NATIONAL INSTITUTE FOR HEATH AND CARE EXCELLENCE

Centre for Health Technology Evaluation

Observational Data Unit

Commissioning through Evaluation Project Report

Left atrial appendage occlusion (LAAO)

1 Lay summary

1.1 Atrial fibrillation (AF) is a heart condition that causes an irregular and often abnormally fast heart rate. People with AF are at increased risk of developing a blood clot blocking the flow of blood and oxygen to the brain (ischaemic stroke). In people with AF, blood clots have a tendency to form in the left atrial appendage (LAA), a tube-like structure in the muscle wall of the left atrium (the top left chamber of the heart). Drugs which help prevent the formation of blood clots (such as warfarin and novel oral anticoagulants) reduce the risk of having a stroke, but these drugs are not suitable for everyone with AF and there are few alternative treatments. Left atrial appendage occlusion (LAAO) is a minimally invasive surgical procedure (carried out under general anaesthetic but without having to make large incisions in the skin) which is thought to reduce the risk of stroke in people with AF. During the procedure the mouth of the LAA is blocked using a plug-like occlusion device which is introduced into the heart through a vein in the groin. Although clinical trials have shown that LAAO is safe and reduces the risk of subsequent stroke, there is limited evidence showing how well it works in normal clinical practice, that is, outside a clinical trial. In order to determine the effectiveness and safety of LAAO in general clinical practice in England, NHS England commissioned a time-limited study in which over 500 people who were not able to have anticoagulation treatment had the LAAO procedure at one of 10 specialised hospitals. The study was part of NHS England's Commissioning through Evaluation (CtE) programme which enables

valuable new clinical and patient experience data to be collected for treatments that are not currently routinely funded by the NHS, but which nonetheless show significant promise for the future. The surgical procedure to fit the occlusion device was successful in about 9 out of 10 people. About 1 in 20 people had a major complication (including death, stroke, major bleed and heart attack) while still in hospital. The in-hospital findings were consistent with the published evidence for LAAO. Patients were followed for a maximum of 2 years with an overall follow up period of 400 patient years (the total accumulated number of years that all the patients in the scheme were followed). Following discharge from hospital, there were 10 ischaemic events (including stroke) reported in the registry giving a rate of 2.6 events per 100 patient years. This was lower than the rate reported in published literature for patients receiving no treatment. For every 100 patient years, there were 9.8 incidents of death (of any cause) or stroke in the study. These longer-term findings show that the number of deaths or strokes following the LAAO procedure were higher in the CtE study compared to the published evidence, however, the patients included were at a greater risk of stroke at the start of the study than those in the clinical trials. LAAO did not affect the quality of life of people in the study, but this would be expected for a treatment that is given to prevent a stroke. The LAAO procedure costs around £11,600 per person. Data collected during the CtE scheme will be considered alongside published data from research trials to inform the development of NHS England's clinical commissioning policy for LAAO, that is whether it will be available on the NHS for a specific population.

2 Background

2.1 This project report is prepared by NICE for NHS England, based on the work of, and advised by, Newcastle and York External Assessment Centre (EAC), which was commissioned by NICE to collaborate on this Commissioning through Evaluation (CtE) scheme. The EAC prepared an evaluation report which contains results of the analysis of evidence compiled during the CtE scheme, alongside relevant evidence published

during the scheme and de novo economic modelling where this is carried out by the EAC. The evidence referred to in section 3 is a summary of the full evidence base analysed by the EAC, which appears in the evaluation report. The evaluation report, including detailed references for all of the studies referred to in this project report, is available at Appendix A, and the project report should be read in conjunction with it.

2.2 The objective of this CtE scheme was to evaluate the clinical and cost-effectiveness of left atrial appendage occlusion (LAAO) in patients with atrial fibrillation.

2.3 The CtE scheme proposals supported in principle by the NHS England Clinical Panel for potential investment were further developed and refined, in partnership with NICE. A set of evaluation questions was agreed between NHS England, NICE and the EAC at the start of the scheme. The questions are set out in a table at section 4 of this project report, with respective answers derived from the CtE work.

3 The evidence

Summary of new CtE evidence

3.1 The aim of this CtE scheme was to generate new evidence from real-world settings to enable a judgement on clinical and cost-effectiveness of LAAO in the identified population.

