Keynote Lecture Series

Minimally invasive left atrial appendage occlusion plus reduced dose direct oral anticoagulant to prevent stroke in patients with atrial fibrillation—the LAAO-PlusRE

Laura Besola[1], Dario Gregori[2], Alessandro Fiocco[1], Andrea Colli[1]

[1]Cardiac Surgery Unit, Department of Surgical, Medical and Molecular Pathology and Critical Care, University of Pisa, Pisa, Italy; [2]Unit of Epidemiology, Biostatistics and Public Health, Department of Cardiology, Thoracic and Vascular Sciences, University of Padova, Padova, Italy

Correspondence to: Prof. Andrea Colli, MD, PhD. Cardiac Surgery Unit, Heart Centre, Cardiac Surgery Unit, Department of Surgical, Medical and Molecular Pathology and Critical Care, University of Pisa, Via Paradisa, 2, 56124 Pisa, Italy. Email: colli.andrea.bcn@gmail.com.

The onset of atrial fibrillation (AF) has a direct association with left atrial appendage (LAA) function, as demonstrated by recent studies demonstrating the link between left atrial (LA) wall fibrosis, impaired contractility, and the development of AF. Non-valvular AF (NVAF) affects almost 30 million people worldwide, with this number expected to increase in the next 20 years. It is the main cause of ischemic stroke, with significant subsequent economic and social impact. Currently, the mainstay of stroke prevention in patients with NVAF is oral anticoagulation (OAC), which reduces the incidence of ischemic events at the stake of increased hemorrhagic events. Despite the introduction and widespread use of direct oral anticoagulants (DOACs), which almost completely replaced vitamin K antagonists (VKAs), the adherence to OAC is still low, hindering the efficacy of stroke prevention. Percutaneous LAA occlusion (LAAO) is now indicated (class IIB) in patients with NVAF at increased ischemic risk who cannot undergo OAC. Recently published data demonstrated that a reduced dose of DOAC after percutaneous LAAO is superior to long-term dual antiplatelet therapy (DAPT) for stroke prevention in the mid-term. One of the possible pitfalls of percutaneous LAAO is postprocedural peri-device leaks (PDLs) that have been associated with increased thromboembolic events. According to LAAOS III results, surgical LAAO during cardiac surgery brings a 33% reduction in risk of stroke at five years, independently from the OAC regimen with a high rate of complete appendage occlusion. The combination of surgical LAAO and reduced dose DOAC might ensure adequate embolic prevention, lowering the hemorrhagic risk. The present manuscript aims to describe the rationale and design of the Minimally Invasive Left Atrial Appendage Occlusion Plus REduced Dose DOAC To Prevent Stroke In Patients With Atrial Fibrillation Randomized Clinical Trial (LAAO-PlusRE).

Keywords: LAAO-PlusRE; atrial fibrillation (AF); epicardial left atrial appendage occlusion (epicardial LAAO); direct oral anticoagulant (DOAC); stroke

Submitted Sep 26, 2023. Accepted for publication Mar 06, 2024. Published online Mar 18, 2024.
doi: 10.21037/acs-2023-afm-18
View this article at: https://dx.doi.org/10.21037/acs-2023-afm-18

Introduction

Atrial fibrillation (AF) affects more than 30 million people worldwide (1,2), and according to European studies, this number is expected to double by 2050 (3). Non-valvular AF (NVAF) is associated with a five-fold increased risk of ischemic stroke and systemic embolism, and is responsible for around 40% of all ischemic strokes in the elderly, accounting for very high morbidity in developed countries and representing a significant social and economic burden (4-6). Moreover, AF is frequently silent, and it is diagnosed only after the patient has presented with a thromboembolic event. Several studies demonstrated that patients who experienced an AF-related stroke usually have more severe functional deficits and increased

complication rates, translating into higher mortality and more extended hospital stays that correspond to higher direct costs (7,8). The left atrial appendage (LAA) has been labeled as the significant embolic source in patients with AF, containing up to 90% of left atrial (LA) thrombi (9). Its increased thrombogenicity has a twofold explanation: a narrow entrance orifice and trabeculated muscle walls, which predispose to blood stasis and thrombus formation (10). Prevention of stroke is based on oral anticoagulation (OAC) with direct oral anticoagulants (DOACs), or vitamin K antagonists (VKAs), which is associated with a two-thirds risk reduction of embolism (11-14). However, OAC is associated with an increased risk of bleeding, and several patients are non-compliant with long-lasting therapies (15,16).

On this basis, surgical or percutaneous LAA occlusion (LAAO) has been proposed as an adjunctive therapy to reduce the risk of thromboembolism in patients with AF. Currently, percutaneous LAAO may be reasonable (class IIB) in patients with NVAF who have contraindications to long-term OAC to prevent stroke (17,18). According to the recent LAAOS III study, surgical LAAO on top of OAC brings a 33% reduction in the risk of stroke in patients with AF who underwent cardiac surgery at five years (19). However, the real benefit of isolated surgical LAAO as first-line therapy to prevent stroke is still to be demonstrated. We therefore developed the Minimally Invasive Left Atrial Appendage Occlusion Plus REduced Dose DOAC To Prevent Stroke In Patients With Atrial Fibrillation Randomized Clinical Trial (LAAO-PlusRE). This manuscript aims to explain why a randomized clinical trial (RCT) to assess the safety and efficacy of thoracoscopic/robotic-assisted isolated LAAO associated with a reduced dose of DOAC in patients with persistent or paroxysmal AF is necessary (rationale) and how it should be carried on (design).

Why LAAO-PlusRE?

Morpho-functional association between the LAA and AF

LA morphology and function are directly related to the risk of developing AF and even stroke (20). A systematic review including 67,875 patients showed that an increased LA size is associated with an increased risk of stroke in patients with sinus rhythm (21). When LA enlargement is associated with altered reservoir function, the risk of AF is even higher; in a study involving 574 patients without arrhythmia, combining these two echocardiographic features led to an increased risk of developing AF or atrial flutter at two years (22). LA dilatation is associated with increased tissue fibrosis affecting atrial myocardial contractility. Strain and strain-rate imaging enable the assessment of myocardial deformation through the cardiac cycle. Prospective studies showed that reduced LA strain relates to wall fibrosis, usually found in patients with AF (20,23). In particular, peak atrial longitudinal strain (PALS) can predict AF development and is superior to other morphologic parameters to predict thromboembolic events (20). Alhakak *et al.* (24) found that in a low-risk general population of 400 patients, PALS was a univariable risk factor of AF [per 5% decrease: hazard ratio (HR) 1.42; 95% confidence interval (CI): 1.19–1.69, P<0.001] and an independent risk factor for AF in patients aged less than 65 years (per 5% decrease: HR 1.46; 95% CI: 1.06–2.02, P=0.021). PALS also resulted in a predictor of the combined endpoint of AF and stroke independently from age. Mannina *et al.* (25) showed that reduced values of LA strain and LA strain rate brought an increased risk of ischemic stroke in patients with average LA size and non-AF at a median follow-up of 10 years (HR 4.64; 95% CI: 1.55–13.89 and HR, 11.02; 95% CI: 3.51–34.62).

