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Low-Dose Direct Oral Anticoagulation vs Dual Antiplatelet Therapy After Left Atrial Appendage Occlusion
The ADALA Randomized Clinical Trial

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IMPORTANCE Optimal antithrombotic therapy after percutaneous left atrial appendage occlusion (LAAO) is not well established as no randomized evaluation has been performed to date.

OBJECTIVE To compare the efficacy and safety of low-dose direct oral anticoagulation (low-dose DOAC) vs dual antiplatelet therapy (DAPT) for 3 months after LAAO.

DESIGN, SETTING, AND PARTICIPANTS The ADALA (Low-Dose Direct Oral Anticoagulation vs Dual Antiplatelet Therapy After Left Atrial Appendage Occlusion) study was an investigator-initiated, multicenter, prospective, open-label, randomized clinical trial enrolling participants from June 12, 2019, to August 28, 2022 from 3 European sites. Patients who underwent successful LAAO were randomly assigned 1:1 to low-dose DOAC vs DAPT for 3 months after LAAO. The study was prematurely terminated when only 60% of the estimated sample size had been included due to lower recruitment rate than anticipated due to the COVID-19 pandemic.

INTERVENTIONS The low-dose DOAC group received apixaban, 2.5 mg every 12 hours, and the DAPT group received aspirin, 100 mg per day, plus clopidogrel, 75 mg per day, for the first 3 months after LAAO.

MAIN OUTCOMES AND MEASURES The primary end point was a composite of safety (major bleeding) and efficacy (thromboembolic events including stroke, systemic embolism, and device-related thrombosis [DRT]) within the first 3 months after successful LAAO. Secondary end points included individual components of the primary outcome and all-bleeding events.

RESULTS A total of 90 patients (mean [SD] age, 76.6 [8.1] years; 60 male [66.7%]; mean [SD] CHADS-VASc score, 4.0 [1.5]) were included in the analysis (44 and 46 patients in the low-dose DOAC and DAPT groups, respectively). A total of 53 patients (58.8%) presented with previous major bleeding events (60 gastrointestinal [66.7%] and 16 intracranial [17.8%]). At 3 months, low-dose DOAC was associated with a reduction of the primary end point compared with DAPT (2 [4.5%] vs 10 [21.7%]; hazard ratio, 0.19; 95% CI, 0.04-0.88; $P = .02$). Patients in the low-dose DOAC group exhibited a lower rate of DRT (0% vs 6 [8.7%]; $P = .04$) and tended to have a lower incidence of major bleeding events (2 [4.6%] vs 6 [13.0%]; $P = .17$), with no differences in thromboembolic events such as stroke and systemic embolism between groups (none in the overall population).

CONCLUSIONS AND RELEVANCE This was a small, randomized clinical trial comparing different antithrombotic strategies after LAAO. Results show that use of low-dose DOAC for 3 months after LAAO was associated with a better balance between efficacy and safety compared with DAPT. However, the results of the study should be interpreted with caution due to the limited sample size and will need to be confirmed in future larger randomized trials.

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Visual Abstract
Editor's Note
Supplemental content

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Optimal antithrombotic therapy (ATT) after percutaneous left atrial appendage occlusion (LAAO) to prevent device-related thrombosis (DRT) is not well established.[1] Dual antiplatelet therapy (DAPT) with aspirin and clopidogrel for 3 months is the most accepted regimen. However, low-dose direct oral anticoagulation (low-dose DOAC) has been shown to represent a potential alternative with good balance among thrombotic and hemorrhagic events.[2-4] To date and to our knowledge, no randomized evaluation of the optimal ATT after LAAO has been performed. This study aimed to compare 2 antithrombotic strategies (low-dose DOAC vs DAPT) after LAAO.

Key Points

Question What is the optimal antithrombotic therapy after percutaneous left atrial appendage occlusion (LAAO)?

Findings In this randomized clinical trial that included 90 participants, low-dose direct oral anticoagulation (low-dose DOAC) showed a better balance between efficacy (less device-related thrombosis, equal thromboembolism events) and safety (equal major bleeding) compared with dual antiplatelet therapy after LAAO.

Meaning Results suggest that low-dose DOAC may be an effective and safe antithrombotic therapy for patients after LAAO.