3.2 Procedural efficacy data reported from the CtE registry are largely complete and consistent with published data from randomised controlled trials (RCTs) and observational studies. Approximately nine in ten LAAO procedures resulted in procedural success (device implanted and no major complications).

3.3 Medium term efficacy (measured as the rate of neurological events, ischaemic events and/or death) was higher in the registry compared with published data (mainly from RCTs). It is important to note, however, that the studies and the CtE registry are not directly comparable because of

differences in the sample populations and the definitions of the outcome measures used.

3.4 The rate of major complications reported by the CtE registry appears to be consistent with that published in the literature.

3.5 No statistically significant changes in individual quality of life components or utility scores were observed over time.

3.6 Uncertainties arising from incomplete data entry will be addressed using data linkage to Hospital Episode Statistics (HES) and Office for National Statistics (ONS) mortality records. A report analysing findings from the data linkage is planned for summer 2018.

3.7 A cost consequence analysis compared LAAO plus conservative medical management (use of antiplatelet drugs) with medical management alone. The estimated NHS costs per patient were £14,960 for LAAO plus conservative medical management and £8,390 for medical management alone. The benefit to the NHS from avoided stroke management and medication costs of almost £5,050 per patient with LAAO were insufficient to offset the initial procedure costs of about £11,620 per patient. LAAO was cost incurring for the NHS by about £6,570 per person.

3.8 The CtE evidence appears to support the use of percutaneous occlusion of the left atrial appendage in non-valvular atrial fibrillation for the prevention of thromboembolism for people who are unable to use anticoagulants because of intolerance or high risk of adverse events. NHS England policy review will need to include assessment of the level of risk at which LAAO could be the preferred option. The data linkage analysis will provide helpful information in that discussion. A report analysing findings from the data linkage is planned for summer 2018.

Population

3.9 People with atrial fibrillation who are at high risk of thromboembolic stroke (CHA_2DS_2-VASc of 2 or more) and for whom anticoagulants are contraindicated or not effective.

Intervention

3.10 Left atrial appendage occlusion (LAAO).

LAAO CtE registry study

3.11 The single-arm LAAO CtE registry study was carried out in 10 NHS centres in England between 1 October 2014 and 10 August 2017. People with atrial fibrillation who were at high risk of thromboembolic stroke (CHA_2DS_2-VASc of 2 or more), and for whom anticoagulants are contraindicated or not effective, were eligible to receive LAAO. Data on patients' baseline characteristics, the LAAO procedure, safety, clinical outcomes, and health-related quality of life were collected in a registry. Data were collected at follow-up appointments at 6 weeks, 6 months, 1 year and 2 years.

3.12 A total of 525 people with a median age of 75 years were included in the analysis. The median CHA_2DS_2-VASc[1] score at baseline was 4 with a median HAS-BLED[2] score of 4. Around 18% of people were receiving oral anticoagulants before having the procedure. Follow up data was available for 70.2% of eligible patients at 2 years.

Procedural safety

3.13 Where the type of device was recorded, most patients received either an AMPLATZER Amulet (46.9%; marketed by St. Jude Medical [now owned by Abbott]) or a WATCHMAN device (38.1%; marketed by Boston Scientific). A smaller proportion of people received either an AMPLATZER Cardiac Plug (an earlier version of the Amulet device; 7.7%) or a

[1] The CHA_2DS_2-VASc score estimates the risk of stroke in people with non-valvular atrial fibrillation on a scale of 1–9, based on the person's age, sex, comorbidities, and whether they have previous had a stroke, transient ischaemic attack or thromboembolism. A higher score equates to a higher risk. Having a score of 2 or greater is classed as a moderate-high risk of stroke. Anticoagulants would normally be offered to these people, taking bleeding risk into account.

[2] The HAS-BLED score estimates the risk of bleeding on a point scale of 1–9, based on the person's age, comorbidities, medication, alcohol intake, and whether they have had a previous stroke or major bleed or have a predisposition to bleeding. A higher score equates to a great risk. Having a score of 3 or greater is classed as a high risk of major bleeding.

