Thoracoscopic surgical ablation versus catheter ablation as first-line treatment for long-standing persistent atrial fibrillation: the CASA-AF RCT

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Scientific summary

The CASA-AF RCT

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Scientific summary

Background

Atrial fibrillation is the commonest heart rhythm disturbance, affecting 1–2% of the population. Its prevalence increases with age, from 0.5% at 40–50 years to 5–15% at 80 years. In the UK alone, NHS admissions related to atrial fibrillation have risen by 60% over 20 years, costing over £2B per year.

Atrial fibrillation is characterised by an irregularly irregular pulse, loss of atrial contractile function and attendant loss of active ventricular filling, and risk of thromboembolic stroke. In addition to the prevention of stroke with anticoagulants, there are two principal therapeutic strategies for treatment of atrial fibrillation: rhythm control (to restore sinus rhythm) and rate control (to accept fibrillation and simply control the ventricular rate). Rhythm control therapy is usually aimed at symptomatic patients, especially those who are younger and more active, whose symptoms persist *despite* adequate rate control. Traditionally, the treatments of choice for rhythm control are antiarrhythmic drugs and direct-current cardioversion. The long-term efficacy of these treatments is poor, and drug side effects and risk of pro-arrhythmia add to unsatisfactory outcomes.

Clinically, atrial fibrillation can be classified into paroxysmal (fibrillation terminates spontaneously within 7 days), persistent (lasts > 7 days) and long-standing persistent atrial fibrillation (lasts > 1 year).

Two interventional treatments, surgical and catheter ablation, have evolved over the years and reliably achieve clinical success in treating paroxysmal and persistent atrial fibrillation, although some patients require more than one treatment. However, it is not known whether or not these treatments are equally successful in patients at the most severe end of the disease spectrum (i.e. long-standing persistent atrial fibrillation). In addition, there are indications in the literature that surgical ablation might be significantly more effective than catheter ablation in restoring and maintaining normal heart rhythm.

Objectives

The primary objective in the Catheter Ablation versus thoracoscopic Surgical Ablation in long-standing persistent Atrial Fibrillation (CASA-AF) trial is to identify whether or not surgical ablation is clinically superior to catheter ablation in the treatment of long-standing persistent atrial fibrillation. The efficacy is measured as the proportion of patients in each treatment arm who remain free from atrial fibrillation/tachycardia (≥ 30 seconds) from the end of the blanking period (3 months after the intervention) to the end of follow-up (12 months after the intervention). Arrhythmia-free survival is calculated from data collected by an implanted loop recorder that allows continuous cardiac monitoring. The primary outcome is evaluated in patients in each treatment arm who had a single intervention and did not have antiarrhythmic drugs during the 12 months' follow-up.

Our secondary objectives in the trial are to:

- evaluate the safety of the two interventions
- compare the clinical success of the two interventions, which we defined as a ≥ 75% reduction in atrial fibrillation burden
- identify changes in atrial anatomy and function following intervention using echocardiographic and cardiac magnetic resonance imaging parameters

- evaluate and compare the effects of the arrhythmia interventions on patients' symptoms and quality of life, assessed as changes in the European Heart Rhythm Association (atrial fibrillation specific scoring system), EuroQol-5 Dimensions, five-level version (general quality-of-life assessment), and Atrial Fibrillation Effect on QualiTy-of-life questionnaire (atrial fibrillation-specific quality-of-life assessment) scores
- estimate the cost-effectiveness of the two interventions from a health and social care perspective, using the quality-adjusted life-year as the summary measure of health effect over the 12 months' follow-up and modelling over a lifetime horizon.

Methods

This study is a prospective randomised control trial which recruited patients referred for ablative treatment from four NHS hospitals in England with the following characteristics.

Inclusion criteria

- Age $\geq$ 18 years.
- Long-standing persistent atrial fibrillation (> 12 months' duration).
- European Heart Rhythm Association symptom score > 2.
- Left ventricular ejection fraction $\geq$ 40%.
- Suitable for either ablative procedure.

Exclusion criteria

- Valvular heart disease with severity greater than mild.
- Contraindication to anticoagulation.
- Thrombus in the left atrium despite anticoagulation in therapeutic range.
- Cerebrovascular accident within the previous 6 months.
- Previous thoracic or cardiac surgery (including surgical interventions for atrial fibrillation).
- Prior left atrial catheter ablation for atrial fibrillation.
- Unable to provide informed written consent.
- Active malignancy, another severe concomitant condition or presence of implanted intracardiac devices that would preclude the patient from undergoing study-specific procedures.
- Pregnant or breastfeeding, or women of childbearing age not using a reliable contraceptive method.

