European Journal of Therapeutics

DOI:10.5152/EurJTher.2022.22047

Original Article

Effective Therapeutic Intervention for Left Atrial Appendage Thrombus: Percutaneous Left Atrial Appendage Closure

Cem Çöteli, Sevda Aygün, Ahmet Hakan Ateş, Uğur Nadir Karakulak, Hikmet Yorgun, Levent Şahiner, Barış Kaya, Kudret Aytemir

Department of Cardiology, Hacettepe University, Faculty of Medicine, Ankara, Turkey

ABSTRACT

Objective: The thrombus formation in the left atrial appendage (LAA) can be challenging for operators and increases periprocedural complication risk. However, recent consensus documents discuss that left atrial appendage closure is a potential therapeutic option for malign left atrial appendage. This clinical study aimed to evaluate the procedural safety and early efficacy outcomes of left atrial appendage closure in patients with left atrial appendage thrombus.

Methods: This observational single-center clinical trial included 18 patients with left atrial appendage thrombus. Transesophageal echocardiography was performed before and during the left atrial appendage closure in all patients. All procedures were performed using the Amplatzer Amulet left atrial appendage closure device (Abbott Medical Inc.).

Results: Ten of the patients were male (55.6%). The mean ages were 69.6 ± 7.5 years. CHA_2DS_2-VASc and HAS-BLED scores were calculated at 5 (2-8) and 3 (1-6), respectively. In 4 patients (22.2%), left atrial appendage occlusion was indicated due to malign left atrial appendage. The significant bleeding event under oral anticoagulant treatment was the main indication in 12 patients (66.7%). All patients were referred to Transthoracic Echocardiography (TTE) and transesophageal echocardiography 30 days after the procedure. There were no major or minor adverse clinical events during the first month of follow-up. Also, no patient faced ischemic cerebrovascular events, including transient ischemic attack, hospitalization due to heart failure, or significant bleeding events. Neither device-related thrombus nor peridevice leak was observed in the Transesophageal echocardiography evaluation.

Conclusions: Left atrial appendage closure in patients with left atrial appendage thrombus is a feasible and effective method to reduce thromboembolic risk. It can be performed as an alternative therapy to oral anticoagulants (OACs) in patients with contraindications to OACs or malign left atrial appendage.

Keywords: Anticoagulants, atrial appendage, atrial fibrillation, catheterization closure devices, thrombosis

INTRODUCTION

Left atrial appendage (LAA) closure is a feasible and effective therapy to prevent thromboembolic events in patients with nonvalvular atrial fibrillation (AF). Recent guidelines suggest the LAA closure (LAAC) for AF patients with oral anticoagulant contraindication or high bleeding risk.[1,2] On the other hand, recent trials showed that the outcomes of LAAC are non-inferior to NOACs.[3] Growing procedural experience and device technology improvements expand the LAAC indications, and LAAC can be performed with the indication such as the patient's choice.

The thrombus formation in LAA can be challenging for operators and increases periprocedural complication risk. Even the challenges, case series, and multicenter observational studies showed that LAAC is a safe and effective procedure in patients with LAA thrombus.[4-6] Although LAA thrombus was considered a contraindication for LAAC several years ago, recent consensus documents discuss that LAAC is a potential therapeutic option for malign LAA.[7,8]

This clinical study aimed to evaluate the procedural safety and early efficacy outcomes of LAAC in patients with LAA thrombus.

METHODS

Study Population

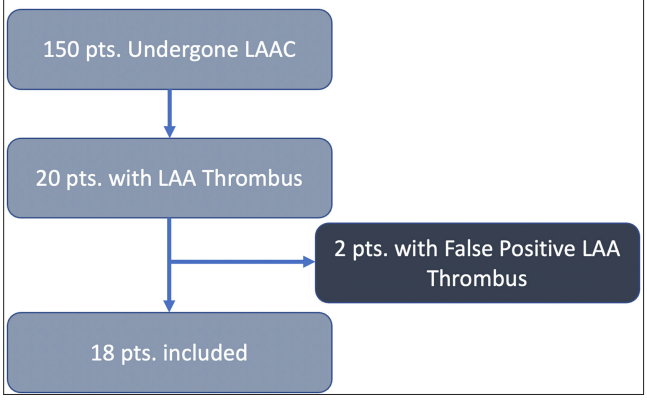
In this trial, the patients who were referred to percutaneous LAAC and had LAA thrombus in preprocedural transesophageal echocardiography (TEE) were enrolled. One hundred fifty-eight consecutive patients had undergone percutaneous LAAC in Hacettepe University Department of Cardiology between 2015 and 2022. Thrombus formation in the LAA was observed in 20 patients in preprocedural assessment. In 2 patients, the

Cite this article as: Çöteli C, Aygün S, Ateş AH, et al. Effective therapeutic intervention for left atrial appendage thrombus: Percutaneous left atrial appendage closure. *Eur J Ther.* 2022;28(3):171–175.