Methods

Study Design

The ADALA (Apixaban vs Dual Antiplatelet Therapy Study After Left Atrial Appendage Occlusion) study was an investigator-initiated, multicenter, prospective, open-label, randomized clinical trial that included patients who underwent successful LAAO. The study design and statistical plan have been previously published (Supplement 1).[5] The study protocol was initially approved by the Hospital Clinic's ethics committee and subsequently by the other participating institutions. Of note, patients who have had an acute coronary syndrome or coronary artery disease requiring DAPT were not included in the study. Adverse events were adjudicated by an independent clinical events committee blinded to treatment assignment. This study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines.

Study Population and Intervention

Patients with atrial fibrillation who underwent successful LAAO without procedural complications within the first 4 hours were potential candidates. Patients who met the inclusion/exclusion criteria[5] and signed the informed consent form were randomized 1:1 to DAPT or low-dose DOAC. Four hours after the procedure, the patients received a first dose of low-dose DOAC (apixaban, 2.5 mg) or clopidogrel, 600 mg. Subsequently, patients in the low-dose DOAC group received apixaban, 2.5 mg every 12 hours, for the first 3 months after LAAO, followed by aspirin, 100 mg per day, and patients in the DAPT group received aspirin, 100 mg per day, plus clopidogrel, 75 mg per day, for the first 3 months after LAAO, followed by aspirin, 100 mg per day. The standard dose of apixaban in the prespecified protocol was 5 mg every 12 hours. Nonetheless, considering that greater than 95% of patients presented with previous bleeding and 100% presented with an increased bleeding risk, the use of apixaban, 2.5 mg every 12 hours, was selected as the standard treatment in the DOAC group.[5] Patient race was self-reported by study participants, and all participants self-identified as White.

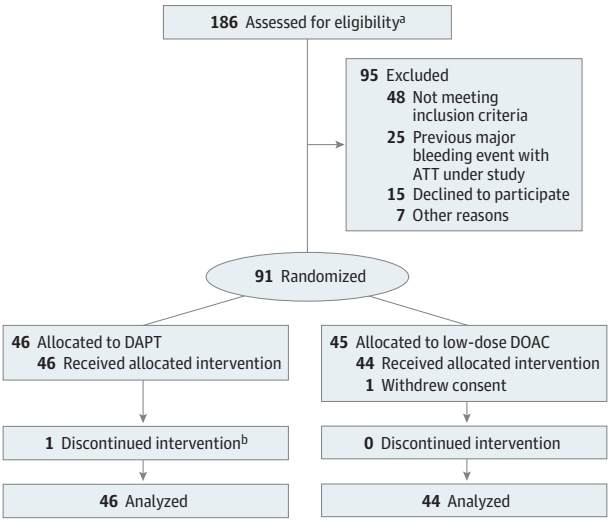
Composite Primary End Point

Clinical and imaging follow-up was performed 1 and 3 months after the index procedure. Imaging follow-up was performed with either transesophageal echocardiography (TEE) and/or computed tomography (CT) scan. The primary end point was a composite of safety (major bleeding defined as Bleeding Academic Research Consortium [BARC] bleeding ≥3) and efficacy (thromboembolic events including stroke, systemic embolism, and DRT) within the first 3 months after successful LAAO.

Statistical Analysis

The present study was initially powered to assess the superiority at 3 months of low-dose DOAC over DAPT.[2-5] We determined that a first occurrence of the primary outcome event among 152 patients would provide the trial with 80% power (at a 2-sided *P* value of .05) to detect a risk of a primary outcome event that would be 16% lower in the low-dose DOAC group than in the DAPT group.[4] Because of a substantially lower

Figure. Trial Flowchart



Enrollment and distribution of patients in the Apixaban vs Dual Antiplatelet Therapy Study After Left Atrial Appendage Occlusion (ADALA) study. ATT indicates antithrombic therapy; DAPT, dual antiplatelet therapy; DOAC, direct oral anticoagulation.

[a]Trial stopped enrollment during COVID-19 crisis (from February 2020 to December 2020).

[b]Patient discontinued intervention after no complicated pulmonary thromboembolism, starting full-dose DOAC.

