1.2 (−7.3 to 9.7)  | 0.999   |
| Prior bleeding, n (%)                                         | 85 (67.5)            | 44 (60.3)                                    | 41 (77.4)        | −17.1 (−33.0 to −11.8) | 0.043   |
| CHA2DS2VASC score*                                            | 4.4 (1.6)            | 4.5 (1.5)                                    | 4.4 (1.6)        | −0.1 (−0.7 to 0.4)  | 0.634   |
| HAS-BLED score*                                               | 3.2 (1.4)            | 3.0 (1.4)                                    | 3.6 (1.4)        | −0.6 (−1.1 to −0.1) | 0.014   |
| Anticoagulation therapy contraindication, n (%)               |                      |                                               |                  |                    |         |
| Relative                                                      | 50 (39.7)            | 31 (42.5)                                    | 19 (35.9)        | 6.6 (−10.7 to 23.8) | 0.454   |
| Absolute                                                      | 40 (31.8)            | 16 (21.9)                                    | 24 (45.3)        | −23.4 (−39.9 to −6.9) | 0.005   |
| **Imaging characteristics**                                   |                      |                                               |                  |                    |         |
| **LAA dimensions**                                            |                      |                                               |                  |                    |         |
| Orifice diameter (mm)*                                        | 22.6 (4.2)           | 22.3 (4.6)                                   | 22.9 (3.7)       | −0.6 (−2.2 to 1.0)  | 0.444   |
| Length (mm)*                                                  | 31.9 (8.4)           | 31.8 (8.5)                                   | 32.0 (8.3)       | −0.2 (−3.5 to 3.0)  | 0.892   |
| Morphology, n (%)                                             |                      |                                               |                  |                    |         |
| Cauliflower                                                  | 18 (14.8)            | 13 (72.2)                                    | 5 (9.4)          | 8.9 (−3.1 to 20.8)  | 0.525   |
| Chicken-wing                                                 | 36 (29.5)            | 19 (27.5)                                    | 17 (32.1)        | −5.3 (−21.6 to 10.9) | 0.782   |
| Windsock                                                     | 60 (49.2)            | 33 (47.8)                                    | 27 (50.9)        | −4.5 (−22.2 to 13.3) | 0.641   |
| Cactus                                                       | 8 (6.6)              | 4 (5.8)                                      | 4 (7.6)          | −1.9 (−10.8 to 7.0) |         |
| **Thrombus location, n (%)**                                  |                      |                                               |                  |                    |         |
| Apex                                                         | 76 (63.9)            | 39 (54.2)                                    | 37 (78.7)        | −24.6 (−41.0 to −8.1) | 0.028   |
| Body                                                         | 22 (18.5)            | 16 (22.2)                                    | 6 (12.8)         | 9.5 (−4.1 to 23.0)  |         |
| Neck                                                         | 5 (4.2)              | 4 (5.6)                                      | 1 (2.1)          | 3.4 (−3.3 to 10.1)  |         |
| Ostium                                                       | 8 (6.7)              | 8 (11.1)                                     | 0               | 11.1 (3.9 to 18.4)  |         |
| Overhanging LAA ostium                                       | 8 (6.7)              | 5 (6.9)                                      | 3 (6.4)          | 0.6 (−0.9 to 9.7)   |         |
| **Thrombus size**                                             |                      |                                               |                  |                    |         |
| Major diameter (mm)*                                         | 14.0 (6.7)           | 14.6 (7.8)                                   | 13.2 (5.5)       | 1.5 (−1.3 to 4.2)   | 0.293   |
| Minor diameter (mm)*                                         | 8.8 (3.5)            | 8.8 (3.5)                                    | 8.9 (3.4)        | −1.0 (−1.5 to 1.3)  | 0.889   |
| Area (mm²)*                                                  | 148.3 (109.5)        | 154.4 (115.8)                                | 142.5 (104.3)    | −11.9 (−35.9 to 59.7) | 0.622   |
| Mobile thrombus†                                              | 45/112 (40.2)        | 34/66 (51.5)                                 | 11/46 (23.9)     | 27.6 (10.4 to 44.8) | 0.003   |
| **Thrombus morphology†, n (%)**                              |                      |                                               |                  |                    |         |
| Mural thrombus†                                               | 60/113 (53.1)        | 32/67 (47.8)                                 | 28/46 (60.9)     | −13.1 (−31.6 to 5.4) | 0.170   |
| Protruding thrombus†                                          | 53/113 (46.9)        | 35/67 (52.2)                                 | 18/46 (39.1)     |                  |         |
| Organised thrombus†                                          | 77/112 (68.8)        | 46/67 (68.7)                                 | 31/45 (68.9)     | −0.2 (−17.7 to 17.3) | 0.979   |
| Spontaneous echo contrast, n (%)                             | 79 (65.8)            | 45 (62.5)                                    | 34 (70.8)        | −8.3 (−25.4 to 8.7) | 0.346   |