WaveCrest device (0.7%; marketed by Coherex [now owned by Biosense Webster]). The registry reported a technical success rate (the proportion of devices successfully implanted where it was attempted) of 93.6% (95% confidence interval [CI] 91.1% to 95.6%). The procedural success rate (device implanted and no major complications) was 89.0% (95% CI 86.0% to 91.6%). The reasons for clinical failure included device not in situ (5.9% of procedures), and LAA not sealed and having a large leak of 3 mm or more (1.6%). The in-hospital major complication rate (includes death, neurological event, major bleed and myocardial infarction) was 5.5% (95% CI 3.7% to 7.8%). The procedural mortality rate was 1% (95% CI 0.3% to 2.2%) and the neurological event rate was 0.8% (95% CI 0.2% to 1.9%). The majority of patients required a hospital stay of one night. A total of 114 procedures (22.4%) resulted in an extended length of stay (2 or more nights in hospital).

Clinical outcome

3.14 Twenty-five patients died during the CtE registry study period (4.8%), and a further 19 people had neurological events (3.6%). As some neurological events were fatal, this equated to a combined total of 39 major complication events (7.4%). Over a total aggregated follow-up period of almost 400 patient-years, the event rates per 100 patient-years were 6.2 (95% CI 4.0 to 9.3) for death and 5.0 (95% CI 3.0 to 7.8) for all neurological events. The event rate per 100 patient-years was 9.8 (95% CI 7.0 to 13.4) for the combined outcome (composite of death and neurological events). There were 10 ischaemic neurological events following hospital discharge, giving a rate of 2.6 (95% CI 1.3 to 4.8) per 100 patient years. Two deaths were attributed to ischaemic stroke. These events could be considered to be associated with device efficacy (that is, they were ischaemic events that had not been prevented by inserting a device), although a causal link was not demonstrated. Around 2% of people were receiving oral anticoagulants at the 2-year follow-up.

Health related quality of life

3.15 Health-related quality of life data were collected using EQ-5D-5L health assessment questionnaires before the LAAO procedure and at all subsequent follow-up visits, and converted to utilities. Visual analogue scale (VAS) scores, the overall health status reported by the patient on the day of follow-up, were also recorded. The mean utility value pre-procedure was 0.78. No statistically significant changes in individual quality of life (EQ-5D) components or utility scores were observed over time. The domain in which the greatest benefit from the procedure was seen was anxiety and depression. There was a statistically significant improvement in the median VAS score at 6 weeks when compared with the score before the procedure. LAAO is a preventative rather than a therapeutic procedure, so it is unclear whether any symptoms of the condition (atrial fibrillation) would be improved by LAAO, other than the possibility of reduced anxiety and reduced adverse effects of drugs or, less commonly, reduced quality of life following stroke or embolism.

Costs and resources

3.16 Data on the resources required to conduct LAAO (pre-operative assessment, peri-operative procedure and post-operative management) were collected from the 10 centres involved in the CtE scheme. The overall cost for an LAAO procedure was estimated to range from almost £9,500 to about £13,330, with a central estimate of £11,589. The device accounts for [redacted]% of the cost, with investigations forming the second largest cost component ([redacted]%). Staff ([redacted]%), consumables and length of stay (each 5%), theatre use (4%), and outpatient follow-up (2%) account for the remaining costs.

Published evidence

Clinical evidence

3.17 As the registry was single-armed, a parallel literature search was undertaken in order to present the registry findings from real word NHS practice in the context of published studies in other populations, and to

assess whether the procedural outcomes were consistent with previously reported studies. The systematic review of published evidence included 2 RCTs and 3 observational studies.

3.18 The 2 RCTs (PROTECT AF and PREVAIL) were carried out by the same research group and compared the WATCHMAN device (used in combination with warfarin) with warfarin alone. The studies showed good methodological quality but lacked generalisability because warfarin was used in both arms of the trials, that is, the population is different to that included in the CtE scheme which only included people for whom warfarin was not suitable or contraindicated. The PROTECT AF trial (n=707; Holmes et al. 2009) showed that LAAO using the WATCHMAN device was non-inferior compared with warfarin over a 3.8 year follow-up period for both efficacy (composite relating to longer term prevention of ischaemic effects) and safety (procedural adverse events and excessive bleeding). The technical success rate was 91%. The procedural adverse event rate was 8.7% and 4.8% of patients had a serious pericardial effusion requiring intervention. The event rates per 100 patient-years were 1.0 (95% CI 0.6 to 1.5) for death and 1.5 (95% CI 1.0 to 2.2) for all neurological events. The event rate was 3.0 (95% CI 1.9 to 4.5) per 100 patient years for the combined outcome (composite of death and neurological events). In the PREVAIL trial (n=407; Holmes et al. 2014), non-inferiority was not achieved for overall efficacy, because of an unusually low event rate in the warfarin arm. However, this study reported a reduction in procedural adverse events (4.5% versus 8.7%) and pericardial effusions requiring intervention (0.4% versus 4.8%) compared with the PROTECT AF trial. The event rates were estimated by the EAC from the raw event rates and median follow up times to be 2.6, 2.2 and 5.2 per 100 patient years for death, all neurological events and for the combined outcome (composite of death and neurological events), respectively. A patient-level meta-analysis of the 2 RCTs showed broad equivalence of the WATCHMAN device (when used in combination with warfarin) and warfarin alone in overall stroke rates, but reported superiority of the WATCHMAN device in the prevention of haemorrhagic

