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# Percutaneous left atrial appendage occlusion discrepancy between randomised trials and clinical practice

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## ABSTRACT

In patients with atrial fibrillation and previous episodes of bleeding on oral anticoagulant treatment, left atrial appendage occlusion (LAAO) has emerged as an alternative way to decrease the risk of stroke.

The use of the procedure has been on the rise, and the news coverage has been dominated by an uncritical acceptance of the benefit of this procedure, which probably have contributed to the increasing number of procedures.

This commentary is a presentation and critical appraisal of the available evidence on the efficacy and safety of left atrial appendage closure as stroke prophylaxis.

We illustrate that LAAO is supported by limited randomised data risk of serious complications, which we do not believe supports the current widespread use.

Stroke prevention in patients with atrial fibrillation is based on anticoagulation using the $CHA_2DS_2$- VASc score with a consideration of the bleeding risk which can be estimated with the HAS-BLED score.[1]

Not infrequently, patients have a high risk of bleeding or previous major bleeding episodes in conjunction with anticoagulation. These patients also have a high risk of stroke, if left untreated with oral anticoagulation.[2]

This schism has introduced new ways to reduce the risk of stroke in patients with atrial fibrillation and percutaneous occlusion of the left atrial appendage (LAAO) is the most emerging strategy.

However, the use of LAAO has been on the rise despite a limited number of smaller randomised studies, all with limitations, but documenting a significant risk of procedural complications.

In non-rheumatic atrial fibrillation, it has previously been demonstrated that only 90% of clots are located in the LAA, and therefore, seems LAAO not to be a foolproof procedure.[3] Especially in patients with permanent atrial fibrillation and in elderly patients, with multiple other causes of stroke.

## RANDOMISED DATA

Three non-inferiority randomised trials have been completed where LAAO has been compared to anticoagulation with warfarin or direct oral anticoagulants (DOAC).[4–6]

PROTECT-AF was a multicentre, randomised (2:1) study, which included 707 patients with nonvalvular AF and at least one additional stroke risk factor to either LAAO with a Watchman device or warfarin. At a mean follow-up of 3.8 years, the composite endpoint including stroke, systemic embolism and cardiovascular/unexplained death met the non-inferiority margin.[6] However, almost 20% of the patients in the warfarin group withdrew from the study during follow-up.

In the FDA-mandated PREVAIL trial, 407 patients with $CHADS_2$ score ≥2 or 1 and another risk factor were randomised to LAAO with a Watchman device or Warfarin. In this study, LAAO did not meet noninferiority for its first co-primary endpoint of stroke, systemic embolism or cardiovascular death/unexplained death due to more than twice as many ischaemic strokes in the LAAO arm.[4]

In PRAGUE-17, 415 high-risk patients with AF were randomised to LAAO or DOAC. Median follow-up was 19.9 months. The $CHA_2DS_2$-VASc score was 4.7 and the HAS-BLED score was 3.0. The primary endpoint was a composite of safety and efficacy characteristics of both strategies: (1) stroke (ischaemic or haemorrhagic) or TIA; (2) systemic embolism; (3) clinically significant bleeding; (4) cardiovascular death or (5) a significant periprocedural or device-related complication. Approximately one-third and nearly half of patients had a history of an embolic event and a history of bleeding, respectively. There were 47 primary outcomes (stroke, transient ischaemic attack, systemic embolism, cardiovascular death, major or nonmajor clinically relevant bleeding or procedure-related/device-related complications) in the DOAC group vs 38 in the LAAC arm, resulting in a HR of 0.84 (95% CI 0.53 to 1.31), which was below the non-inferiority margin of 1.47.[5]



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## LIMITATIONS OF AVAILABLE DATA

1. Only 1521 patients have been included in randomised trials, of which 1117 are from studies comparing one type of device (watchman device) with warfarin, which is no longer the preferred choice of oral anticoagulation in most patients.
2. The PREVAIL study did not meet non-inferiority for its first coprimary endpoints.
3. All three randomised studies were non-inferior and unblinded in design and the chosen non-inferiority margins were wide in the Watchman (2.00 and 1.75) trials. In a systematic review, Aberegg *et al* found that the design and interpretation of non-inferiority trials lead to significant and systematic bias in favour of the experimental therapy.[7]
4. In PRAGUE-17 the non-inferiority margin was 1.47, but here the problem with non-inferiority was particularly pronounced since the investigators chose a broad composite endpoint comprising both efficacy and safety endpoints. Each component occurred in small numbers leading to wide confidence intervals. Moreover, drop-out was not uniform with more patients dropping out of the LAAO arm.
5. The volume of implanting centres and operators should be considered as low-volume centres could lead to lower quality of the procedure.[8]