OAC for stroke prevention

OAC, either with conventional VKA or new DOAC, is the mainstay in AF medical management, reducing the risk of ischemic stroke, systemic embolism, and all-cause mortality (11-14,26). Warfarin was associated with a 67% reduction in the risk of stroke in a large meta-analysis including 28,044 patients concerning no therapy and a 37% reduction when compared to aspirin therapy (27). DOAC proved to be non-inferior or superior to warfarin for stroke prevention with reduced bleeding events (12,14). Significant bleeding rates were, however, 3%. Thus, hemorrhage is still a limitation of VKA and DOAC (16). According to international guidelines, OAC is indicated in all patients with a high CHA2DS2-VASc score (≥2 for men and ≥3 for women).

Apart from the bleeding risk, the necessity to constantly monitor the international normalized ratio (INR) represents a vital limitation reducing the patient's compliance to the therapy. Approximately less than 60% of patients on VKA maintain the INR in the desired range because of scarce adherence to INR monitoring, enormously increasing the risk of stroke and bleeding. In several cases, patients underestimate the importance of VKA therapy, affecting

their compliance, in particular when they receive it on a chronic base. Although the introduction of DOAC has overcome some of the limitations of VKA therapy, persistent barriers, including costs and ongoing bleeding risks with no reversal agent for most DOAC, might preclude a broader use of OAC in clinical practice (28) in elderly patients, which are at the highest risk of developing AF. Noncompliance and discontinuation due to other medical conditions are observed in 33% of patients and are responsible for a significantly higher risk of embolic events (15,16). According to a large study including more than 6,000 patients admitted for ischemic stroke, less than 50% of those who had a known history of AF were on OAC (29). In a systematic review and meta-analysis of 39 studies and 593,863 patients, one-year compliance with a DOAC was <80% (30). The possibility to reduce or avoid OAC would, therefore, provide an important improvement in managing patients with persistent AF.

Evidence regarding percutaneous LAAO

Percutaneous LAAO is now a class IIB indication in Europe and the US in patients with NVAF at increased risk of stroke who have contraindication to long-standing OAC (17,18). The Watchman 2.5 and the Watchman FLX (Boston Scientific, Marlborough, MA, USA) are plug-designed percutaneous occluders, while the Amplatz and the Amulet are pacifier-shaped. Watchman FLX and Amulet are the second generation devices currently in use. Both devices are designed to be introduced percutaneously in the LAA orifice, isolating the appendage from the atrial cavity. RCTs demonstrated that percutaneous LAAO is not inferior to VKA and DOAC in patients with AF (31,32). The Continued Access to PROTECT AF (CAP) and the Continued Access to PREVAIL (CAP2) registries that continued to enroll patients in the original Watchman RCTs showed an essential reduction in ischaemic stroke in each registry compared to what had been expected with the CHA2DS2-VASc score (1.30 and 2.20 respectively, per 100 patient-years for CAP and CAP2, respectively) as well as a reduction of hemorrhagic stroke (33). The Amulet IDE Trial randomized patients either to LAAO with Amulet or Watchman 2.5 and showed that at 12 months Amulet was not inferior to Watchman 2.5 in terms of mortality and stroke (34).

Evidence regarding reduced dose DOAC

A significant proportion of patients is treated with reduced dose of DOAC independently from the presence of correct indications such as advanced age, low body weight or impaired renal function (35). However, only dabigatran was tested as a reduced dose, confirming its effectiveness in reducing the risk of stroke with lower bleeding risk compared to a full dose (11). A recent study (36) including 40,564 patients with newly initiated DOAC (apixaban, dabigatran, or rivaroxaban) (11,083 patients) or warfarin treatment (29,481 patients) compared the effectiveness and safety of reduced dose DOAC *vs.* warfarin. It showed that DOACs are associated with lower risk of all-cause stroke (HR 0.87, 95% CI: 0.76–0.99), major bleeding (HR 0.85, 95% CI: 0.78–0.93), intracranial bleeding (HR 0.64, 95% CI: 0.51–0.80), hemorrhagic stroke (HR 0.68, 95% CI: 0.50–0.92) and gastrointestinal bleeding (HR 0.81, 95% CI: 0.69–0.96) than high-quality warfarin treatment. Combining surgical LAAO with a reduced dose of DOAC would provide an enhanced protective effect against stroke and thromboembolic events while reducing the risk of bleeding derived from the lower dose of administered anticoagulant. If a sufficiently powered RCT confirmed this hypothesis, isolated surgical LAAO would become a valuable option for all patients with NVAF independently from their coagulation profile.

The original protocols for antithrombotic therapy after percutaneous LAAO consisted of aspirin 100 mg plus warfarin for 45 days, followed by dual antiplatelet therapy (DAPT) if no peri-device leak (PDL) or device-related thrombosis is detected at follow-up transesophageal echocardiography (TEE). After six months of DAPT, patients were maintained on aspirin-only, lifelong. Recent studies showed that endocardial LAAO is superior to full-dose OAC alone to prevent stroke, even when followed by a reduced dose of OAC. In a recent study, Della Rocca *et al.* (37) showed that in patients with LAAO with Watchman device, a lifelong standing reduced dose of NOAC was superior to the standard antithrombotic regiment (DOAC plus aspirin 81 mg for 45 days, aspirin 81 mg and clopidogrel 75 mg for six months, and then indefinite aspirin 81 mg monotherapy after that) with fewer thrombotic and bleeding complications over about one year of follow-up. Authors found a HR of 9.8% (95% CI: 2.3–40.7%) for the primary composite endpoint of thromboembolic events [ischemic stroke, transient ischemic attack (TIA), peripheral thromboembolism], device-related thrombosis, and major bleeding events in favor of reduced-dose DOAC.

Experimental studies demonstrated that implantable

occluders are more thrombogenic within the first 30–90 days from implantation, due to the incomplete endothelialisation of the atrial surface of the device that activates the coagulation system. OAC was associated with an increased reduction of the biomarkers of coagulation activation with respect to DAPT during the initial weeks after implantation (38,39). As demonstrated by recent retrospective studies, the presence of PDL, particularly when more significant than 3–5 mm, is associated with an increased risk of new thromboembolic events. Dukkipati *et al.* (40) analyzed 1,054 patients enrolled in the two pivotal Watchman device trials and their nested registries and found that patients with persistent small PDL at one year had a two-fold increase in the adjusted risk of ischemic stroke or systemic embolization at five years (HR: 1.94; 95% CI: 1.15–3.29), driven by an increase in non-disabling stroke (HR: 1.97; 95% CI: 1.03–3.78). Similarly, a sub-analysis of the Amulet IDE trial (41) showed that the primary endpoint (18-month rates of ischemic stroke or systemic embolization) was higher in patients with PDL ≥3 mm compared with those with PDL <3 mm [3.6% *vs.* 1.8%; unadjusted HR: 2.03 (95% CI: 0.96–4.29); adjusted HR: 1.98 (95% CI: 0.93–4.19)] and the secondary endpoint (18-month rates of ischemic stroke, systemic embolization, or cardiovascular death) was also significantly higher in patients with PDL ≥3 mm [8.1% *vs.* 4.7%; unadjusted HR: 1.75 (95% CI: 1.08–2.83); adjusted HR: 1.66 (95% CI: 1.02–2.69)]. In our opinion, to maximize the effect of LAAO against stroke occurrence, a procedure is needed to occlude the LAAO with low risk of PDL and no blood flow contact.