χ² test was used to compare binary variables, with Fisher’s exact test being used when n<5.

*The denominator in each cell indicates the number of patients with available data.

CHA2DS2VASC, congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke, vascular disease, age 65–74 years, sex category; HAS-BLED, hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs/alcohol concomitantly; LAA, left atrial appendage; LAAC, left atrial appendage closure.
found to have LAA thrombus, current recommendations suggest the use of full-dose LMWH followed by VKA, aiming for an international normalized ratio (INR) between 2.5 and 3.5 prior to carrying out the procedure. However, this approach is not always feasible in patients referred for LAAC due to their high bleeding risk. Of the patients in our study, 58% underwent IAT, with the remaining undergoing direct LAAC, reflecting the clinical dilemma and the paucity of data in this challenging situation. However, the relatively high rates of bleeding complications (9.6%) and stroke (2.7%) raise some concerns with the IAT strategy. A careful, individualised assessment of patients’ clinical and anatomical characteristics should be performed to weigh the bleeding risk with IAT versus a direct LAAC in the presence of LAA thrombus.

**Direct LAAC with LAA thrombus**

The presence of atrial thrombi has been an exclusion criterion in randomised LAAC clinical trials to date due to the risk of periprocedural embolic events on manipulation of the LAA. However, an absolute contraindication for anticoagulation (nearly 30% in our cohort) or failure of IAT to resolve the thrombus (40% in our cohort) has resulted in many operators performing percutaneous LAAC in the presence of thrombus, with many taking steps to minimise potential embolisation.

Data regarding LAAC in the presence of thrombus are restricted to case reports and one retrospective multicentre registry of 28 patients. Recently, a systematic review has collected all 58 published cases showing 100% successful device implantation. In this study, lobe- and-disc devices were more frequently used (76%), EPD was used in 29% patients, and no periprocedural complications were reported. Despite these promising results, publication bias might be of concern since a considerable amount of the data came from case reports. Our study included 126 consecutive patients with LAA thrombus, analysing both medical and invasive approaches and their outcomes. Our results support the feasibility and safety of direct LAAC in selected patients, with procedural success being 96% and no cases of systemic embolism observed.

**Figure 2** Flow of patients according to treatment strategy. *Six patients showed no thrombus during LAAC imaging. EPD, embolic protection device; IAT, intensification of antithrombotic therapy; LAAC, left atrial appendage closure.

**Figure 3** Antithrombotic therapy at baseline, first line of treatment intensification and response of thrombus resolution. OAC, oral anticoagulation.
could be considered when planning LAAC in patients with EPDs are a common adjunct in many cardiac procedures and CT, respectively) or thrombus within LAA trabeculae. The new-generation Watchman FLX with the possibility of advancing technique for device implantation may also be effective in trapping thrombus distally. Future studies will have to determine the feasibility and efficacy of this device in a larger cohort.