stroke and cardiovascular death compared with warfarin alone (Holmes et al. 2015). This was largely supported by a network analysis (Koifman et al. 2016).

3.19 The three observational studies were single-armed and could not be appraised for risk of bias. A UK audit study (Betts et al. 2017) reported a retrospective audit of routinely collected data from patients (n=371) undergoing LAAO (any device, principally WATCHMAN or AMPLATZER Cardiac Plug), with a mean follow up of 24.7 months. The EWOLUTION registry (Boersma et al. 2016) investigated the use of the WATCHMAN device (n=1014) but was limited to peri-procedural outcomes (mainly 30 days post-procedure or less). The ACP registry (n=1053; Tzikas et al. 2016) investigated the AMPLATZER Cardiac Plug device, with a mean follow up of 13 months. Although these studies lacked internal validity and did not provide comparative data, they reflected real-life practice (used mainly in patients for whom warfarin was unsuitable). In particular, the study by Betts et al. (2017) is highly generalisable, being set in the UK NHS and enrolling patients with similar indications to the CtE registry. Procedural safety in these studies was comparable to the RCTs (ranging from 92.5% for the UK audit to 98.5% for EWOLUTION). The ACP registry and the UK audit reported superior efficacy outcomes than would be expected according to standardised risk scores.

3.20 One relevant study on quality of life changes associated with LAAO was identified in the literature (Alli et al. 2013). This was a piggyback study performed on the participants of the PROTECT-AF study using the Short-Form 12 Health Survey (SF-12) at baseline and 12 months. This study showed that at 12 months, patients receiving LAAO had an increase in their quality of life (total physical score, physical functioning, and physical role limitation domains) compared to baseline, while those treated with warfarin experienced a decline in their quality of life. The authors of the study hypothesised that improvements in physical wellbeing were due to the knowledge that LAAO was protecting the patients from having a stroke which empowered them to be more active. Conversely, subjects receiving

warfarin continued to have INR monitoring, dietary restrictions, and were at risk of bleeding, which may have curtailed their physical activity. They also noted that the relatively small sample size and short follow up, as well as the potential for selection bias, were limitations of the study. This study, which compared patients on warfarin with those who had stopped taking warfarin (but were not contraindicated to it), lacks generalisability to the cohort represented by the CtE registry. Additionally, it did not use the EQ-5D system of quality of life analysis favoured by UK guideline groups such as NICE.

3.21 The short term results from the CtE registry were consistent with values from the RCTs and observational studies reported in the literature. The results from the medium term outcomes (death and neurological events) compared favourably with historical epidemiology data in patients with similar baseline risk. Although the neurological and ischaemic event rates were higher in the CtE cohort than reported by the PROTECT-AF and PREVAIL RCTs, results from these studies were not considered generalisable due to fundamental differences in the study population and intervention. That is, patients in the CtE registry had a greater number of comorbidities and were at greater risk of ischaemic stroke than those in the published clinical trials, and most patients were unable to receive warfarin as part of the intervention.

Costs and cost effectiveness

Systemic review of cost effectiveness evidence

3.22 A systematic review of economic literature on the cost-effectiveness of LAAO identified 15 studies that met the inclusion criteria. Eight of the studies reported that the WATCHMAN device was cost-effective in certain high cost settings (such as North America), compared with patients managed on novel oral anticoagulants (NOACs) or warfarin. The costs in the LAAO arm were initially higher but, over time, savings from fewer strokes resulted in lower total costs and higher quality-adjusted life years (QALYs) compared to anticoagulants. Financial break-even was around 8

to 10 years depending on the comparator, and was shorter when compared with NOACs than warfarin.