Participant recruitment took place between September 2015 and July 2018. Eligible participants attended a hospital appointment at the start of the study to sign the consent form, undergo electrocardiography and transthoracic echocardiography, participate in the cardiac magnetic resonance imaging study, complete haematology and biochemistry tests and questionnaires (Atrial Fibrillation Effect on QualiTy-of-life questionnaire and EuroQol-5 Dimensions, five-level version) and provide information about their medical history.

Once eligibility was confirmed, 120 participants were randomised to receive minimally invasive thoracoscopic surgical ablation or catheter ablation in a 1 : 1 ratio using the method of minimisation. Variables used in the minimisation algorithm were sex (male or female), study site and left atrial diameter (< 50 and $\geq$ 50 mm). The process of randomisation allowed for concealment of treatment allocation.

Most of the study participants were recruited from the Royal Brompton Hospital (58/120, 48%) and Harefield Hospital (39/120, 33%). Liverpool Heart and Chest Hospital recruited 18 patients (15%) and Brighton and Sussex University Hospital recruited five patients (4%) to the study.

Following randomisation, the patients underwent ablation and had an implanted loop recorder (Reveal LINQ™; Medtronic plc, Dublin, Ireland) inserted subcutaneously at the end of the procedure. On discharge, the patients were instructed on how to regularly transmit their cardiac rhythm data using a home-monitoring kit.

Following discharge, the patients were contacted by telephone once per week to monitor their postoperative recovery and collect information about any adverse events in the early follow-up period (first 30 days following discharge).

The patients completed hospital visits at 3, 6, 9 and 12 months after ablation, at which additional data were collected.

Results

The intervention was received by 115 patients, 55 in the surgical ablation group and 60 in the catheter ablation group. Of patients randomised at the Royal Brompton Hospital and Harefield Hospital, 97% of patients underwent treatment ($n = 56$ and $n = 38$, respectively), compared with 89% of patients (16/18) at Liverpool Heart and Chest Hospital and 100% (5/5) of patients at Brighton and Sussex University Hospital.

Intention-to-treat analysis was performed on complete cases (randomised and treated patients who reached the required end point) using sensitivity analyses to examine the effect of the missing data.

Five participants in the surgical arm withdrew consent after randomisation and did not receive any treatment (two participants from the Royal Brompton Hospital, one participant from Harefield Hospital and two participants from Liverpool Heart and Chest Hospital). They were excluded from the analyses. Baseline characteristics in this treatment group were not altered by this exclusion.

Six participants in the surgical ablation group could not complete the procedure owing to adhesions and had to undergo catheter ablation (four patients from Harefield Hospital, one patient from the Royal Brompton Hospital and one patient from Liverpool Heart and Chest Hospital). Their data are considered in the treatment arm to which they were randomised.

One patient died following surgical ablation and they were excluded from heart rhythm data analysis.

All study follow-ups were completed by 110 participants (59 in the catheter ablation group and 51 in the surgical ablation group). Patients had a mean (± standard deviation) age of 62.3 (± 9.6) years, were predominantly male (74%), with a mean (± standard deviation) left atrial diameter of 44.6 mm (± 5.9 mm) and were in continuous atrial fibrillation for a median of 22 (range 16–31) months prior to procedure.

Heart rhythm outcomes

At the end of follow-up, 26% of patients in the surgical ablation arm (14/54) were free from atrial arrhythmias after a single procedure and without antiarrhythmic drugs, compared with 28% of patients in the catheter ablation arm (17/60) (odds ratio 1.13, 95% confidence interval 0.46 to 2.83; $p = 0.84$). After one procedure and without antiarrhythmic drugs, the burden of atrial arrhythmias (episodes of atrial fibrillation/tachycardia $\geq$ 30 seconds) was reduced by $\geq$ 75% in 36 out of 54 patients (67%) in the surgical ablation arm, compared with 46 out of 60 (77%) patients in the catheter ablation arm (odds ratio 1.64, 95% confidence interval 0.67 to 4.08; $p = 0.3$).

Sensitivity analyses, including per-protocol and multiple imputation technique for missing data, did not change the direction or the significance of these results.

Procedure-related complications

Procedure-related major complications (serious adverse events) within 30 days of intervention occurred in 15% (8/55) of patients in the surgical ablation arm compared with 10% (6/60) of patients in the catheter ablation arm ($p = 0.46$). Over the entire follow-up period, procedure-related serious adverse events were recorded in 10 out of 55 (18%) patients in the surgical ablation group and in 8 out of 60 patients (13%) in the catheter ablation group ($p = 0.65$). When non-serious complications during the entire follow-up period are considered, surgery was associated with a significantly greater burden, as 22 out of 55 (40%) patients had an event adjudicated to be related to the procedure, compared with 9 out of 60 (15%) patients in the catheter ablation arm ($p = 0.003$). One death within 30 days of the procedure was recorded in the surgical ablation group.