Evidence in favor of surgical LAAO

Surgical LAAO during cardiac surgery in patients with pre-existing AF is quick and inexpensive and does not significantly increase surgical time or risk, as demonstrated by LAAOS II results (42). Until publication of the LAAOS III in 2021, only retrospective underpowered studies evaluated the effect of surgical LAAO suggesting its additional effect with OAC to prevent stroke in patients undergoing cardiac surgery (43,44). Based on recent reports of the LAAOS III, LAAO is now recommended during cardiac heart surgery procedures because it sensibly decreases, with a long-lasting effect, the risk of stroke or systemic embolism on top of usual OAC (19). According to the authors, patients who had LAAO had a reduced risk of stroke or systemic embolism (HR 0.68, 95% CI: 0.53–0.86, P=0.001) at five years. LAAO also protected against thromboembolic events in patients who were not consistently taking OAC therapy during follow-up. Patients randomized to occlusion were treated with different techniques, but in all cases, complete occlusion, defined as a residual stump ≤1 mm with no evidence of residual flow across the suture line, was confirmed with intraoperative TEE and when not reached, adjunctive manoeuvres were performed. In case of appendage thrombosis, the appendage was opened to remove the thrombus before being occluded.

Surgical occlusion provides very high rates of complete appendage exclusion thanks to the direct vision of the anatomy, thus eliminating the risk of PDL-related embolic events (19,43). Occlusion can be carried out from inside the left atrium or from the epicardium, either by amputating the appendage and hand-sewing the cut line or using epicardial closure devices. There are currently two available devices on the market to perform epicardial LAAO: AtriClip (AtriClip Pro, AtriCure, Inc., Cincinnati, OH, USA) and LARIAT (SentreHeart, Redwood City, CA, USA); both are used to perform LAAO with a thoracotomy or thoracoscopic approach, minimizing surgical invasiveness in patients with persistent NVAF with a contraindication to OAC. Studies showed that isolated thoracoscopic/thoracotomy LAAO with the AtriClip device is safe and provides a high rate of successful LAA exclusion with a very low rate of thromboembolic events at five years (45). According to the literature, epicardial occlusion is superior to endocardial occlusion in terms of residual leaks (25) that might be associated with increased device-related thrombogenicity. The evidence in favor of epicardial LAAO and the high economic and social burden associated with AF-related stroke supports the necessity of a trial assessing the safety and effectiveness of isolated epicardial LAAO as first-line therapy to prevent stroke in NVAF patients. As OAC is associated with an increased risk of bleeding, there is also the need for strong evidence supporting the reduction of the dose of OAC in patients treated with epicardial LAAO. On the basis of these considerations, we propose a randomized trial (RT) aiming to assess the safety and efficacy of isolated epicardial LAAO plus halved dose of DOAC to prevent stroke in patients affected with NVAF.

LAAO-PlusRE design

We plan to perform a multicentre non-inferiority RT with a 1:1 randomization between isolated minimally

invasive epicardial LAAO plus full-dose DOAC *vs.* isolated minimally invasive epicardial LAAO plus half dose DOAC in patients with NVAF and increased thromboembolic risk. Patient crossover is allowed considering possible treatment dose changes performed independently by external physicians, the onset of ischemic/thromboembolic events, or modifications in the patient's renal function requiring dose adjustments. We will follow an intention-to-treat protocol for outcomes analysis, including all patients in their assignment group independently from the actual DOAC dose. The target population size is 200 patients. Our primary hypothesis is that the association of half-dose DOAC plus LAAO is not inferior to full-dose DOAC plus LAAO regarding safety and efficacy to prevent ischemic stroke. Randomization of the enrolled patients will be performed at the leading centre with an interactive web randomization system (IWRS), and each patient will be blindly assigned to one group, full-dose (FDOA) or half-dose oral anticoagulant (HDOA). IWRS is a web-based service that enables on-site randomization by adding the selected patient to an online system. This method provides stratified randomization of each patient added by the Site principal investigator, who immediately receives an e-mail assigning the patient to one of the two study arms.

Hypothesis

We suggest that isolated minimally invasive epicardial LAAO followed by reduced-dose DOAC is not inferior to epicardial LAAO plus full-dose DOAC to prevent stroke and thromboembolic events in patients with NVAF and increased thromboembolic risk calculated based on the CHA2DS2-VASc score and LA echocardiographic parameters. Furthermore, we hypothesize that minimally invasive epicardial LAAO plus half-dose DOAC is as safe as full-dose DOAC. If our hypothesis should turn out to be correct, it would have a significant impact on the clinical management of patients with NVAF and an increased risk of stroke.

Patient selection

To be enrolled, patients must be: (I) ≥18 years; (II) have a history of persistent or paroxysmal NVAF; (III) have a CHA2DS2-VASc ≥2 for women and ≥3 for men; (IV) at least one of the two following echocardiographic criteria, an indexed left atrial volume (iLAV) ≥38 mL/m^2 and a PALS ≤40; (V) provided written informed consent. The patient will be excluded if: (I) presenting appendage thrombus; (II) presenting significant carotid or intracranial arteries atherosclerosis or severe thrombophilic conditions; (III) presenting criteria for receiving a reduced dose DOAC (e.g., weight, renal function); (IV) having contraindications to thoracoscopic/thoracotomic approach; (V) if they had previous percutaneous LAAO. Finally, patients with incomplete exclusion of the LAAO at intraoperative TEE will be excluded. Patients accessing Cardiology, Arrhythmology, Electrophysiology and Cardiac Surgery outpatient and inpatient clinics will be screened for possible inclusion in the present study. Patients who accept the enrollment and meet all the inclusion and exclusion criteria will be added for randomization.