Acute brain lesions detected by MRI occur in up to 48% after LAAC. EPD might reduce the incidence of these lesions, as has been shown in transcatheter aortic valve replacement. In the presence of LAA thrombus, the use of these devices may be particularly appropriate; however, in our study, EPD was used in only 34% of patients with LAA thrombus undergoing direct LAAC, a percentage slightly higher than previous LAAC randomised trials.28 EPD might reduce the incidence of these lesions, as has been shown in transcatheter aortic valve replacement. 29 In our study, antilatelet therapy was the most frequent treatment (68%). However, ~25% were maintained on anticoagulant therapy. Although peripheral embolism was uncommon, DRT occurred in 13% of patients at 3-month follow-up. This rate is higher compared with previous LAAC randomised trials and registries, which have reported rates between 1.5% and 5.7% at 2-month and 18-month follow-up, respectively. The high incidence of DRT probably reflects a prothrombotic environment in this population. LAA exclusion with systems such as LARIAT might be an alternative since an endocardial device is not implanted, avoiding the risk of DRT. However, ~25% were maintained on anticoagulant therapy. Although peripheral embolism was uncommon, DRT occurred in 13% of patients at 3-month follow-up. This rate is higher compared with previous LAAC randomised trials and registries, which have reported rates between 1.5% and 5.7% at 2-month and 18-month follow-up, respectively. The high incidence of DRT probably reflects a prothrombotic environment in this population. LAA exclusion with systems such as LARIAT might be an alternative since an endocardial device is not implanted, avoiding the risk of DRT. However, advancement of an endocardial guidewire into the LAA apex is needed during the procedure, representing a limitation for patients with residual thrombus. The clinical implications of DRT justify further studies to confirm our findings and analyse its impact and management in this particular clinical scenario.
Table 3  In-hospital and mid-term outcomes according to treatment strategy

| Outcome                                      | Overall cohort (N=126) | Intensification of antithrombotic therapy n=73 | Direct LAAC n=53 | Difference (95% CI) | P value |
|----------------------------------------------|------------------------|-----------------------------------------------|------------------|---------------------|---------|
| Device success, n (%)                        | 124 (98.4)             | 71 (97.3)                                     | 53 (100)         | −2.7 (−6.5 to 1.0)  | 0.509   |
| Procedural success, n (%)                    | 114 (90.5)             | 63 (86.3)                                     | 51 (96.2)        | −9 to 9 (−19.3 to −0.5) | 0.072   |
| Residual shunt                               | 4 (3.2)                | 3 (4.1)                                       | 1 (1.9)          | 2.2 (−3.6 to 8.1)   | 0.638   |
| Complete LAA occlusion                       | 122 (96.8)             | 70 (95.9)                                     | 52 (98.1)        | −2.2 (−8.1 to 3.6)  | 0.638   |
| Pericardial effusion                         | 3 (2.4)                | 3 (4.1)                                       | 0                | 4.1 (−0.4 to 8.7)   | 0.263   |
| Transient ischaemic attack                   | 1 (0.8)                | 1 (1.4)                                       | 0                | 1−4 (−1.3 to 4.0)   | 0.999   |
| Intraprocedural stroke                       | 0                      | 0                                             | 0                |                     |         |
| Systemic embolism                            | 0                      | 0                                             | 0                |                     |         |
| Bleeding                                     | 7 (5.6)                | 5 (6.9)                                       | 2 (3.8)          | 3.1 (−4.6 to 10.8)  | 0.698   |
| Death                                        | 0                      | 0                                             | 0                |                     |         |
| Length of hospital stay*                     | 1 (1−2)                | 2 (1−3)                                       | 1 (1−2)          |                     | 0.013   |
| Medical therapy at discharge, n (%)          |                        |                                               |                  |                     |         |
| None                                         | 10 (8.1)               | 3 (4.2)                                       | 7 (13.5)         | −9.2 (−19.6 to 1.2) | 0.153   |
| SAPT                                         | 23 (18.7)              | 11 (15.5)                                     | 12 (23.1)        | −7.6 (−21.8 to 6.6) | 0.365   |
| DAPT                                         | 61 (49.6)              | 40 (56.3)                                     | 21 (40.4)        | 15.9 (−1.7 to 33.6) | 0.999   |
| Anticoagulation (VKA or DOAC)                | 18 (14.6)              | 9 (12.7)                                      | 9 (17.3)         | −4.6 (−17.5 to 8.2) | 0.570   |
| Anticoagulation+SAPT                         | 9 (7.3)                | 7 (9.9)                                       | 2 (3.9)          | 6.0 (−2.7 to −14.7) | 0.177   |
| Anticoagulation+DAPT                         | 2 (1.6)                | 1 (1.4)                                       | 1 (1.9)          | −0.5 (−5.1 to 4.1)  | 0.688   |
| Primary endpoint at 18-month follow-up       |                        |                                               |                  |                     |         |
| Major adverse events (death, bleeding and stroke)†, % | 29.3                  | 31.5                                          | 26.1             | HR: 1.4 (0.7 to 2.8) | 0.365   |