Table 1. Baseline and Procedural Characteristics

Characteristic	Low-dose DOAC (n = 44)	DAPT (n = 46)
Patient characteristics[a]		
Age, mean (SD), y	76.2 (7.2)	77.1 (8.9)
Sex, No. (%)		
Female	15 (34.1)	15 (32.6)
Male	29 (65.9)	31 (67.4)
Weight, mean (SD), kg	76.3 (15.2)	77.1 (14.2)
Permanent AF, No. (%)	28 (63.6)	28 (60.9)
Hypertension, No. (%)	35 (79.6)	39 (84.8)
Diabetes, No. (%)	16 (36.4)	19 (41.3)
Chronic heart failure, No. (%)	6 (13.6)	7 (15.2)
Previous CAD, No. (%)	8 (18.2)	7 (15.2)
Previous ischemic stroke, No. (%)	8 (18.2)	9 (19.6)
Previous bleed event, No. (%)	43 (97.7)	43 (93.5)
Type of bleed event, No. (%)		
Gastrointestinal	28 (65.1)	32 (74.4)
Intracranial	12 (27.9)	4 (9.3)
Abdominal/kidney	3 (7.0)	5 (11.6)
ENT bleed	0	2 (4.7)
Pulmonary	0	0
Previous major bleeding, No. (%)	26 (59.1)	27 (58.7)
Previous major bleeding <6 mo, No. (%)	2 (7.6)	7 (25.9)
No. of bleed events, median (IQR)	1 (1-2)	1 (1-2)
CHA_2DS_2-VASc score, median (IQR)	4.0 (3.0-5.5)	4.0 (3.0-5.0)
HAS-BLED score, median (IQR)	3.5 (3.0-4.0)	3.6 (3.0-4.0)
Creatinine, mean (SD), median (IQR), mg/dL	1.0 (0.8-1.0)	1.1 (0.9-1.25)
Glomerular filtration rate, median (IQR)[b]	60.4 (47.5-73)	54.2 (43.5-64)
Hemoglobin, mean (SD), mg/L	120 (38.8)	115 (38.9)
Platelet count, mean (SD), $\times 10^9$/L	196.2 (66.5)	180.5 (59.0)
LVEF, mean (SD), %	59.2 (6.9)	57.3 (7.7)
LAAC indication, No. (%)		
Relative contraindication OAC	29 (65.9)	32 (69.6)
Known bleeding risk	15 (34.1)	14 (30.4)
Procedural characteristics		
Device type, No. (%)		
Amulet (Abbott)	31 (70.4)	30 (65.2)
Lambre (Lifetech Scientific)	2 (4.6)	6 (13.1)
Watchman FXL (Boston Scientific)	11 (25.0)	10 (21.7)
Patients with procedure- or device-related SAEs ≤7 d, No. (%)	0	1 (2.2)
All-cause death (related to the procedure)	0	0
Device embolization	0	0
Ischemic stroke	0	0
Cardiac tamponade	0	0
Vascular access complication	0	0
Major bleeding (BARC ≥3)	0	1 (2.2)

Abbreviations: AF, atrial fibrillation; ASA, acetylsalicylic acid; AT, antithrombotic treatment; BARC, Bleeding Academic Research Consortium; CAD, coronary artery disease, CHADS-VASc score, congestive heart failure, hypertension, age ≥75 years, age 65-74 years, diabetes mellitus, stroke/transient ischemic attack/thromboembolism, vascular disease, sex female; DAPT, dual antiplatelet therapy; DOAC, direct oral anticoagulation; ENT, ear, nose, throat; HAS-BLED score, hypertension, abnormal liver/kidney function, stroke history, bleeding history or predisposition, labile INR, elderly, drug/alcohol usage; LAAC, left atrial appendage closure; LMWH, low molecular weight heparin; LVEF, left ventricular ejection fraction; SAE, serious adverse event.

SI conversion factor: To convert creatinine to micromoles per liter, multiply by 88.4; to convert hemoglobin to grams per deciliter, multiply by 0.001 then divide by 10; to convert platelets to $\times 10^3$ per microliter, divide by 1.

[a] Race was self-reported by study participants, and all participants self-identified as White.

[b] Measured as milliliter per minute per 1.73 meters squared.

recruitment rate than anticipated due to COVID-19 pandemic, the enrollment was prematurely terminated when 60% of the estimated sample size had been included in the study. Data analysis was performed using Stata software, version 14 (StataCorp).