3.23 Evidence in the population contraindicated to NOACs or warfarin was limited to 6 studies, of which 1 generalised to the UK setting (Panikker et al. 2016). This study used clinical data from a UK hospital registry (n=110) and reported that at 10 years, LAAO was cost saving against all therapies (NOACs, warfarin and aspirin) and no treatment. Savings were most pronounced for higher risk patients and those for whom anticoagulants are not suitable when compared with the wider population. Further evaluations are required to confirm these findings, particularly since it was not based on direct randomised evidence. It is likely patient selection is important and cost-effectiveness will be dependent on the risk of stroke and bleeding. Further evaluations are also required on the relative efficacy and costs of alternative devices.

Economic analysis

Model structure

3.24 A new model was created by the EAC to estimate the cost consequences of LAAO plus conservative medical management (use of antiplatelet drugs) compared with conservative medical management only in people with atrial fibrillation who are at high risk of thromboembolic stroke and for whom anticoagulants are contraindicated or not effective. The model was constructed as a combination of a decision tree to determine LAAO procedural success and operative complications, followed by a Markov model for long term outcomes following discharge. The comparator was conservative medical management only, that is antiplatelet treatment without LAAO. In the decision tree, people could have a device successfully implanted or not, and could develop major or minor bleeds or other complications. The Markov model had 3 health states; stroke-free, neurological event (ischaemic stroke, haemorrhagic stroke or transient ischaemic attack) or death. Once a patient experiences an ischaemic or haemorrhagic stroke, there is a chance in each future cycle that a subsequent stroke can occur. For all patients, regardless of previous

neurological events, a transient ischaemic attack can occur in each cycle. Bleeds (major or minor) can also occur in each cycle. Death can occur in each cycle but with a higher probability if a patient has experienced a neurological event. The model start age was 75 years, the same as the median age in the CtE registry. The time horizon was 15 years and the cycle length was 1 week. Total costs were reported from an NHS-only perspective and from a wider NHS and social care perspective. A 3.5% discount rate was applied.

Model inputs

3.25 The LAAO CtE registry data, national databases, published studies and clinical opinion were used as sources of model inputs. Patients in the comparator arm (conservative medical management only) were estimated to have stroke and bleeding risks in accordance with their baseline CHA_2DS_2-VASc and HAS-BLED risk scores.

Cost

3.26 The estimated cost of the LAAO procedure (£11,589) was calculated using data from the CtE register and a costing template completed by the CtE provider sites. NHS Supply Chain provided costs for the device as 'commercial in confidence'. These included overheads of 3% for its internal costs. A further 15% overhead was added to the device costs to meet the procurement and supply costs incurred by NHS trusts to ensure an adequate stock of devices is available for theatres. Costs for medications, prescriptions and GP attendances were applied to both the LAAO and the conservative medical management arms.

Base case results

3.27 When NHS costs only were considered, the total discounted cost of the LAAO pathway was estimated at £14,963 per patient. The procedure itself together with bleeds recorded in the registry prior to discharge accounted for 74% of these costs. Management of strokes and transient ischaemic attacks (TIAs) was the second largest component (15%), followed by medicines (9%), with subsequent bleeds accounting for the balance of

2%. The total discounted cost of the conservative medical management pathway was estimated at £8,392 per patient. Management of haemorrhagic and ischaemic strokes and TIAs was the largest component (76%), followed by medicines (18%), with bleeds accounting for the balance of 6%.

3.28 When the costs of LAAO plus medical management were compared to the costs of medical management alone, the discounted NHS costs were £6,571 per person higher in the LAAO arm, a 78% increase on the cost of medical therapy only. The benefit from avoided stroke management and medication costs of almost £5,050 per patient with LAAO was insufficient to offset the initial procedure costs of about £11,620 per patient. LAAO was cost-incurring by about £6,570 per person over a 15 year time horizon. The cost of the procedure would need to reduce by 57% to £5,050 before the NHS could achieve financial breakeven on the procedure.