χ² test was used to compare binary variables, with Fisher’s exact test being used when n<5.

*Mann-Whitney U test used.

†Kaplan-Meier survival analysis, compared with log-rank test.

DAPT, dual antiplatelet therapy; DOAC, direct oral anticoagulant; LAA, left atrial appendage; LAAC, left atrial appendage closure; SAPT, single antiplatelet therapy; VKA, vitamin K antagonist.

Figure 4 Kaplan-Meier survival estimates for MAE, bleeding and stroke. Plot of survival functions for (A) MAE (composite of bleeding, stroke and death), (B) bleeding and (C) stroke at 18-month follow-up according to the treatment strategy. Median and IQR for time from thrombus diagnosis to LAAC in each group are represented as reference lines on the x axis. IAT, intensification of antithrombotic therapy; LAAC, left atrial appendage closure; MAE, major adverse event.
Study limitations
This study had the limitations inherent to a non-randomised, observational study, without external adjudication of events. The therapeutic approach (i.e. direct LAAC), antithrombotic therapy, modifications in LAAC technique and the use of EPD were left to clinicians’ and operators’ discretion, representing real-world practice. Therefore, there is a potential selection bias between treatment groups, and we cannot rule out the possibility that direct LAAC was performed in patients with more favourable anatomy. Imaging follow-up was not available for all patients. Because of the low incidence of procedural complications, predictors of these complications could not be analysed. Additionally, there were no data available for patients with LAA thrombus who ultimately did not undergo LAAC procedure.

CONCLUSIONS
Percutaneous LAAC in the presence of LAA thrombus as an initial or deferred strategy is feasible and safe, with high procedural success and low rates of periprocedural complications. Intensification of antithrombotic treatment for thrombus resolution was the initial strategy in half of the population, with a relatively high rate of bleeding events before LAAC and at 18-month follow-up. Device thrombosis remains a concern during follow-up and further work is required to determine the optimal treatment strategy following LAAC.

What is already known on this subject?
⇒ The management of patients with atrial fibrillation referred for left atrial appendage closure (LAAC) who are found to have left atrial appendage (LAA) thrombus is challenging.
⇒ No specific data exist regarding the safety and efficacy of different management options for these patients with high risk of bleeding.

What might this study add?
⇒ In this multicentre registry comparing management and outcomes of patients with LAA thrombus referred for percutaneous LAAC, intensification of antithrombotic therapy ultimately resulted in complete thrombus resolution in 75% cases after several lines of antithrombotic treatment; however, a relatively high bleeding rate was observed before LAAC.
⇒ Patients undergoing direct LAAC had higher bleeding risk and more frequently apically located and immobile thrombi.
⇒ In these selected patients, direct LAAC was feasible with a high procedural success rate and absence of embolic complications.
⇒ Both approaches had a high rate of device-related thrombosis during follow-up.

How might this impact on clinical practice?
⇒ Direct LAAC might be considered as treatment strategy in selected patients with an indication for LAAC and evidence of LAA thrombus.
⇒ Experienced operators, a modified procedural technique and use of embolic protection device should be considered in this scenario.

Key messages

What is already known on this subject?
⇒ The management of patients with atrial fibrillation referred for left atrial appendage closure (LAAC) who are found to have left atrial appendage (LAA) thrombus is challenging.
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