Results

From June 2019 to August 2022, 186 patients were initially screened. Among them, 91 patients were randomized, but 1

Table 2. Outcomes at 3-Month Follow-Up

Outcome	Low-dose DOAC (n = 44)	DAPT (n = 46)	Hazard ratio (95% CI)	*P* value
Primary end point, No. (%)	2 (4.6)	10 (21.7)	0.19 (0.04-0.88)	.02
Primary effectiveness end point, No. (%)	0	4 (8.7)	NA[a]	.045
Ischemic stroke, No. (%)	0	0	NA	NA
Systemic embolism, No. (%)	0	0	NA	NA
Device-related thrombosis, No. (%)[b,c]	0	4 (8.7)	NA[a]	. 045
Primary safety end point (major bleeding), No. (%)	2 (4.6)	6 (13.0)	0.34 (0.07-1.69)	.17
All-cause mortality, No. (%)	0	0	NA	NA
All bleeding (major & minor), (%)	2 (4.6)	13 (28.3)	0.14 (0.03-0.63)	.002

Abbreviations: CT, computed tomography; DAPT, dual antiplatelet therapy; DOAC, direct oral anticoagulation; HAT, hypoattenuated thickening; NA, not applicable.

[a] Not possible to calculate hazard ratio as one of the groups did not present any event (low-dose DOAC group).

[b] No differences in type of image used for device-related thrombosis assessment between groups (CT: 13 patients in the DAPT group [28.3%] and 9 patients in the low-dose DOAC group [20.5%]; *P* value = 0.40). Specifically for CT, high-grade HAT criteria were used to diagnose device-related thrombosis.

[c] No differences in peridevice leaks rates were observed between DAPT (2 [4.3%]) and low-dose DOAC (1 [2.3%]; *P* = .82).

patient withdrew consent after randomization. Hence, a total of 90 patients (mean [SD] age, 76.6 [8.1] years; 30 female [33.3%]; 60 male [66.7%]; mean [SD] CHADS-VASc score, 4.0 [1.5]) were included in the final analysis (**Figure**). Baseline and procedural characteristics were well balanced among groups (**Table 1**). A total of 53 patients (58.8%) presented with previous major bleeding events (60 gastrointestinal [66.7%] and 16 intracranial [17.8%]). The antithrombotic treatment before LAAO included anticoagulation therapy (57 [64%]), single antiplatelet therapy (19 [21%]), DAPT (4 [4%]), and no antithrombotic therapy (10 [11%]). Disc/lobe devices were more commonly used (69 [76.6%]) than single-lobe disc devices (21 [23.4%]). Device depth implantation did not differ among groups. There were no reported deaths during the index hospitalization. One patient (2.2%) allocated to the DAPT group experienced a major bleeding characterized by severe hematuria during hospitalization.

The preferred imaging modality was TEE at both 1 month (83 [92.2%]) and 3 months (68 [75.5%]). The primary end point occurred in 12 patients (13.3%) at 3-month follow-up. As detailed in **Table 2** and eFigure 1 in Supplement 2, the use of low-dose DOAC was associated with a significant reduction in the primary end point compared with DAPT (2 [4.6%] vs 10 [21.7%]; hazard ratio [HR], 0.19; 95% CI, 0.04-0.88; *P* = .02 and fragility index = 1). In addition, the individual analysis of end points showed that low-dose DOACs were also associated with a significant reduction of the effectiveness end point (0% vs 6 [8.7%]; *P* = .045) with no significant differences in the safety end point (2 [4.6%] vs 6 [13.0%]; *P* = .17). There was a significant decrease in DRT rate in the low-dose DOAC group compared with DAPT, with no difference in stroke/embolism events. The overall rate of DRT was 4.4% (low-dose DOAC, 0 vs DAPT, 4 [8.7%]) (eFigure 2 in Supplement 2). None of the patients with DRT showed spontaneous echocontrast at baseline TEE. In addition, no patients experienced concomitant DRT and clinical thromboembolic events.

Regarding DRT management, for the majority of DRT cases (3 [75%]), low-dose DOAC was administered for 1 month with complete resolution confirmed by TEE. After DRT resolution, low-dose DOAC was discontinued, and single antiplatelet therapy was initiated. In 1 case, DAPT was discontinued in favor of low-molecular-weight heparin and aspirin. At 3 months, CT imaging revealed improvement in thrombus size, and at 6 months, DRT was resolved. The patient was then transitioned to aspirin alone. However, DRT recurred 5 months later, prompting the initiation of vitamin K antagonist therapy.