Study intervention

The investigated procedure is minimally invasive epicardial LAAO coupled with full-dose DOAC versus reduced-dose DOAC. All patients in the trial will undergo LAAO with one of the available epicardial devices (AtriClip). Procedures will be performed with minimally invasive access through a small anterolateral thoracotomy, or thoracoscopically with an endoscopic or robot-assisted procedure. In either case, the procedure is performed in a standard operating room under general anesthesia and with a double-lumen endotracheal tube. For totally endoscopic and robot-assisted surgery, instruments and cameras are inserted through three to four ports. A small incision in the pericardium is performed above the phrenic nerve, and the LAA is exposed, measured, and occluded with the dedicated device. Successful occlusion, obtained when a residual stump of <10 mm is obtained, is checked intraoperatively using TEE. In case of incomplete occlusion, adequate adjustments should be performed to achieve the target stump length; otherwise, the patient is excluded from the study. After surgery, patients are 1:1 randomized to full-dose DOAC or half-dose DOAC. The accepted DOACs are apixaban, dabigatran, edoxaban, and rivaroxaban at a dosages of 2.5 mg BID, 75 mg BID, 30 mg QD, and 10 mg QD, respectively, for half dosage, and 5 mg BID, 150 mg BID, 60 mg QD and 20 mg QD, respectively, for full dosage. Patients with absolute contraindications to OAC will be enrolled in the present trial but not randomized to one arm. These patients will undergo LAAO but will receive antiplatelet therapy with acetylsalicylic acid 100 mg QD and no anticoagulation and will be included in a side arm of the registry. This arm will also include all patients who had to discontinue DOAC after LAAO for any reason.

Table 1 Previous studies

Study	Composite, % (# of events/sample size)
Della Rocca 2021, (37)	9.5 (34/357)
Cepas-Guillen 2021, (47)	11 (13/119)

Study endpoints

The efficacy primary endpoint is the composite of (I) any ischemic stroke; (II) any thromboembolic event; and (III) cardiovascular death. The efficacy endpoint will be assessed at five-year follow-up. The primary safety endpoint is the composite of (I) perioperative death; and (II) major bleeding. The safety endpoint will be assessed at 30 days and five years. Secondary endpoints are (I) incomplete appendage occlusion confirmed at intraoperative TEE not amenable of rectification; (II) ischemic stroke; (III) thromboembolic events; (IV) cardiovascular death; (V) overall death; (VI) any bleeding; (VII) major bleeding; (VIII) intraoperative complications (cardiac arrest requiring resuscitation, uncontrollable bleeding, circumflex artery injury, cardiac injuries, lung injuries, pneumothorax and need of conversion to sternotomy). Follow-up phone calls will be completed at 6, 12 months, and then yearly. Thereafter, for up to five years, the participating centers will perform FU to assess for endpoints. The occurrence of stroke and TIA will be investigated using a validated stroke questionnaire to determine if symptoms indicating a possible embolic event had occurred. If symptoms occur, a dedicated physician will obtain and review source documentation to confirm the actual event occurrence.

Sample size determination and outcome analysis

The study is a randomized non-inferiority trial for occlusion with HDOA *vs.* occlusion with FDOA. The study design is a full Bayesian design following the approach of Chen *et al.* (46), borrowing from the literature. Historical information can be borrowed from previously conducted OAC and occlusion trials. Data are taken from Della Rocca *et al.* (37) and Cepas-Guillen *et al.* (47). *Table 1* summarizes the historical data.

A non-inferiority margin has been pre-specified at 1%. From the computation of the posterior probability for the difference between the two expected endpoint rates (in the treatment and control group), a per-group sample size greater than 50 is required to achieve a power of at least 0.8 when the degree of borrowing α_0>0.10 (Figure S1, with details in Appendix 1). Notice that an α_0=0 coincides with non-informative prior and α_0=1 with entire borrowing. The design was tailored to have a higher reliance on the historical data, choosing a degree of borrowing slightly higher than that recommended by the Food and Drug Administration (FDA) (α_0=0.05). It was decided to increase study efficiency given the consistency of the historical data with the actual study design. Moreover, to achieve a slightly greater power, a sample size of 100 patients per group was chosen, also given feasibility of recruitment in the center and to account for potential loss at follow-up.

All analyses are performed as an intention-to-treat protocol where patients are included in the assigned randomization arm independently of the treatment dosage received. The composite primary efficacy and safety endpoints analysis will be performed as a time-to-event analysis. It will be calculated using Kaplan-Meier survival curves. Cox proportional-hazard models will calculate HR for the treatment effects with a 95% CI and P value of <0.05. The same analysis is also planned for the secondary outcomes of ischemic stroke, thromboembolic events, cardiovascular death, and overall death. As appropriate, the remaining secondary outcomes will be compared using a *t*-test, chi-square test, or non-parametric tests. The institution of a Data Safety Monitoring Board (DSMB) composed of external independent expert members is planned. It will periodically supervise and confirm all adverse events reported by the participating centers. Safety will be monitored after developing prespecified stopping rules based on the Bayesian beta-binomial method. Official analysis will be performed when 50% and 75% of the expected events are observed and carried out by the DSMB.

Discussion

LAAO is now reserved for patients with NVAF who have contraindications for OAC because of increased bleeding risk or pre-existing bleeding events. In this condition, a class IIB indication is given for LAAO (17,18). In most cases, the procedure is performed percutaneously; despite the promising results provided by randomized and non-randomized trials, percutaneous LAAO might be associated with a significantly increased risk of thromboembolic events due to the exposure of the device surface to blood, in particular when a significant PDL is present. LAAOS

III (19) demonstrated that surgical LAAO can reduce the risk of stroke on top of standard OAC in patients with AF undergoing cardiac surgery. Still, no evidence is available in support of isolated LAAO for all patients with NVAF. When the procedure is performed with an epicardial device and though a minimally invasive approach it could provide the important benefits of surgical occlusion (24,25) with low surgical risk (24).

The opportunity to pair a reduced dose of DOAC to LAAO would provide a further improvement in the management of patients with NVAF, offering an effective prevention over ischemic stroke with a lower risk of haemorrhagic events. The results of the proposed study would determine a significant reduction in healthcare costs since stroke is related to a very substantial economic and social burden. Being safe and performed through a minimally invasive procedure, LAAO with an epicardial device can protect against cardio-embolic events. It would also demonstrate that a reduced dose of DOAC provides the same protection as a full dose of DOAC when associated with LAAO, reducing the risk of bleeding, and providing a significant improvement for elderly and high bleeding-risk patients. These patients represent a particularly challenging clinical scenario in which the thromboembolic event is accepted only because their bleeding risk is too high. Finally, the inclusion in a side-arm of patients with absolute contraindication for OAC, therefore being treated only with antiplatelets therapy, will provide further important safety and efficacy information about LAAO as the only treatment to prevent stroke in patients with NVAF and high risk of stroke. In case these preliminary findings are in favor of the safety and efficacy of LAAO alone to prevent stroke, it would provide sufficiently strong support to justify a dedicated RT where patients with NVAF are randomized to LAAO alone *vs.* OAC alone.