## RISK OF COMPLICATIONS

Safety is a central point when considering an invasive procedure aiming at reducing the risk of stroke and patients should be well informed before they undergo a LAAO procedure. Complications include embolisation of the device or perforation of the atrial appendage which can cause a life-threatening pericardial effusion. Other adverse events are access site bleeding, stroke and death.[9]

There seems to be a significant improvement in the safety of the Watchman LAAO device with increased operator experience.[10]

In PRAGUE-17, 5% of patients in the LAAO arm had a serious complication, and two patients died from the procedure.[5]

The Amulet IDE trial (Amplatzer Amulet Left Atrial Appendage Occluder IDE Trial) examined the safety and effectiveness of the Amulet LAA occluder compared with the Watchman device. In this trial, almost 10% experienced a complication within the first 90 days after the procedure.[11]

Recently, the U.S. Food and Drug administration published a letter to healthcare providers stating that procedural outcomes such as major adverse events and lengthened hospital stay may be more common in women compared with men (LAAO Devices Potentially Associated with Procedural Outcome Differences Between Women and Men—Letter to Healthcare Providers, 27 September 2021. https://www.fda.gov/medical-devices/letters-health-care-providers/left-atrial-appendage-occlusion-laao-devices-potentially-associated-procedural-outcome-differences). This was based on data from The National Cardiovascular Data (US NCDR) LAAO Registry including 49 357 patients in which the risk of a major adverse event occurred in 4.1% in women vs 2.0% in men (mean age 76 years).[12]

Patients with either chronic kidney disease or end-stage renal disease have an even higher risk of in-hospital mortality or adverse events.[13] These patients represent more than 10% of patients eligible for LAAO.[13]

## PERIDEVICE LEAKS

Complete occlusion of the atrial appendage is important, but device implantation can be difficult. A peridevice leak (PDL) leads to considerations on whether antiplatelet or anticoagulation should be continued after LAAO.

In the recent AMULET IDE study that represents state of the art LAAO techniques only 63% of the cases with an AMULET device achieved complete occlusion and the number was lower with the watchman device (46%).[11] In patients undergoing LAAO in everyday clinical practice the numbers seem similar. In a recent study from the National Cardiovascular Data Registry LAAO Registry (US NCDR LAAO Registry) that included 51 333 patients, small PDLs (0–5 mm) were present in 25% of the cases and these PDLs were associated with a modestly higher thromboembolic and bleeding events during 1-year follow-up.[14] Large PDLs (>5 mm) were not associated with adverse events, possibly because of the small number of patients in this group (379 patients, 0.7 %). There could be a learning curve of the procedure since a study with data from 2016 to 2018 only reported 1,9% PDLs >5 mm.[15]

In the US NCDR LAAO Registry, 3%–4% were on warfarin or DOAC and more than 10% on a P2Y12 inhibitor at 1-year of follow-up.[8] This illustrates that in patients undergoing LAAO in everyday clinical practice, several patients remain on anticoagulation, which was the treatment the procedure was aiming to eliminate.

Although the assessment of residual PDL after LAAO remains crucial for postprocedural management, there is a lack of knowledge and recommendations on how to assess PDL. This includes when to check, what modality to use and what consequence should be taken in patients with insufficient closure.[16]

In a study from Denmark, the number of PDLs was higher when assessed with CT compared with transoesophageal echocardiogram (TEE), with a large discrepancy between modalities in leak quantification.[17] Using transoesophageal echocardiography, a PDL was present in 110 patients (32%), while cardiac CT found 210 patients (61%) with PDL at the disc and contrast patency in 204 patients (59%).[17] In this study, a CT-detected PDL was not significantly associated with worse outcome, HR: 1.82 (95 % CI 0.95 to 3.50); p<0.07. However, this may be due to insignificant statistical power.[17]

So as a healthcare provider, we need good data on how to adjust the medical treatment after an LAAO and who to keep on antiplatelet or anticoagulation therapy.



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However, current randomised data provide limited data on this subject.

## ANTITHROMBOTIC THERAPY

In the PROTECT and PREVAIL trials, patients were treated with warfarin after implantation and aspirin (81 mg) for 45 days to prevent large thrombus formation on the device during its endothelialisation. TEE was performed at 45 days', 6 months' and 12 months' follow-up. If the 45-day TEE documented either complete closure of the LAA, or if residual peridevice flow was <5 mm in width and there was no definite visible large thrombus on the device, warfarin was discontinued. After discontinuation of warfarin, only daily clopidogrel 75 mg and aspirin 81–325 mg were prescribed until the 6-month follow-up visit, at which time clopidogrel was discontinued and aspirin alone was continued indefinitely. If an adequate seal was not obtained or a thrombus was detected (figure 1), patients continued warfarin until an adequate seal was attained or the thrombus was resolved before transitioning to aspirin monotherapy.[4 6]