There were no statistically significant differences in the incidence of major bleeding events between groups (Table 2). However, the overall rate of bleeding events (major and minor) was lower in the low-dose DOAC group (2 [4.6%] vs 13 [28.3%]; HR, 0.14; 95% CI, 0.03-0.63; *P* = .002) (eFigure 3 in Supplement 2). Among the 8 patients with major bleeding, 6 (75%) were gastrointestinal in origin, and 2 (25%) were urologic in origin. Minor bleeding occurred in 7 patients, with 5 experiencing gastrointestinal bleeding and 2 presenting with a urologic etiology.

Discussion

This is a small, randomized clinical trial that compared 2 antithrombotic strategies after LAAO. Our results support previous observational studies favoring low-dose DOAC over DAPT[2-4,6]; however, larger and more definitive trials are needed. Although no thromboembolism events were reported, patients receiving DAPT presented with a high rate of DRT (8.7%), whereas no cases were detected in the low-dose DOAC group. The overall DRT rate (4.4%) aligns with previous LAAO reports.[7] All DRT cases were sessile (more than 3 mm) and irregular (eFigure 2 in Supplement 2). Nonetheless, the high DRT rate in the DAPT group might result from an increased sensitivity after conducting 2 imaging tests within the first 3 months. Similar rates or even higher rates of DRTs have been reported when multiple imaging tests were performed.[8,9]

The other major finding of the present study was the observed differences in hemorrhagic events among patients in the low-dose DOAC and DAPT groups. Our study showed that low-dose DOAC was associated with a reduction of any

bleeding (major and minor) compared with DAPT (4.6% vs 28.2%) with no difference in major bleeding events (4.6% vs 13.0%). Gastrointestinal hemorrhage (75%) was the most frequent source of major bleeding, possibly explaining the poor outcomes with DAPT.[10,11] As shown in Table 1, the higher prevalence of baseline gastrointestinal bleeding in the DAPT group (74.4%) compared with the low-dose DAOC group (65.1%) might have also influenced the observed results.

Limitations

The present study has some important limitations. As previously noted, the initial plan was to include 156 patients. However, the study was prematurely stopped after ceasing enrollment for almost 1 year due to the COVID-19 pandemic and observing a postpandemic reduction in the number of referrals. Thus, our study is underpowered to assess efficacy, and our findings should be considered hypothesis generating. The second limitation is the absence of an independent core laboratory for imaging assessment, although a blinded imaging expert assessed all TEE and CT scans. Third, the difference in the thromboembolic events between groups was driven by DRT rates only detected by imaging (TEE or CT). However, early DRT diagnosis and treatment may have prevented ischemic events at follow-up.

Conclusions

The ADALA study was a small, randomized clinical trial that compared different antithrombotic strategies after LAAO. According to our results, the use of low-dose DOAC for 3 months after LAAO was associated with a better balance between efficacy (thromboembolic protection) and safety (major bleeding prevention) compared with DAPT. Considering the limitations of the study, our findings should be considered hypothesis generating and emphasize the need for larger clinical trials to validate and expand on these results.

ARTICLE INFORMATION

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Concept and design: Freixa, Cruz-González, Arzamendi.
Acquisition, analysis, or interpretation of data: Freixa, Cruz-González, Cepas-Guillén, Millan, Antúnez Muiños, Flores-Umanzor, Asmarats, Regueiro, López-Tejero, Pedro Li, Sanchis, Rodés-Cabau.
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Supervision: Freixa, Cruz-González, Antúnez Muiños, Pedro Li, Sanchis, Rodés-Cabau, Arzamendi.

Conflict of Interest Disclosures: Dr Freixa reported receiving grants from Bristol Myers Squibb and proctor fees from Abbott Medical and Lifetech during the conduct of the study. Dr Cruz-González reported receiving proctor fees from Abbott, Boston Scientific, and Lifetech outside the submitted work. Drs Millan, Asmarats, Regueiro, and Pedro Li reported receiving proctor fees from Abbott outside the submitted work. Dr Sanchis reported receiving speaker/proctor fees from Abbott, GE Healthcare, and Edwards Lifesciences outside the submitted work. Dr Rodés-Cabau reported receiving grants from Boston Scientific outside the submitted work. Dr Arzamendi reported receiving proctor fees from Abbott Medical and Boston Scientific. No other disclosures were reported.

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