Acknowledgments

Funding: None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Di Carlo A, Bellino L, Consoli D, et al. Prevalence of atrial fibrillation in the Italian elderly population and projections from 2020 to 2060 for Italy and the European Union: the FAI Project. Europace 2019;21:1468-75.
2. Chugh SS, Havmoeller R, Narayanan K, et al. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. Circulation 2014;129:837-47.
3. Benjamin EJ, Wolf PA, D'Agostino RB, et al. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. Circulation 1998;98:946-52.
4. Go AS, Hylek EM, Phillips KA, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. JAMA 2001;285:2370-5.
5. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. Stroke 1991;22:983-8.
6. Gage BF, van Walraven C, Pearce L, et al. Selecting patients with atrial fibrillation for anticoagulation: stroke risk stratification in patients taking aspirin. Circulation 2004;110:2287-92.
7. Sussman M, Menzin J, Lin I, et al. Impact of atrial fibrillation on stroke-related healthcare costs. J Am Heart Assoc 2013;2:e000479.
8. Li X, Tse VC, Au-Doung LW, et al. The impact of ischaemic stroke on atrial fibrillation-related healthcare cost: a systematic review. Europace 2017;19:937-47.
9. Klein AL, Grimm RA, Murray RD, et al. Use of transesophageal echocardiography to guide cardioversion in patients with atrial fibrillation. N Engl J Med 2001;344:1411-20.
10. Al-Saady NM, Obel OA, Camm AJ. Left atrial appendage: structure, function, and role in thromboembolism. Heart 1999;82:547-54.
11. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009;361:1139-51.
12. Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban

versus warfarin in patients with atrial fibrillation. N Engl J Med 2013;369:2093-104.
13. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2011;365:981-92.
14. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011;365:883-91.
15. Steinberg BA, Shrader P, Pieper K, et al. Frequency and Outcomes of Reduced Dose Non-Vitamin K Antagonist Anticoagulants: Results From ORBIT-AF II (The Outcomes Registry for Better Informed Treatment of Atrial Fibrillation II). J Am Heart Assoc 2018;7:e007633.
16. Ruiz Ortiz M, Esteve-Pastor MA, Roldán I, et al. Prognostic impact of inappropriate doses of direct oral anticoagulants in clinical practice. Rev Esp Cardiol (Engl Ed) 2020;73:329-30.
17. 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:e125-51.
18. 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;42:373-498. Erratum in: Eur Heart J 2021;42:507; Eur Heart J 2021;42:546-7; Eur Heart J 2021;42:4194.
19. Whitlock RP, Belley-Cote EP, Paparella D, et al. Left Atrial Appendage Occlusion during Cardiac Surgery to Prevent Stroke. N Engl J Med 2021;384:2081-91.
20. Hauser R, Nielsen AB, Skaarup KG, et al. Left atrial strain predicts incident atrial fibrillation in the general population: the Copenhagen City Heart Study. Eur Heart J Cardiovasc Imaging 2021;23:52-60.
21. Pritchett AM, Jacobsen SJ, Mahoney DW, et al. Left atrial volume as an index of left atrial size: a population-based study. J Am Coll Cardiol 2003;41:1036-43.
22. Abhayaratna WP, Fatema K, Barnes ME, et al. Left atrial reservoir function as a potent marker for first atrial fibrillation or flutter in persons > or = 65 years of age. Am J Cardiol 2008;101:1626-9.
23. Oakes RS, Badger TJ, Kholmovski EG, et al. Detection and quantification of left atrial structural remodeling with delayed-enhancement magnetic resonance imaging in patients with atrial fibrillation. Circulation 2009;119:1758-67.
24. Alhakak AS, Biering-Sørensen SR, Møgelvang R, et al. Usefulness of left atrial strain for predicting incident atrial fibrillation and ischaemic stroke in the general population. Eur Heart J Cardiovasc Imaging 2022;23:363-71.
25. Mannina C, Ito K, Jin Z, et al. Association of Left Atrial Strain With Ischemic Stroke Risk in Older Adults. JAMA Cardiol 2023;8:317-25.
26. Camm AJ, Lip GY, De Caterina R, et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. Eur Heart J 2012;33:2719-47.
27. Segal JB, McNamara RL, Miller MR, et al. Prevention of thromboembolism in atrial fibrillation. A meta-analysis of trials of anticoagulants and antiplatelet drugs. J Gen Intern Med 2000;15:56-67.
28. Perreault S, de Denus S, White-Guay B, et al. Oral Anticoagulant Prescription Trends, Profile Use, and Determinants of Adherence in Patients with Atrial Fibrillation. Pharmacotherapy 2020;40:40-54.
29. Hsu JC, Maddox TM, Kennedy KF, et al. Oral Anticoagulant Therapy Prescription in Patients With Atrial Fibrillation Across the Spectrum of Stroke Risk: Insights From the NCDR PINNACLE Registry. JAMA Cardiol 2016;1:55-62.
30. Yao X, Abraham NS, Alexander GC, et al. Effect of Adherence to Oral Anticoagulants on Risk of Stroke and Major Bleeding Among Patients With Atrial Fibrillation. J Am Heart Assoc 2016;5:e003074.
31. Holmes DR, Reddy VY, Turi ZG, et al. Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomised non-inferiority trial. Lancet 2009;374:534-42.
32. Holmes DR Jr, Kar S, Price MJ, et al. Prospective randomized evaluation of the Watchman Left Atrial Appendage Closure device in patients with atrial fibrillation versus long-term warfarin therapy: the PREVAIL trial. J Am Coll Cardiol 2014;64:1-12.
33. Holmes DR Jr, Reddy VY, Gordon NT, et al. Long-Term Safety and Efficacy in Continued Access Left Atrial Appendage Closure Registries. J Am Coll Cardiol