3.29 When both NHS and social care costs were considered, the total discounted cost per person receiving an LAAO procedure was estimated at almost £17,840, of which procedure-related costs formed 65%. The second largest contributor to costs was the social care related costs to manage subsequent strokes (16%), followed by NHS stroke-related costs (11%), medical therapy (6%) and managing subsequent bleeds (2%). For conservative medical management, the total discounted cost per person was estimated at about £17,905. The largest contributor to costs are those to manage subsequent strokes in social care (53%) and then NHS-stroke related costs (35%), with medicines contributing 9% and bleeds 3%.

3.30 Comparing LAAO plus conservative medical management and medical management alone suggests that both the intervention and the comparator have similar costs for the NHS and Social Services, with LAAO offering a small potential saving of £70 per person. Whilst LAAO has an initial cost per person of £11,621 (including procedure bleeds), the procedure will avert £11,690 costs per person of neurological events and

medication costs. Savings from fewer stroke costs account for 94% (£11,004) of the total savings. The majority of costs to manage patients with stroke (60% of the total) are incurred in social care settings. These savings plus reduced medication costs outweigh the cost of the procedure.

3.31 The model predicted that the total number of strokes per 1,000 patients (ischaemic, haemorrhagic and subsequent strokes) reduced from over 500 when patients are managed on medical therapy to 164 after the LAAO procedure (a reduction in all-stroke risk from over 50% to 16%). Associated with this reduction were 100 forecast fewer deaths in the patients receiving the LAAO procedure.

Analysis of alternative scenarios

3.32 The relative risk reduction for stroke following the LAAO procedure, the costs to manage strokes and the costs of the LAAO procedure were the main drivers in the model. Removing the 15% overhead on the device cost included within the procedure cost in the base case, increased the estimated NHS and social care savings to about £960 a year. Changes in other parameters had little impact on the absolute saving from LAAO over conservative medical management. Scenarios analyses demonstrated that LAAO was cost incurring where a shorter time horizon estimate was used. LAAO was found to be no longer cost saving if there were small changes in the cost of the procedure or annual stroke rate post a LAAO procedure.

Sensitivity analyses

3.33 Probabilistic sensitivity analyse showed that estimated cost and clinical event savings with LAAO were robust.

Limitations of the economic analyses

3.34 Limitations in the analyses include the absence of long term clinical data meaning that assumptions on the absolute and relative risk reductions over time had to be made. In addition, data from a well-conducted

randomised head to head trial were not available therefore the risk of stroke for the conservative medical management arm had to be assumed from risk scoring algorithms given the baseline characteristics of patients in the CtE registry.

4 Responses to the Commissioning through Evaluation questions

4.1 Table 1 lists the questions agreed by NHS England for the CtE scheme, and summarises the answers derived from the project, along with comments from NICE.

Table 1: CtE questions with responses

Q	CtE project question	Conclusions/results from the CtE scheme	NICE comments
1.	Can UK clinical teams reproduce the short and medium success rates for left atrial appendage occlusion reported in existing clinical trials, with equivalent or lower complication rates?	Procedural efficacy data reported from the registry are largely complete and consistent with published data from RCTs and observational studies. Approximately nine in ten LAAO procedures resulted in procedural success (closure of LAA without major complication). Medium term efficacy (measured as the rate of neurological events, ischemic events and/or death) was higher in the registry compared with published data (mainly from RCTs). However, interpretation is limited by issues with generalisability because the patients in the registry were at greater risk of neurological events compared with the patients enrolled in RCTs. The rate of major complications reported by the CtE registry appears to be consistent with that published in the literature.	Clinical efficacy data will be validated through data linkage to HES and ONS mortality data. A report analysing findings from the data linkage is planned for summer 2018.
2.	Does left atrial appendage occlusion offer patients a lower risk of stroke or other embolic clinical events in the short and medium term compared with those that would have been predicted on the basis of validated risk scores?	Although limited by incomplete follow up, point estimate data reported by the CtE registry on the incidence of post-procedural ischaemic events is consistent with LAAO conferring a protective effect.	Clinical efficacy data will be validated through data linkage to HES and ONS mortality data. A report analysing findings from the data linkage is planned for summer 2018.