Corresponding author: Cem Çöteli, e-mail: cemcoteli@hacettepe.edu.tr

Received: July 4, 2022 **Accepted:** July 25, 2022

Figure 1. Flowchart of study. LAA, left atrial appendage; LAAC, LAA closure.



intravenous isoproterenol test showed that the thrombus image in preprocedural TEE was false positive for LAA thrombus. This observational single-center clinical trial included the rest of the 18 patients. Patients with overflowing LAA thrombus (type 0), concomitant mechanic heart valve, false-positive LAA thrombus (according to intravenous isoproterenol test), and are younger than 18 years were excluded (Figure 1).

Their baseline characteristics, antithrombotic medication, LAAC indications, and adverse events, including intraprocedural and during follow-up, were recorded. The written informed consent was taken from all patients before the procedure. Hacettepe University Ethics Committee approved the study (May 28, 2019, GO 19/483).

Preprocedural and Intraprocedural Thrombus Evaluation

All patients were examined with TEE cardiography before and during the procedure. After 2021, if any thrombus formation was observed or any suspicion was present in preprocedural TEE, an intravenous isoproterenol test was performed in intraprocedural TEE to confirm the presence of LAA thrombus. The intravenous isoproterenol test was done following the protocol (2 μg/min/kg over 3 min), previously described in the case report by Enomoto et al.[9]

All thrombus formations were defined according to the classification (Type 0 (overflowing), 1 (proximal to distal), and 2 (distal)) that we described in our previous study.[5]

Main Points

- The thrombus formation in left atrial appendage (LAA) is not a contraindication for percutaneous LAA closure.
- Percutaneous LAA closure can be used as a potential therapy for LAA thrombus which is resistant to OACs. Further large-scale trials are needed.
- Left atrial appendage closure in patients with LAA thrombus should be performed carefully to avoid unnecessary manipulations by experienced operators.

Procedure

The procedural technique of LAA occlusion in the patients with LAA thrombus was described in detail in our previous study.[5] All procedures were performed under general anesthesia and with fluoroscopy and TEE guidance. Amplatzer Amulet LAA closure device (Abbott Medical Inc.) was used in all patients. The inferoposterior septum was targeted for transseptal puncture to align the LAA ostium optimally. The manipulations to engage LAA ostium were minimized to avoid interaction with thrombus. Measurements of LAA and decisions on device size were made based on intraprocedural TEE. After optimal engagement to the LAA ostium, the lobe of the device was opened. Then, the disc was opened at the ostium after settlement of correctly placing the lobe in the LAA (Figure 2). The circumflex artery and mitral valve functions were evaluated with 3D-TEE. The device stability was tested before release. Intravenous heparin infusion was continued during the procedure, and dosage was adjusted with activated clotting time monitoring.

Procedural Success

After implantation, all patients were apprised of an effective occlusion (peridevice leak < 3 mm). Successful implantation is defined as the implantation that results in effective occlusion without migration of the device. MACE includes mortality, myocardial infarction, urgent surgery requirement, and clinically significant cerebrovascular ischemic or hemorrhagic events.

Postprocedural Follow-Up

The antiplatelet therapy was planned according to individual characteristics, including the indication of LAAC and each patient's thromboembolism and bleeding risk. It was scheduled as dual-antiplatelet therapy (DAPT) or a continuation of anticoagulant therapy.

The patients were examined with TTE and TEE in the first month after the procedure. Any adverse events were recorded, including bleeding complications, thromboembolic events, and heart failure or myocardial infarction hospitalization.