2019;74:2878-89.
34. Lakkireddy D, Thaler D, Ellis CR, et al. Amplatzer Amulet Left Atrial Appendage Occluder Versus Watchman Device for Stroke Prophylaxis (Amulet IDE): A Randomized, Controlled Trial. Circulation 2021;144:1543-52.
35. Steinberg BA, Shrader P, Thomas L, et al. Off-Label Dosing of Non-Vitamin K Antagonist Oral Anticoagulants and Adverse Outcomes: The ORBIT-AF II Registry. J Am Coll Cardiol 2016;68:2597-604.
36. Jansson M, Själander S, Sjögren V, et al. Reduced dose direct oral anticoagulants compared with warfarin with high time in therapeutic range in nonvalvular atrial fibrillation. J Thromb Thrombolysis 2023;55:415-25.
37. Della Rocca DG, Magnocavallo M, Di Biase L, et al. Half-Dose Direct Oral Anticoagulation Versus Standard Antithrombotic Therapy After Left Atrial Appendage Occlusion. JACC Cardiovasc Interv 2021;14:2353-64.
38. Rodés-Cabau J, O'Hara G, Paradis JM, et al. Changes in Coagulation and Platelet Activation Markers Following Transcatheter Left Atrial Appendage Closure. Am J Cardiol 2017;120:87-91.
39. Duthoit G, Silvain J, Marijon E, et al. Reduced Rivaroxaban Dose Versus Dual Antiplatelet Therapy After Left Atrial Appendage Closure: ADRIFT a Randomized Pilot Study. Circ Cardiovasc Interv 2020;13:e008481.
40. Dukkipati SR, Holmes DR Jr, Doshi SK, et al. Impact of Peridevice Leak on 5-Year Outcomes After Left Atrial Appendage Closure. J Am Coll Cardiol 2022;80:469-83.
41. Price MJ, Ellis CR, Nielsen-Kudsk JE, et al. Peridevice Leak After Transcatheter Left Atrial Appendage Occlusion: An Analysis of the Amulet IDE Trial. JACC Cardiovasc Interv 2022;15:2127-38.
42. Martín Gutiérrez E, Castaño M, Gualis J, et al. Beneficial effect of left atrial appendage closure during cardiac surgery: a meta-analysis of 280 585 patients. Eur J Cardiothorac Surg 2020;57:252-62.
43. Yao X, Gersh BJ, Holmes DR Jr, et al. Association of Surgical Left Atrial Appendage Occlusion With Subsequent Stroke and Mortality Among Patients Undergoing Cardiac Surgery. JAMA 2018;319:2116-26.
44. Whitlock RP, Vincent J, Blackall MH, et al. Left Atrial Appendage Occlusion Study II (LAAOS II). Can J Cardiol 2013;29:1443-7.
45. Toale C, Fitzmaurice GJ, Eaton D, et al. Outcomes of left atrial appendage occlusion using the AtriClip device: a systematic review. Interact Cardiovasc Thorac Surg 2019;29:655-62.
46. Chen MH, Ibrahim JG, Lam P, et al. Bayesian design of noninferiority trials for medical devices using historical data. Biometrics 2011;67:1163-70.
47. Cepas-Guillen PL, Flores-Umanzor E, Regueiro A, et al. Low Dose of Direct Oral Anticoagulants after Left Atrial Appendage Occlusion. J Cardiovasc Dev Dis 2021;8:142.

Cite this article as: Besola L, Gregori D, Fiocco A, Colli A. Minimally invasive left atrial appendage occlusion plus reduced dose direct oral anticoagulant to prevent stroke in patients with atrial fibrillation—the LAAO-PlusRE. Ann Cardiothorac Surg 2024;13(2):146-154. doi: 10.21037/acs-2023-afm-18

Appendix 1

Outcomes definition

Stroke

New focal neurological symptoms lasting at least 24 hours with or without CT scan confirmation.

Thromboembolic event

Local clinical signs of persistent tor transient ischemia (acute loss of blood flow in a peripheral artery) supported by objective evidence of embolism.

Major bleed

Perioperative major bleed is classified according to VARC criteria as:

A) Major Overt bleeding is either associated with a drop in the hemoglobin of ≥3.0 g/dL or requiring transfusion of ≥3 U of whole blood or packed RBCs AND does not meet the criteria of life-threatening or extensive bleeding.
B) Extensive Overt source of bleeding with a drop in hemoglobin of ≥4 g/dL or whole blood or packed RBC transfusion ≥4 U within any 24-h period, or bleeding with a drop in hemoglobin of ≥6 g/dL or whole blood or packed RBC transfusion ≥4 U (BARC type 3b) within 30 days of the procedure.
C) Life-threatening Bleeding in a critical organ, such as intracranial, intraspinal, intraocular, or pericardial, necessitating surgery or intervention, or intramuscular with compartment syndrome OR bleeding causing hypovolemic shock or hypotension (systolic blood pressure <90 mmHg lasting >30 min and not responding to volume resuscitation) or requiring significant doses of vasopressors or surgery.
D) Fatal Bleeding adjudicated as being a proximate cause of death. Severe bleeding adjudicated as being a major contributing cause of a subsequent fatal complication, such as MI or cardiac arrest, is also considered fatal bleeding.

During FU, major bleed is defined as type 3a, 3b, 3c, 5a, and 5b as per BARC criteria.

Hospitalization with heart failure

Admission to the inpatient unit or ward in the hospital for 24 hours, including an emergency department stay. Hospitalizations planned for pre-existing conditions are excluded unless the baseline condition worsens. Symptoms, signs and laboratory evidence of worsening heart failure must be reported.

Sample size determination

The study is a randomized non-inferiority trial for occlusion with half-dose oral anticoagulant (HDOA) *vs.* occlusion with full-dose oral anticoagulant (FDOA).

- Primary endpoint (efficacy): composite endpoint of ischemic stroke, thromboembolic events, cardiovascular death.
- Primary endpoint (safety): composite endpoint of perioperative death, major bleeding.
- Secondary endpoint: incomplete appendage occlusion, ischemic stroke, thromboembolic events, cardiovascular death, overall death.

For two group models (i.e., HDOA as treatment and FDOA as control group with no covariates), we denote the parameter for the treatment group by μ_t and the parameter for the control group by μ_c. The default null and alternative hypotheses are given by

$$H_0: \mu_t - \mu_c \geq \delta$$

and

$$H_1: \mu_t - \mu_c < \delta,$$

where δ is a prespecified constant.

Let Θ_0 and Θ_1 denote the parameter spaces corresponding to $H_0$and H_1. Let $y^{(n)}$ denote the simulated current data associated with a sample size of n and let $\theta=(\mu_t,\mu_c,\tau_c)$ denote the model parameters. Let $\pi^{(s)}(\theta)$ denote the sampling prior and let $\pi^{(f)}(\theta)$ denote the fitting prior. The sampling prior is used to generate the hypothetical data while the fitting prior is used to fit the model after the data is generated. Let $\pi_0^{(s)}(\theta)$ denote a sampling prior that only puts mass in the null region, i.e., $\theta \subset \Theta_0$. Let $\pi_1^{(s)}(\theta)$ denote a sampling prior

https://dx.doi.org/10.21037/acs-2023-afm-18

that only puts mass in the alternative region, i.e., $\theta \subset \Theta_1$. To determine the Bayesian sample size, we estimate the quantity

$$\beta_{sj}^{(n)} = E_s[I\{P(\mu_t-\mu_c<\delta \mid y^{(n)},\pi^{(f)})\geq\gamma\}]$$

where j=0 or 1, corresponding to the expectation taken with respect to $\pi_0^{(s)}(\theta)$ or $\pi_1^{(s)}(\theta)$. The constant $\gamma>0$ is a prespecified posterior probability threshold for rejecting the null hypothesis (e.g., 0.975). The probability is computed with respect to the posterior distribution given the simulated data $y^{(n)}$, and the fitting prior $\pi^{(f)}(\theta)$, and the expectation is taken with respect to the marginal distribution of $y^{(n)}$ defined based on the sampling prior $\pi^{(s)}(\theta)$. Then $\beta^{(n)}_{s0}$ corresponding to $\pi^{(s)}(\theta)=\pi_0^{(s)}(\theta)$ is the Bayesian type I error rate, while $\beta^{(n)}_{s1}$corresponding to $\pi^{(s)}(\theta)=\pi_1^{(s)}(\theta)$ is the Bayesian power.