Q	CtE project question	Conclusions/results from the CtE scheme	NICE comments
3.	Is left atrial appendage occlusion associated with an improved quality of life?	CtE registry data showed no significant changes in individual quality of life (EQ-5D) components or utility scores over time. The median visual analogue scale (VAS) score at 6 weeks showed a statistically significant improvement compared to pre-procedure. One quality of life study identified in the literature reported LAAO was associated with significant improvements in quality of life in the physical domains after 1 year.	LAAO is a preventative rather than a therapeutic procedure. It is unclear whether any symptoms of atrial fibrillation should be improved, other than the possibility of reduced anxiety and reduced adverse effects of drugs or, less commonly, reduced quality of life following stroke or embolism.
4.	Are there any longer-term cardiac complications associated with the use of these devices (e.g. erosion with penetration through the wall of the atrium)?	The registry did not follow up patients for sufficiently long to answer this question.	
5.	How many patients with atrial fibrillation with a contra-indication to oral anticoagulants (including previous significant bleed), or who have had a thromboembolic event despite being on oral anticoagulants, are candidates for left atrial appendage occlusion?	This question could not be answered using data from the registry. Using published data, the EAC has estimated that the unmet need of LAAO in England could range from 19,500 to 127,700 people, with 1,400 to 9,400 patients over 65 years becoming eligible each year. This represents a crude estimate and is dependent on the precise indication definitions for LAAO.	

Q	CtE project question	Conclusions/results from the CtE scheme	NICE comments
6.	Which devices are used to undertake LAAO and what are the device-specific efficacies and safety outcomes in CtE funded patients undergoing the procedure?	Where the type of device was recorded, AMPLATZER Cardiac Plug/Amulet devices and WATCHMAN devices were used in 54.6% and 38.1% of the CtE procedures, respectively. An analysis of efficacy in terms of death and neurological event between WATCHMAN and AMPLATZER Cardiac Plug/Amulet devices showed no statistical differences between the two devices. There was no significant differences in the proportion of major and minor complications reported.	
7.	Is the frequency of complications seen with the intervention clinically acceptable? (This question has already been considered by the NICE Interventional Procedures Advisory Committee when developing the IP guidance on this procedure. If the CtE project indicated that this procedure has a more risky safety profile than appears in the current NICE Interventional Procedures guidance, it could potentially lead to NICE updating the guidance, in line with normal processes).	There was no safety flag identified from the registry that would require an update of NICE IPG349.	

Q	CtE project question	Conclusions/results from the CtE scheme	NICE comments
8.	Are clinical outcomes from left atrial appendage occlusion associated with particular patient characteristics (clinical or demographic)?	There were insufficient data reported in the registry to allow for subgroup analysis.	
9.	What are the full procedural costs of left atrial appendage occlusion to the NHS?	The central estimate of the cost of an LAAO procedure is about £11,600 (range £9,500 to £13,300).	
10.	What are the potential cost savings for the NHS through provision of left atrial appendage occlusion for appropriate patients?	The LAAO procedure plus conservative medical management is estimated to have higher NHS-related costs of about £6,570 per patient compared to medical management alone over a 15-year time horizon from the date of the procedure.	
11.	Is left atrial appendage occlusion cost-effective from the perspective of the NHS? (Note that this question will be answered by a NICE Technology Appraisal of devices used in Left Atrial Appendage Occlusion.)	In a cohort of 1,000 patients with similar characteristics to those in the registry, over a 15-year time horizon, the LAAO procedure plus conservative medical management was estimated to reduce the number of strokes from over 500 when patients are managed only on conservative medical therapy to 164, a reduction in strokes of 343 (68%). Associated with this reduction were 100 forecast fewer deaths in the cohort receiving the LAAO procedure, giving a life-year gain of 1.2 years. The EAC cannot advise whether the additional cost to the NHS of £6,570 per patient is cost-effective given the forecast savings in strokes and deaths.	NICE does not have a Technology Appraisal of devices used in LAAO scheduled on its work programme.

5 Issues for consideration

5.1 The following issues should be considered when reviewing the evidence on LAAO and the answers to the specific questions in section 4.

Project process and oversight

5.2 NHS England commissions CtE projects from NICE, and NICE manages the projects to a timescale, process and methods devised by NHS England. In June 2017, NHS England published a policy document governing these projects (Methods: Commissioning through Evaluation), but the majority of the LAAO scheme was developed, conducted and concluded before this document was published. Generally, however, the process followed was similar to the currently published process.

