



Topic Exploration Report

Topic explorations are designed to provide a high-level briefing on new topics submitted for consideration by Health Technology Wales. The main objectives of this report are to:

1. Determine the quantity and quality of evidence available for a technology of interest.
2. Identify any gaps in the evidence/ongoing evidence collection.
3. Inform decisions on topics that warrant fuller assessment by Health Technology Wales.

Topic exploration report number:	TER309
Topic:	Left atrial appendage occlusion in patients with atrial fibrillation
Summary of findings:	<p>A proportion of people with atrial fibrillation are unable to take anti-coagulants. For these people, left atrial appendage occlusion (LAAO) may be an alternative treatment.</p> <p>Clinical experts have highlighted that this treatment is currently not commissioned in Wales. This topic exploration report focused on the evidence for clinical and cost effectiveness of LAAO in AF patients that are contraindicated to anti-coagulants.</p> <p>We identified a substantial amount of secondary and primary evidence, supported by guidance, economic evaluations, and health technology assessments. The evidence suggests LAAO may be a suitable alternative treatment to anti-coagulants for those that cannot take them. However, there is a lack of randomised controlled trials (RCTs) within this specific patient cohort which has been highlighted as a limitation in much of the evidence found.</p>

Introduction and aims

Atrial fibrillation (AF) is the most common cardiac arrhythmia and causes a five-fold increased risk of thromboembolic stroke (CtE, 2019). This is mainly because the irregular heartbeat stops the efficient emptying of the heart chambers, leaving blood behind to pool and subsequently form clots. The left atrial appendage is a small pouch in the atrium and is thought to be where 90% of the blood clots form in patients with AF (SHTG, 2019).

Oral anticoagulants (OACs), such as warfarin and direct-acting oral anticoagulants (DOACs) are recommended for patients with AF to reduce the risk of stroke. However, a proportion of people with AF cannot take these drugs due to contraindications.

Left atrial appendage occlusion (LAAO) is a surgical intervention that mechanically blocks the left atrium appendage where most of the clots are known to form. This treatment has been recommended in England and Scotland as an alternative treatment for patients that are unable to take OACs.

Health Technology Wales researchers searched for evidence on the clinical and cost effectiveness of left atrial appendage occlusion in patients with atrial fibrillation that are contraindicated to OACs.

Evidence overview

Guidance and Health Technology Assessments

We identified recently updated NICE guidance and one international guidance from Australia, both recommending the use of LAAO for stroke prevention in patients contraindicated to anticoagulants. We also identified two health technology assessments, one from Scotland advising the use of LAAO in contraindicated patients and one from Austria, reporting insufficient evidence to support LAAO for stroke prevention.

Guidance

NICE updated their guidance for 'Atrial Fibrillation: Diagnosis and Management' (NG196) in June 2021 and this includes information on stroke prevention and specifically LAAO. The guidance recommends LAAO if anticoagulation is contraindicated and states to not offer LAAO as an alternative to anticoagulation unless anticoagulation is contraindicated or not tolerated. NG196 refers to IPG349 'Percutaneous occlusion of the left atrial appendage in non-valvular atrial fibrillation for the prevention of thromboembolism' where LAAO is described as efficacious in reducing the risk of thromboembolic complications associated with non-valvular atrial fibrillation (AF).

The National Heart Foundation of Australia published guidance on the management of atrial fibrillation in 2018. The guidance recommended LAAO be considered for stroke prevention in patients with non-vascular atrial fibrillation at moderate to high risk of stroke and with contraindications to oral anticoagulation therapy. The guidelines highlight the lack of randomised trials comparing LAAO to standard therapy in patients with contraindications to anticoagulation.

Health Technology Assessments

In August 2019 the Scottish Health Technologies Group (SHTG) published advice on LAAO in patients with atrial fibrillation. SHTG advised that, 'Left atrial appendage occlusion (LAAO) may be offered to patients with non-valvular atrial fibrillation deemed to be at high risk of ischaemic stroke, who have absolute contraindications to oral anticoagulation with warfarin and direct oral anticoagulants'.

The rapid evidence review conducted by the SHTG consisted of one systematic review, eight single-arm primary studies and data from the Commissioning through evaluation (CtE) registry in England. SHTG also highlighted the lack of RCT evidence in this patient cohort.

SHTG reported that LAAO was found to be cost incurring from an NHS perspective due to the cost per devices unit (approx. £4000) and cost per complete procedure (approx. £9500 to £13,000). However, when social care costs were incorporated, LAAO become cost neutral.