In PRAGUE-17, the recommended antithrombotic regimen was aspirin 100 mg/day plus clopidogrel 75 mg/day for 3 months. If a TEE then showed no device-related thrombus or leak of ≥5 mm, clopidogrel was discontinued; aspirin was continued indefinitely. Based on patient characteristics and device type, this postimplant antithrombotic regimen could be individualised and was ultimately left to the physician's discretion However, in all cases aspirin was continued indefinitely.[5]

Several points relating on stroke prevention and antiplatelet therapy are worth a comment:

1. TEE controls at 45 days', 6 months' and 12 months' follow-up are rarely performed in everyday clinical practice.
2. A substantial number of patients does not fulfil the criteria for stopping anticoagulation, which is the sole indication for LAAO. In the AMULET IDE trial around 10% remained on OAC.[11] Moreover, it is unknown how many patients develop an indication for oral anticoagulation later in life that is, due to venous thromboembolism.
3. There are no well-established data or guidelines for the management of cardioverting patients with LAAO.
4. Patients with non-paroxysmal atrial fibrillation can embolise from thrombi evolved outside the LAA.[18] These patients have a significantly higher risk of death, stroke and systemic embolism after LAAO compared with patients with non-paroxysmal atrial fibrillation.[18]
5. Although the randomised trials all recommend aspirin indefinitely following LAAO, in clinical practice, aspirin is not seldom discontinued after 6 months. The AVERROES study randomised 5599 patients with atrial fibrillation for whom vitamin K antagonist therapy was unsuitable to either apixaban (at a dose of 5 mg two times per day) or aspirin (81–324 mg per day—91% had 162 or 81 mg per day), with no significant difference in the risk of major bleeding.[19] When patient populations in PRAGUE-17[5] and AVERROES are compared they are comparable regarding sex and age distribution and the frequency of hypertension, heart failure and type of atrial fibrillation, but the patients in PRAGUE-17 had a higher thromboembolic risk, frequency of diabetes and previous stroke. However, if aspirin is mandatory after LAAO, then many patients could potentially be able to tolerate apixaban without the need for LAAO.
6. It was recently documented that adherence to the U.S. Food and Drug administration post procedure protocols from the pivotal trials of LAAO was rare.[15] This includes medications, follow-up visits and imaging, with the most common deviation being the discharge with unstudied antithrombotic regimens.[15]

## PATIENT SELECTION

Despite that the recommendations in international atrial fibrillation guidelines remains weak, with a European Society of Cardiology grading of LAAO as class IIb (level of evidence B), the randomised studies have led to an increased utilisation of LAAO.[1]

A US registry recently reported data from 38000 high-risk patients, with patients being generally older with more comorbidities than those enrolled in the pivotal trials.[8]

In a study including nearly 22000 patients undergoing LAAO, almost half were considered frail.[20] Frailty confers a high risk of poor outcome and survival. Mortality rates at up to 3 years were 41% for the high-risk group. After adjusting for age, sex and comorbidities, the highest frailty group had an eightfold higher risk of prolonged hospital stay, sixfold higher rate of death at 30 days and a threefold higher mortality rate at 1 year. There was a high prevalence of dementia—in one-fifth of the overall cohort and in nearly half of the group with the highest frailty score.

These studies document that many LAAO procedures are performed in older, sicker and more frail patients than the approving trials. The (potential) longer-term benefit of LAAO takes time to develop as documented in a post hoc

**Figure 1** Thrombus on LAAO device. LAAO, left atrial appendage occlusion.



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analysis of the PROTECT and PREVAIL studies looking at net clinical benefit. Here, the findings are that the net positives for the device take 3–5 years to be seen.[21] Many patients will not live that long.

## CONCLUSION

As we have tried to illustrate, decision-making regarding LAAO is complex.

1. There should be postprocedure protocols regarding follow-up, imaging and medication in departments managing patients undergoing LAAO.
2. Patients should be included in clinical trials comparing LAAO and DOAC treatment to improve our knowledge about areas of uncertainty and our ability to select patients. This includes the potential consequences of PDL and device-related thrombus.[22]

Fortunately, there are several planned or ongoing clinical trials underway, comparing LAAO with DOAC/OAC treatment-OPTION (NCT03795298), CATALYST (NCT04226547), CHAMPION AF (NCT04394546).

A randomised controlled trial including apixaban as a comparator and inclusion of patients at higher risk of bleeding and risk factors such as age, frailty and female gender could provide valuable information.

3. The risk and frequency of LAAO procedural complication should be part of the decision-making process and weighed against the risk of bleeding on aspirin and DOAC treatment, the patient's comorbidity and prognosis.

We believe the strength of the evidence is presently too weak to warrant the current use of the procedure. It is our opinion, based on the available evidence, that LAAO can be considered in very selected patients, especially in cases with previous life-threating bleeding episodes, limited modifiable bleeding risk factors, a continuously high risk of bleeding, combined with a high risk of thrombosis and limited comorbidity. Above and beyond all other considerations, is to provide solid information to the patient.

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