1. Primary endpoint (composite endpoint of ischemic stroke, thromboembolic events, cardiovascular death)

The basic model targets composite rates (a binary outcome) for treatment and control groups with no covariates. Patients with atrial fibrillation and CHA2DS2-VASc ≥3 with left auricle closed in thoracoscopy are randomized on the first day half-dose postoperative anticoagulant *vs.* continue full dose anticoagulant, annual telephone FU for various endpoints.

We consider the non-inferiority design application of Chen *et al.* (46).

Historical information can be borrowed from previously conducted OA and occlusion trials. Data are taken from Della Rocca *et al.* (37) and Cepas-Guillen *et al.* (47). *Table 1* summarizes the historical data.

Let $y_t^{(nt)}=(y_{t1},\ldots,y_{tnt})$ and $y_{c(nc)}=(y_{c1},\ldots,y_{cnc})$ denote the responses from the current trial for HDOA and the FDOA, respectively. The total sample size is $n=n_t+n_c$.

We assume the i-th observation from the test group y_{ti} follows Bern(μ_t), and the i-th observation from the control group y_{ci} follows Bern(μ_c).

A Bayesian sample size determination (SSD) approach incorporates historical data using the power prior with fixed $\alpha_0$and the normalized power for $\alpha_0$modeled as random.

The hypotheses for non-inferiority testing are

H0: $\mu_t-\mu_c\geq\delta$

and

H1: $\mu_t-\mu_c<\delta$,

where δ is a prespecified non-inferiority margin. We set δ=1%.

We choose beta(10^{-4},10^{-4}) for the initial prior for μ_c, which performs similarly to the uniform improper initial prior for $\log(\mu_{c1}-\mu_c)$ used in Chen *et al.* (46) in terms of operating characteristics.

Power is computed under the assumption that $\mu_t=\mu_c$ and type I error rate is calculated under the assumption that $\mu_t=\mu_c+\delta$.

For sampling priors, a point mass prior at μ_c=1% is used for $\pi^{(s)}(\mu_c)$ where 1% is the pooled proportion for the historical control datasets, and a point mass prior at $\mu_t=\mu_c$ is used for $\pi_{(s)}(\mu_t)$.

We use N=10,000, n_t/n_c=1, and γ=0.95 for all computations.

1.1 Power prior with fixed α0

When α0 is fixed, the historical matrix is fixed, each row represents a historical dataset, and the three columns represent the sum of responses, sample size and α0, respectively, of the historical control data. The FDA 2010 Guidance recommends α0=0.05 but this needs to be explored further. In a sensitivity analysis we evaluated a range of α0 values, from 0 to 0.4 by 0.05. Note that α0=0 coincides with non-informative prior and α0=1 with full borrowing.

We consider n_t values ranging from 50 to 100 to achieve the desired power of 0.8.

Since point mass sampling priors are used for μ_t and μ_c, samp.prior.mu.t and samp.prior.mu.c are both scalars.

For Bernoulli outcomes, beta initial priors are used for μ_t and μ_c, with hyperparameters specified by prior.mu.t.shape1, prior.mu.t.shape2, prior.mu.c.shape1 and prior.mu.c.shape2.

We can see that a sample size (test group) greater than 50 is required to achieve a power of at least 0.8 when α0>0.10 (*Figure S1*).

We then compute the type I error rate for these sample sizes.

Since the type I error rate is computed under the assumption that $\mu_t=\mu_c+\delta$, we use a point mass at μ_c=1% for the sampling prior for μ_c, and a point mass at μ_t=1%+1% for the sampling prior for μ_t (*Figure S2*).

2. Secondary endpoint: incomplete appendage occlusion, ischemic stroke, thromboembolic events, cardiovascular death, overall death

We will conduct a Bayesian analysis for the secondary endpoint if non-inferiority between devices is established for the primary endpoint. A Bayesian approach to compare proportions of incomplete appendage occlusion, ischemic

https://dx.doi.org/10.21037/acs-2023-afm-18

stroke, thromboembolic events, cardiovascular death, overall death between the test group and the control group is adopted. The observed data consists of the sample sizes (nt=100 and nc=100) and the number of migraine episodes (stand x_c) in the test and control groups, respectively.

The parameters section defines the unknown probabilities p_t and p_c for the test and control groups. These probabilities are assumed to follow a beta distribution with hyperparameters (0.001, 0.001), representing non-informative diffuse priors.

The model section specifies the likelihood of the observed data given the parameters. The binomial distribution models the number of successes out of the corresponding sample sizes for the test and control groups. The difference in proportions is calculated as the difference between p_t and p_c.

Four separate Markov chains will be run with a total number of iterations set to N=10,000 and 1,000 iterations used for warm-up or burn-in.

Instead of controlling the Type I error rate, Bayesian analysis allows us to assess the posterior probabilities of hypotheses and make decisions based on those probabilities. *Figure S3* shows the posterior distribution of the difference corresponding to the scenario in which the observed migraine rates $x_t/n_t=x_c/n_c$ are both set at 15% according to the historical information.

The Bayesian model is specified using the Stan modeling language through R software v4.3.0 (R Core Team. 2023. R: A Language and Environment for Statistical Computing. Vienna, Austria: R Foundation for Statistical Computing).