The International HTA database included an assessment of LAAO by the Austrian Institute for Health Technology Assessment (AIHTA) that was published in 2018. The HTA compared LAAO with OACs and found there was insufficient evidence to suggest LAAO was better. The authors highlighted the lack of comparative studies on non-vitamin K oral anticoagulants (NOACs). They have proposed a re-evaluation in 2023.

Secondary Evidence

As the initial search for guidance and HTAs identified recent relevant evidence, our search for primary and secondary evidence was date restricted from August 2019 to present to avoid duplication of SHTG work.

We identified two meta-analyses and one systematic review/meta-analysis. Most studies included were observational with only three RCTs included across all meta-analyses. All results either favoured LAAO or reported it to be non-inferior to OACs.

Systematic reviews and meta-analyses

Labori et al. (2021) conducted a systematic review and meta-analysis to estimate the long-term clinical effectiveness of LAAO as stroke prevention in patients with AF that are contraindicated to OACs. The study included 29 observational studies with a total of 7951 participants. The authors used Poisson random effect models to estimate the incidence rate (events per 100 patient-years) of ischemic stroke, transient ischemic attack, major bleeding, and all-cause death after LAAO. Risk reduction of ischaemic stroke compared with no stroke prevention was also calculated. The study concluded that LAAO is effective in this cohort of patients and reported an estimated risk reduction of 74.7% with LAAO compared to predicated risk with no stroke prevention.

Razzack et al. (2021) conducted a meta-analysis comparing clinical outcomes of LAAO vs DOACs. Three studies were included with a total of 3039 participants (LAAO = 1465 and DOACs = 1574). The mean age for the LAAO group was 74.2 years and 75.3 years for the DOAC group. The primary outcome for the study was cardiac mortality and secondary outcomes included ischaemic stroke. After a follow up period of two years, the study found no significant difference ($p=0.45$) between the groups for ischaemic stroke and concluded that LAAO has the similar safety and efficacy profile as DOACs.

Ibrahim et al. (2019) also conducted a meta-analysis that reported on the efficacy of LAAO for ischaemic stroke. 10 studies were included in the meta-analysis included three randomised trials.

A total of 13,352 participants were included, 6779 that underwent LAAO and 6573 that did not. The authors reported a significant difference between groups for ischaemic stroke, that favoured LAAO (p=0.0004).

Economic Evidence

We identified one economic evaluation study in addition to the SHTG report in 2019.

Reddy et al. (2019) reported on the cost-effectiveness of LAAO for stroke reduction in patients with AF. The authors used a Markov model in an analysis of pooled, 5-year, long-term data from a US payer perspective with a lifetime horizon. The model was populated with a cohort of 10,000 patients, aged 70 years, at moderate stroke and bleeding risk. The authors concluded that LAAO proved to be not only cost-effective, but cost saving relative to warfarin and NOACs.

Primary Evidence

We identified two RCTs involving LAAO since the SHTG report in 2019, however neither trial includes patients that are contraindicated to oral anticoagulants. Three multicentre observational studies were also identified. All studies either favoured LAAO or reported it to be non-inferior to OACs.

Randomised Controlled Trials

Whitlock et al. (2021) conducted a multicentre randomised trial with patients that had atrial fibrillation who were scheduled to undergo cardiac surgery for another indication. 2379 patients were randomised to the occlusion group and 2391 to the no occlusion group. The mean age of all participants was 71 and all participants continued to take oral anticoagulants. The primary outcomes were occurrence of ischaemic stroke or systemic embolism. The study found stroke or systemic embolism occurred in 114 participants (4.8%) in the occlusion group and in 168 (7.0%) in the no-occlusion group (hazard ratio, 0.67; 95% confidence interval, 0.53 to 0.85; P = 0.001). The authors concluded that the risk of stroke is lower in participants with atrial fibrillation that undergo LAAO.

Osmančik et al (2020) (PRAGUE-17) conducted a multicentre randomised trial with patients that had non-valvular atrial fibrillation and were indicated for anticoagulants. Moderate or high-risk patients with nonvalvular AF were eligible if indicated for anticoagulation and had: 1) history of bleeding 2) history of a cardio embolic event while taking anticoagulation agents; or 3) a moderate to high risk profile. 201 patients were randomised to the LAAO group and 201 to the DOAC group. The median follow-up time was 19.9 months. The results showed among patients at high risk of stroke and increased risk of bleeding, LAAO was noninferior to DOAC in preventing major AF-related cardiovascular, neurological, and bleeding events.