Statistical Analysis

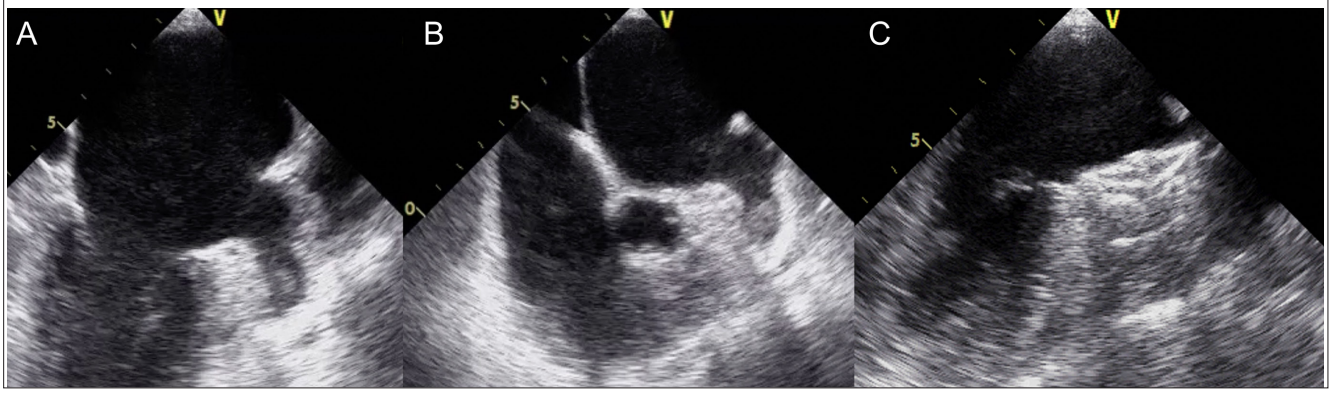
We used Statistical Package for the Social Sciences statistical software, version 20 for statistical analysis. Frequencies and percentages were used to present descriptive categorical variables. Mean values and standard deviation were used to give continuous data with the Gaussian distribution. Quantitative variables with non-Gaussian distribution are expressed with median and range. The distribution of variables was evaluated with the Kolmogorov–Smirnov test.

RESULTS

Baseline Characteristics

Eighteen patients were enrolled in the study. Ten of the patients were male (55.6%). The mean ages were 69.6 ± 7.5 years. Hypertension (17; 94.4%) was the most common comorbidity in the study population. CHA_2DS_2-VASc and HAS-BLED scores were calculated at 5 (2-8) and 3 (1-6), respectively. In 4 patients

Figure 2. (A-B) Thrombus formation in LAA (type 1). (C) Implanted Amulet device. LAA, left atrial appendage.



(22.2%), LAA occlusion was indicated due to malign LAA. The significant bleeding event under oral anticoagulant treatment was the main indication in 12 patients (66.7%). Baseline characteristics are listed in Table 1.

Left Atrial Appendage Thrombus Features

Type 1 and type 2 LAA thrombus were observed in 5 (27.8%) and 13 (72.2%) patients, respectively. Amplatzer Amulet Device was used in all patients. In 6 patients (33.3%) who had performed LAAC after 2021, intravenous isoproterenol was given to confirm LAA thrombus presence and its localization.

Procedural and Follow-up Outcomes

The LAA was occluded successfully in all 18 patients. All patients were discharged after the procedure and applied for 1 month after discharge. The median postprocedural hospitalization duration was 1 day (1-3). No MACE was observed during hospitalization.

Table 1. Baseline Characteristics

Age (years)	69.6 ± 7.5
Male sex	10 (55.6%)
Permanent atrial fibrillation	18 (100%)
Hypertension	14 (77.8%)
Heart failure	7 (39%)
Diabetes mellitus	7 (39%)
Coronary heart disease	12 (66.7%)
Chronic kidney disease	8 (44.4%)
Ischemic stroke	6 (33.3%)
$CHA2DS_2$–VASc score	5 (2–8)
HAS–BLED score	3 (1–6)
LAA closure indication	
• Bleeding	12 (66.7%)
• High bleeding risk	2 (11.1%)
• Malign LAA	4 (22.2%)

LAA, left atrial appendage.

All patients were referred to TTE and TEE 30 days after the procedure. There were no major or minor adverse clinical events during the first month of follow-up. Also, no patient faced ischemic cerebrovascular events, including transient ischemic attack, hospitalization due to heart failure, or significant bleeding events. Neither device-related thrombus nor peridevice leak was observed in the TEE evaluation.

Postprocedural antiplatelet treatment was decided on clopidogrel, DAPT, or oral anticoagulant plus clopidogrel in 4, 10, and 4 patients, respectively. Procedural and follow-up outcomes are stated in Table 2.

DISCUSSION

The main finding of this trial is that percutaneous LAAC can be performed effectively and safely in patients with LAA thrombus. Procedural feasibility is independent of the LAA occlusion indication. Left atrial appendage occlusion could be an alternative and effective treatment for patients with LAA thrombus resistant to effective oral anticoagulation therapy.