Repeat treatments during follow-up

Direct-current cardioversion was performed during the follow-up period in 10 out of 55 (18%) patients in the surgical ablation group, compared with 11 out of 60 (18%) patients in the catheter ablation group (odds ratio 0.99, 95% confidence interval 0.384 to 2.552; $p = 0.98$).

Ten patients in the surgical arm (18%) and nine patients in the catheter ablation arm (15%) had additional catheter ablation to treat recurrent atrial fibrillation/tachycardia (odds ratio 1.260, 95% confidence interval 0.47 to 3.38; $p = 0.65$) during follow-up.

Secondary outcomes from echocardiography and cardiac magnetic imaging

Left atrial anatomy and size were evaluated pre and post ablation using transthoracic echocardiography and cardiac magnetic resonance imaging in a subgroup of trial participants from whom appropriate data had been collected at all relevant time points. These were exploratory analyses only, based on a reduced number of data points.

Reduced left atrial volumes, improved reservoir function and left atrial emptying fraction were apparent on echocardiography at 3 months and maintained at 12 months post ablation in both treatment groups. There were noticeable improvements in reservoir, conduit and contractile functions of the left atrium in both treatment arms, measured by multiple echocardiographic modalities. Left atrial late diastolic strain rate function at 3 months' follow-up was a predictor of atrial fibrillation recurrence.

Analyses of cardiac magnetic resonance imaging data largely corroborate the findings from echocardiography. Notably, the ejection fraction of both atria significantly improved following ablation, but their function was still below the levels expected for healthy subjects.

Reverse remodelling of the left and right atria occurred in both treatment arms, but was greater in the catheter ablation group.

As part of the mechanistic substudy of the trial, we have developed a novel fully automatic segmentation method to detect atrial scarring in late gadolinium-enhanced magnetic resonance images and have validated it against manual ground truth segmentation by experienced imaging cardiologists. Automated scar segmentation was used to quantify scar pre and post ablation. We found a significant increase in the proportion of scar in the left atrium following ablation ($p < 0.0001$) regardless of the modality (mean ± standard deviation 19.5 ± 8.9% in the catheter ablation arm and 16.3 ± 10.8% in the surgical ablation arm). The proportion of left atrial scar at baseline or in follow-up did not differ between patients who maintained sinus rhythm throughout follow-up and those who experienced atrial fibrillation recurrence. Scar measurements in our patients appear to be smaller than those in other studies, and we found no correlation between scar and left atrial volume and left atrial ejection fraction.

Patient-reported quality of life and health economic analyses

Improvements in symptoms related to atrial fibrillation (European Heart Rhythm Association checklist), fibrillation-related quality of life (Atrial Fibrillation Effect on QualiTy-of-life questionnaire) and generic measures of quality of life (EuroQol-5 Dimensions visual analogue scale and index score) were evident in the first 3 months following ablation and were sustained up to the end of follow-up. There were small, non-significant, but consistent, trends between the groups, with slightly larger gains for patients randomised to catheter ablation than to surgical ablation. Over the year, catheter ablation was associated with a statistically significant gain of 0.069 quality-adjusted life-years (95% confidence interval 0.01 to 0.13) and an NHS cost saving of £3399 (95% confidence interval £517 to £26,282) per patient compared with surgical ablation. This translates to an incremental net benefit of £4801 (95% confidence interval £1477 to £8124) for catheter ablation compared with surgical ablation at a conservative cost-effectiveness threshold of £20,000 per quality-adjusted life-year. At this threshold, the estimated probability that catheter ablation is less expensive and more effective than surgical ablation is 99.1%.

Conclusions

In this study, we found no evidence that standalone thoracoscopic surgical ablation was clinically superior to catheter ablation in achieving freedom from atrial arrhythmias after a single procedure without antiarrhythmic drugs. The use of an implanted loop recorder may have had significant impact on the assessment of treatment efficacy when compared with the non-continuous methods of monitoring used in previous studies.

The results of our analyses are based on a study cohort with documented long-standing persistent atrial fibrillation only, who were naive to ablative treatments. We observed significant clinical improvements demonstrated by a reduction in arrhythmia burden and related symptoms in both treatment arms.

These results are further supported by changes in left and right atrial anatomy and function that are positively associated with the maintenance of sinus rhythm.

Both ablation strategies are safe, as demonstrated by the small number of procedure-related serious adverse events, but significantly more complications during follow-up, including one death, occurred in the surgical ablation arm.

Catheter ablation is associated with greater improvements in patients' health outcomes, significant gain in quality-adjusted life-years and lower health-care costs, and is more cost-effective than surgical ablation.

Trial registration

This trial is registered as ISRCTN18250790 and NCT02755688.

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