Observational Studies

A multicentre, prospective, non-randomised observational registry study by Parikh et al (2019) analysed patients screened for a LARIAT device LAAO from 2009 to 2012 across four centres. Of the 153 patients screened, 109 underwent the LAAO and the remaining 45 were included in the control group. In the mean 6.5 year follow up the authors reported significantly lower thromboembolic events in the LAAO group compared with the control group (1.9% vs 24% p = 0.001). Significant heterogeneity and the small size in control group indicates the results should be interpreted with caution.

Brachmann et al. (2019) conducted a registry study that included 641 patients (mean age in years: 75.9 + 8.0 SD years) across 38 hospitals in Germany from 2014 to 2016. Patients that were enrolled

had bleeding events as the main indication for LAAO and were followed up after one year. The authors reported a favourable outcome at 1-year follow-up in terms of stroke/TIA (1.3%) and major bleeding (1.6%) while using a single anti-platelet therapy.

Boersma et al. (2019) conducted a multicentre study that collected real-life clinical outcomes of the WATCHMAN device across 13 countries and reported favourable results for LAAO in patients that are contraindicated to OACs. The authors reported on 1020 patients (mean age: 73.4 + 8.9 SD years), 740 (72.2%) of which were contraindicated to OACs. After a two year follow up the WATCHMAN device showed consistently low rates of stroke and nonprocedural bleeding.

On-going Evidence

We identified four systematic reviews that are currently ongoing and are yet to publish their results.

Areas of uncertainty

- There are several occlusive devices available for LAAO including Amplatzer (Cardiac Plug), Watchman, Amplatzer (Amulet).
- Patients undergoing LAAO are recommended to have anti-platelet therapy, this addition to the pathway may alter the cost effectiveness of the intervention depending on the time horizon of the economic analysis.
- Currently there is not any published evidence on RCTs including patients with atrial fibrillation and contraindications to OACs however the SHTG report included 5 upcoming RCTs in this group of patients.

Literature search results

Health Technology Assessments and Guidance

[NICE](#)

NICE Interventional procedures guidance [IPG349]. Percutaneous occlusion of the left atrial appendage in non-valvular atrial fibrillation for the prevention of thromboembolism. Published 23 June 2010. <https://www.nice.org.uk/guidance/ipg349>

NICE guideline [NG196]. Atrial fibrillation: diagnosis and management. Published 27 April 2021. <https://www.nice.org.uk/guidance/ng196/chapter/Recommendations#stroke-prevention>

[Healthcare Improvement Scotland](#)

SHTG (August 2019). Left atrial appendage occlusion (LAAO) in patients with atrial fibrillation who have contraindications to oral anticoagulation. <file:///C:/Users/sa097928/Downloads/left-atrial-appendage-occlusion-laa0-in-patients-with-atrial-fibrillation-shtg-adv-state-06-19-cardiology.pdf>

[Health Information and Quality Authority](#)

No evidence found.

[EUnetHTA](#)

No evidence found.

[International HTA Database](#)

Ludwig Boltzmann Institute for Health Technology Assessment (2018) (Percutaneous) left atrial appendage closure for the prevention of thromboembolic events in patients with atrial fibrillation. <https://database.inahta.org/article/18742>

[International Guidelines Library](#)

National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand: Australian Clinical Guidelines for the Diagnosis and Management of Atrial Fibrillation (2018) <https://www.heartlungcirc.org/action/showPdf?pii=S1443-9506%2818%2931778-5>

Evidence reviews and economic evaluations

<https://www.epistemonikos.org/en/>

Razzack AA, Garimella R, Bajwa RS, et al. (2021). A meta analysis comparing the clinical outcomes of left atrial appendage occlusion (LAAO) vs direct oral anticoagulation (DOAC) in high-risk patients with atrial fibrillation. Catheter. Cardiovasc. Interventions. 97(SUPPL 1): S96-None. doi: <https://doi.org/10.1002/ccd.29644>

Labori F, Bonander C, Persson J, et al. (2021). Clinical follow-up of left atrial appendage occlusion in patients with atrial fibrillation ineligible of oral anticoagulation treatment-a systematic review and meta-analysis. Journal of interventional cardiac electrophysiology: an international journal of arrhythmias and pacing. doi: <http://dx.doi.org/10.1007/s10840-021-00953-9>