5.3 A Cardiology CtE Steering Group was established by NHS England to oversee the project and involved clinical leads and other stakeholders. NICE and the EAC worked closely with the steering group and with the LAAO Individual Technology Group, in the design of the LAAO registry and to ensure all parties were aware of data collection requirements and to reinforce clinical ownership of the project.

5.4 NICE is accountable to Ann Jarvis, Head of Acute Programmes for Specialised Services at NHS England, for delivery of the CtE schemes. For this scheme, NICE reported on a quarterly basis via standard reports and monitoring meetings with NHS England.

5.5 This project did not follow the planned timelines because, at NHS England's request, the clinicians were given an extra 2 months to improve data submission rates towards the end of the data collection period. The National Institute for Cardiovascular Outcomes Research (NICOR) was contracted by Newcastle and York EAC to design and host the on-line registry for LAAO procedures, to provide a project management function to promote data entry quality and completeness by commissioned CtE provider sites, and to link registry data with HES and ONS mortality datasets. Problems with the Data Access Request Service application to

NHS Digital has meant that data linkage with HES and ONS mortality data is not yet available. A report analysing findings from the data linkage is planned for summer 2018.

Strengths and limitations

5.6 The registry had several strengths. It enrolled indicated patients consecutively, reported important clinical outcomes, and represented a pragmatic real-world cohort of patients receiving LAAO as it might be performed in the NHS. Thus the external applicability of the registry to future practice is high, although improvements in the procedure protocol and a learning curve effect may ultimately lead to improved outcomes. In addition, following an initial disappointing response from centres in providing follow-up data, this improved considerably such that there was about 400 patient years follow up available for analysis. This improved the precision and certainty of time-to-event analysis. Where follow up was achieved (for 70.2% of eligible people [n=121] at 2 years), overall completion of data fields was regarded as good, although this varied for individual fields.

5.7 The CtE registry had several limitations. It was a single armed study therefore comparisons had to be made implicitly with results published in the literature. This had 2 limitations. Firstly, no statistical or quantitative comparisons could be made with the comparator of interest, which was conservative medical management (use of antiplatelet drugs). Secondly, much of the published literature was not directly generalisable to the data collected from the CtE registry, thus inferences of equivalence (or not) are subject to considerable uncertainty. Other specific and non-specific limitations with the registry include the following:

- The registry was funded for a maximum follow up of 2 years, meaning that data on long term efficacy outcomes or complications were not available.

- Most patients did not reach the 2 year follow up date because the procedures were carried out at different times during the duration of the

CtE scheme. Of the 525 patients eligible for analysis, only 121 (25.8%) had an LAAO device implanted, were still alive and reached the second anniversary of their procedure during the data collection phase of the CtE scheme. It is possible that this cohort of patients who received treatment early in the project may not be representative of the overall cohort (for example, because patients were prioritised on the waiting list due to pressing clinical needs, or because the outcomes improved with the number of procedures carried out, that is, there was a learning effect).

- The registry analysis would be more robust with data linkage to the ONS mortality dataset, to validate calculated mortality rates in the CtE cohort and provide greater coverage. Data linkage to HES could also provide further validation and coverage of neurological event data. A report analysing findings from the data linkage is planned for summer 2018.

- In addition, the analysis relies on complete reporting of all event data. Patients who are lost to follow up are censored from the analysis, but it is unclear if these are representative of the overall cohort.

- Finally, patients may have multiple events (excluding death), but the Kaplan-Meier protocol only analyses time to first event.

5.8 The registry captured information on the resources required to conduct LAAO, enabling the cost of the procedure to be estimated. This information together with the quality of life data may be of use in any future cost-effectiveness studies. Data linkage to HES will also inform these analyses. A report analysing findings from the data linkage is planned for summer 2018.

6 Equality considerations

6.1 Atrial fibrillation is the most common cause of abnormal heart rhythm. No particular equality issues relating to people with AF were identified in the

CtE data or in the literature presented, although atrial fibrillation is more common in men than women, and the prevalence increases with age.

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Appendix A: Sources of evidence considered in the preparation of the project report

- Commissioning through Evaluation (CtE). Percutaneous occlusion of the left atrial appendage in non-valvular atrial fibrillation for the prevention of thromboembolism (LAAO): Final report – Newcastle and York External Assessment Centre, February 2018