The LAA is the primary location in the heart for thrombus formation in non-valvular AF. It is responsible for 90% of the thrombus

Table 2. Outcomes

Procedural outcomes	(n = 18)
General anesthesia	18 (100%)
Amplatzer Amulet device	18 (100%)
Implantation at first attempt	16 (92%)
Procedural success	18 (100%)
Periprocedural bleeding	0 (0%)
Length of stay at hospital (days)	1 (1–3)
One month follow-up outcomes	(n = 18)
Ischemic events	0 (0%)
Bleeding events	0 (0%)
Thrombus on device at 1-month follow-up	0 (0%)
Peridevice leak at 1-month follow-up	0 (0%)

in the left atrium.[10] First-line therapy for preventing thromboembolic events in AF is oral anticoagulants. Non-vitamin K oral anticoagulants are safe and effective in non-valvular AF.[1] However, many non-valvular AF patients have a contraindication for oral anticoagulation or significant bleeding history under oral anticoagulant treatment. In addition, thrombus formation can be observed with TEE in patients who use the effective dosage of oral anticoagulants. The recent guidelines suggest LAA occlusion for AF patients with an oral anticoagulant contraindication or high bleeding risk.[1,2] On the other hand, optimal therapy for LAA thrombus resistant to OACs is not clear. In addition, there is no consensus on managing the patients with high bleeding risk and LAA thrombus. Consequently, we aimed to evaluate the feasibility of LAAC in our study group, which is the patients with LAA thrombus with or without OACs contraindication.

The Munich consensus document on LAAC emphasized that LAA thrombus, resistant to OACs, is one of the indications of LAAC.[7] More recent consensus documents stated that LAAC in patients with malign LAA is considerable.[8] We had published the first case report, which reported LAAC in a patient with high bleeding risk and LAA thrombus.[4] In addition, recent studies showed that LAAC in patients with LAA thrombus is feasible.[11]

Tarantini et al.[11] published the multicenter case series, which included 32 patients with or without high bleeding risk. In this multicenter case series, there were 3 patients with malign LAA. There was no thromboembolic event during the 1-year follow-up after the procedure. Sharma et al.[6] evaluated the patients from Tarantini et al's case series and 26 patients from other case reports. Their findings also supported that LAAC in patients with LAA thrombus is feasible and safe. The findings from our trial were similar to the previous studies and showed that short-term results of LAAC in this patient group are excellent for thromboembolic prevention.

Cerebral protection devices (CPD) are designed to reduce the risk of cardiovascular event (CVE) during cardiovascular procedures, but their role and effect in LAAC are unclear. The case series by Boccuzziet al[12], which included 27 patients, reported that using CPD during LAAC is safe and effective. Limite et al[13] supported these findings with another case series, which enrolled 14 patients. However, they were not designed as controlled studies evaluating CPDs' efficacy in LAAC. In contrast, CPD was used according to the operators' discretion in Marroquin et al's[14] multicenter registry. Although they observed macroscopic embolic material in 19.4% of the cases in which CPD was used, no intraprocedural stroke was observed in patients in which CPD was not used. In our study, CPD was not used in any cases, and we had not attended who had any intraprocedural thromboembolic event.

Bellmann et al[15] defined a fish ball technique to trap thrombus in LAA using an amulet device. Jalal et al[16] reported the thrombus trapping technique in 3 patients. Each technique was similar and performed using an amulet device. The authors of these papers emphasized the importance of minimal manipulation and avoiding interaction with thrombus. We used the same principle, and we believe that this principle should be the cornerstone of the procedure for the operators. Consequently, we preferred to define this technique as a "no-touch technique," previously described in Tarantini et al.'s[11] paper.

Medical treatment for LAA thrombus was compared with LAAC in patients referred to LAAC in Luis Marroquin et al's trial.[14] They performed LAAC on 53 patients, and intensive antiplatelet therapy was decided for 73 patients. Luis Marroquin et al[14] reported that thrombus did not change in 18 of 73 patients and partially resolved in 11 patients. Even though there was no statistical significance, LAAC was feasible with device-related thrombus, and intensified antiplatelet treatment resulted in resolution with higher bleeding events in 60% of the patients. In our study group, we think it is not optimal to intensify the antiplatelet regimen in patients with high bleeding risk. However, LAAC was performed in 4 patients with resistant LAA thrombus after intensifying or changing the anticoagulant regimen. Combining the intensifying antiplatelet treatment and LAAC seems to be the most appropriate therapeutic decision.

Although our study is the clinical trial with the highest volume that enrolled the patient who had undergone LAAC with a single device, it has several significant limitations. First, this study is observational, and the study population is small. Second, the follow-up duration is short. Third, the indications of LAAC are not homogenous in the study group. We think that indication of LAAC may affect the outcomes of LAAC.