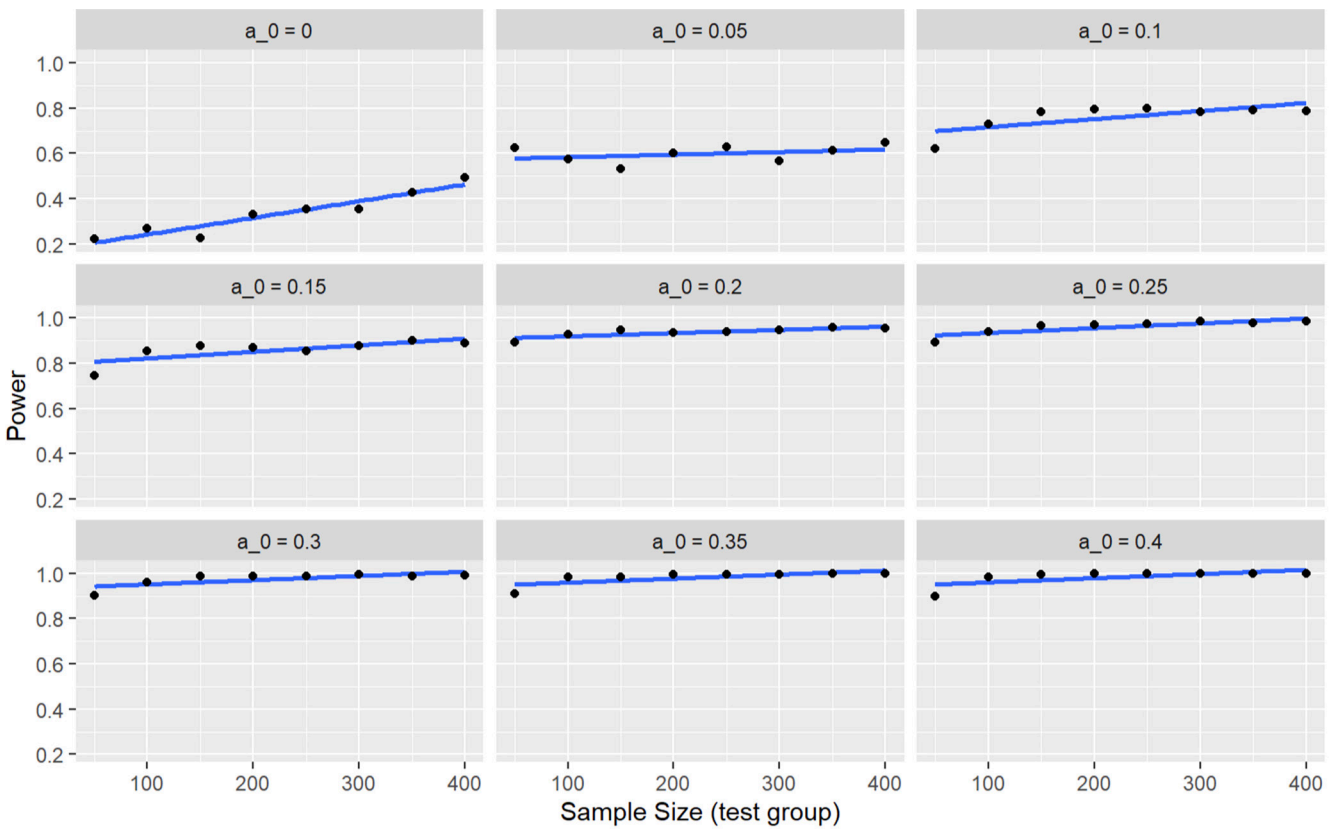

Figure S1 Power curve for sample sizes ranging from 50 to 400.

https://dx.doi.org/10.21037/acs-2023-afm-18

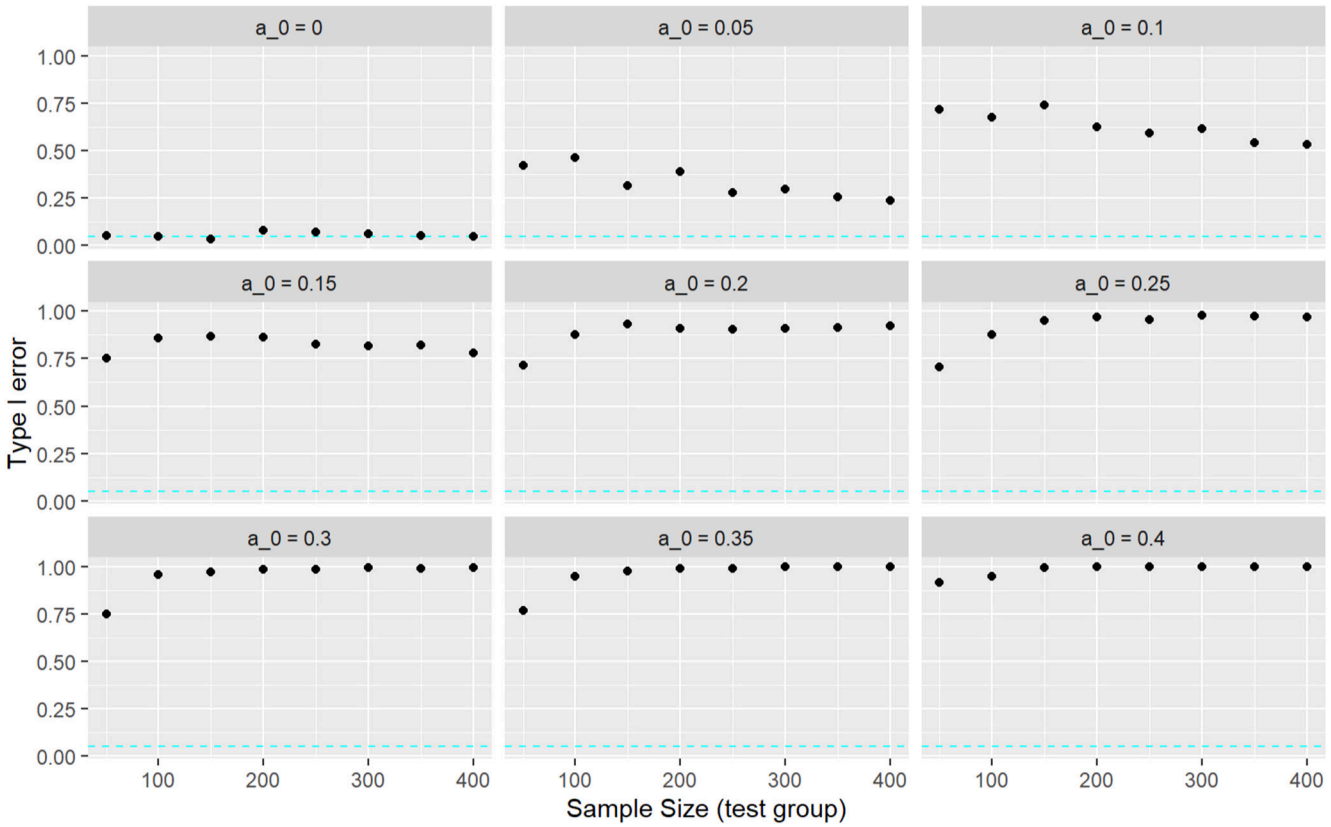

Figure S2 Type I error curve for sample sizes ranging from 50 to 400.

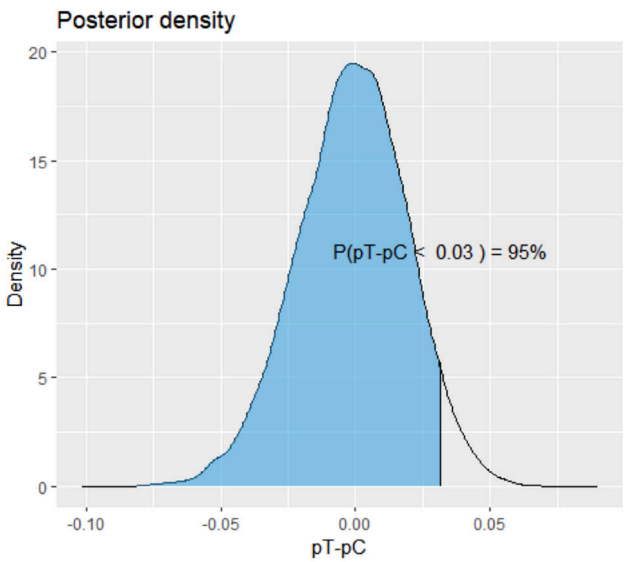

Figure S3 Curve showing the posterior distribution of the difference for observed rates $x_t/n_t=x_c/n_c$ set at 15%.

https://dx.doi.org/10.21037/acs-2023-afm-18