Ibrahim AM, Tandan N, Koester C, et al. (2019). Meta-Analysis Evaluating Outcomes of Surgical Left Atrial Appendage Occlusion During Cardiac Surgery. The American journal of cardiology. 124(8): 1218-25. doi: <http://dx.doi.org/10.1016/j.amjcard.2019.07.032>

<https://www.tripdatabase.com/>

No evidence found

[Cochrane library](#)

Reddy YV, Akehurst R, Gavaghan M, et al. (2019). Cost-effectiveness of left Atrial appendage closure for stroke reduction in Atrial fibrillation: analysis of pooled, 5-year, long-term data. Journal of the American Heart Association. 8(13). <https://doi.org/10.1161/JAHA.118.011577>

[Medline \(via Ovid or Pubmed\)](#)

No evidence found

Individual studies

Commissioning Through Evaluation Report (2019) Percutaneous Occlusion of the Left Atrial Appendage in Non-Valvular Atrial Fibrillation for the Prevention of Thromboembolism (LAAO). <https://www.england.nhs.uk/wp-content/uploads/2018/07/Left-Atrial-Appendage-Occlusion-CtE-Report.pdf>

<https://www.epistemonikos.org/en/>

No evidence found

<https://www.tripdatabase.com/>

No evidence found

[Cochrane library](#)

Whitlock RP, Belley-Cote EP, Paparella D, et al. (2021). Left Atrial Appendage Occlusion during Cardiac Surgery to Prevent Stroke. New England Journal of Medicine. 384(22): 2081-91. doi: <https://doi.org/10.1056/NEJMoa2101897>

Osmancik P, Herman D, Neuzil P, et al. (2020). Left Atrial Appendage Closure Versus Direct Oral Anticoagulants in High-Risk Patients With Atrial Fibrillation. Journal of the American College of Cardiology. 75(25): 3122-35. doi: <https://doi.org/10.1016/j.jacc.2020.04.067>

Parikh V, Bartus K, Litwinowicz R, et al. (2019). Long-term clinical outcomes from real-world experience of left atrial appendage exclusion with LARIAT device. Journal of Cardiovascular Electrophysiology. doi: <https://doi.org/10.1016/j.jacc.2020.04.067>

Cruz-Gonzalez I, Trejo-Velasco B. (2021). Percutaneous left atrial appendage occlusion in the current practice. Kardiologia Polska. 79(3): 255-68. doi: <https://doi.org/10.33963/KP.15864>

[Medline \(via Ovid or Pubmed\)](#)

Brachmann J, Lewalter T, Akin I, et al. (2020). Interventional occlusion of left atrial appendage in patients with atrial fibrillation. Acute and long-term outcome of occluder implantation in the LAARGE Registry. Journal of Interventional Cardiac Electrophysiology. 58(3): 273-80. doi: <https://dx.doi.org/10.1007/s10840-019-00635-7>

Boersma LV, Ince H, Kische S, et al. (2019). Evaluating Real-World Clinical Outcomes in Atrial Fibrillation Patients Receiving the WATCHMAN Left Atrial Appendage Closure Technology: Final 2-Year Outcome Data of the EWOLUTION Trial Focusing on History of Stroke and Hemorrhage. Circulation: Arrhythmia and Electrophysiology. 12(4): e006841. doi: <https://dx.doi.org/10.1161/CIRCEP.118.006841>

Ongoing research

[PROSPERO database](#)

Ahmad Y, Howard J (ongoing) Percutaneous left atrial appendage closure versus oral anticoagulation for non valvular atrial fibrillation. https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020201642

Baman J, Biton Y (ongoing) Percutaneous left atrial appendage occlusion in the prevention of stroke in atrial fibrillation. https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42017058386

Garg J, Shah K, Turagam M, et al. (ongoing) Left atrial appendage occlusion with Watchman FLX: Clinical Outcomes. https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021226767

Liang B, Gu N, Liang Y (ongoing) Comparison of Left Atrial Appendage Occlusion versus Non-Vitamin-K Antagonist Oral Anticoagulation in High-Risk Atrial Fibrillation. https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021266279

Date of search:	August 2021
Concepts used:	Left atrial appendage occlusion, oral anticoagulants, warfarin, percutaneous atrial appendage occlusion, left atrial appendage closure