Left atrial appendage closure in patients with LAA thrombus is a feasible and effective method to reduce thromboembolic risk. It can be performed as an alternative therapy to OACs in patients with contraindications to OACs or malign LAA.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of Hacettepe University (Date: May 28, 2019, Decision no: GO/19483).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – C.Ç., K.A.; Design – L.Ş., B.K.; Supervision – K.A.; Funding –; Materials – A.H.A., U.N.K.; Data Collection and/or Processing – S.A.; Analysis and/or Interpretation – C.Ç., S.A.; Literature Review – H.Y.; Writing – C.Ç., A.H.A.; Critical Review – K.A.

Declaration of Interests: The authors declare that they have no competing interest.

Funding: The authors declared that this study has received no financial support.

REFERENCES

1. Hindricks G, Potpara T, Dagres N, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): the Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology

(ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J* 2021;42(5):373-498. [CrossRef]
2. January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice guidelines and the Heart Rhythm Society in collaboration with the Society of Thoracic Surgeons. *Circulation*. 2019;140(2): e125-e151. [CrossRef]
3. Osmancik P, Herman D, Neuzil P, et al. Left atrial appendage closure versus direct oral anticoagulants in high-risk patients with atrial fibrillation. *J Am Coll Cardiol*. 2020;75(25):3122-3135. [CrossRef]
4. Aytemir K, Aminian A, Asil S, et al. First case of percutaneous left atrial appendage closure by amulet™ device in a patient with left atrial appendage thrombus. *Int J Cardiol*. 2016;223:28-30. [CrossRef]
5. Sahiner L, Coteli C, Kaya EB, et al. Left atrial appendage occlusion in patients with thrombus in left atrial appendage. *J Invasive Cardiol*. 2020;32(6):222-227.
6. Sharma SP, Cheng J, Turagam MK, et al. Feasibility of left atrial appendage occlusion in left atrial appendage thrombus: a systematic review. *JACC Clin Electrophysiol*. 2020;6(4):414-424. [CrossRef]
7. Tzikas A, Holmes DR, Jr, Gafoor S, et al. Percutaneous left atrial appendage occlusion: the Munich consensus document on definitions, endpoints, and data collection requirements for clinical studies. *Europace*. 2017;19(1):4-15. [CrossRef]
8. MichaelG, Rafael W, Gerhard H, et al. EHRA/EAPCI expert consensus statement on catheter-based left atrial appendage occlusion – an update. *EuroIntervention*. 2020;15(13):1133-1180.
9. Enomoto Y, Hara H, Makino K, et al. Usefulness of an isoproterenol infusion to differentiate a left atrial appendage thrombus in a patient with nonvalvular atrial fibrillation. *Pacing Clin Electrophysiol*. 2021;44(1):192-193. [CrossRef]
10. Watson T, Shantsila E, Lip GY. Mechanisms of thrombogenesis in atrial fibrillation: Virchow's triad revisited. *Lancet*. 2009;373(9658): 155-166. [CrossRef]
11. Tarantini G, D'Amico G, Latib A, et al. Percutaneous left atrial appendage occlusion in patients with atrial fibrillation and left appendage thrombus: feasibility, safety and clinical efficacy. *EuroIntervention*. 2018;13(13):1595-1602. [CrossRef]
12. Boccuzzi GG, Montabone A, D'Ascenzo F, et al. Cerebral protection in left atrial appendage closure in the presence of appendage thrombosis. *Catheter Cardiovasc Interv*. 2021;97(3):511-515. [CrossRef]
13. Limite LR, Radinovic A, Cianfanelli L, et al. Outcome of left atrial appendage closure using cerebral protection system for thrombosis: no patient left behind. *Pacing Clin Electrophysiol*. 2022;45(1):23-34. [CrossRef]
14. Marroquin L, Tirado-Conte G, Pracoń R, et al. Management and outcomes of patients with left atrial appendage thrombus prior to percutaneous closure. *Heart*. 2022;108(14):1098-1106. [CrossRef]
15. Bellmann B, Rillig A, Leistner DM, et al. Left atrial appendage closure in a patient with left atrial appendage thrombus using a novel fish ball technique. *Int J Cardiol*. 2017;234:146-149. [CrossRef]
16. Jalal Z, Iriart X, Dinet ML, et al. Extending percutaneous left atrial appendage closure indications using the AMPLATZER™ Cardiac Plug device in patients with persistent left atrial appendage thrombus: the thrombus trapping technique. *Arch Cardiovasc Dis*. 2016;109(12):659-666. [CrossRef]