Amaze: a double-blind, multicentre randomised controlled trial to investigate the clinical effectiveness and cost-effectiveness of adding an ablation device-based maze procedure as an adjunct to routine cardiac surgery for patients with pre-existing atrial fibrillation

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Scientific summary

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Scientific summary

Background

Atrial fibrillation (AF) is characterised by an irregular heartbeat resulting from abnormal electrical signals in the atria. Prevalence is 1–2% of the population in high-income countries, and this increases with age and comorbidities such as obesity, diabetes and hypertension. The UK prevalence is 7.2% in patients aged ≥ 65 years and 10.3% in patients aged ≥ 75 years. With the advancing age of the population and the increasing prevalence of obesity, this is likely to increase.

Atrial fibrillation causes palpitations, chest pain, dizziness and breathlessness, and imposes a heavy burden on both patient health-related quality of life (HRQoL) and NHS resources. Inefficient heart pumping as a result of AF increases the risk of blood clot formation, which can lead to stroke; anticoagulant medication reduces the risk of stroke, but confers an increased risk of bleeding. AF may also exacerbate existing heart failure or cause heart failure; treatment of AF and its consequences is expensive for the NHS.

The maze procedure, developed in the 1980s, involves multiple cutting and sewing of the atria and pulmonary veins to prevent AF. Despite success in restoring sinus rhythm (SR), the technical challenges required for this procedure mean that it is reserved for severely symptomatic patients. Less demanding methods of achieving the electrical block, using a range of energy sources (heat, cold, radiofrequency or microwave) to ablate atrial tissue, have been developed. Although technically easier, quicker and safer, these methods are a new and costly technology.

There is evidence that AF ablation increases rates of freedom from AF, atrial flutter and atrial tachycardia and decreases antiarrhythmic medication use 3 months after surgery. However, effects on cardiovascular mortality, adverse events (AEs), HRQoL and long-term outcomes are uncertain. Results of cost-effectiveness analyses are mixed and limited by the lack of evidence on HRQoL and other key outcomes in the medium term (1–5 years), which means that long-term economic models are not robust.

The Amaze trial aimed to evaluate the clinical and HRQoL benefits, as well as the cost-effectiveness for the NHS, of this technology. The HESTER (Has Electrical Sinus Translated into Effective Remodelling?) observational substudy explored atrial contractile function in maze patients who were in SR at least 1 year after the procedure, compared with cardiac surgery patients who were in SR both before and at 1 year after the procedure.

Objectives

The primary objective was to compare the maze procedure as an adjunct to routine cardiac surgery with routine cardiac surgery alone in terms of:

- return to stable SR at 12 months
- quality-adjusted survival over 2 years.

The key secondary objective was to assess cost-effectiveness over 2 years from a NHS perspective.

The other secondary objective was to compare the two trial arms for return to stable SR at 2 years, overall survival, thromboembolic neurological complications (e.g. stroke), stroke-free survival, anticoagulant and antiarrhythmic drug use and HRQoL.

Prespecified subgroup analysis explored differences in treatment effects between patients with paroxysmal AF and non-paroxysmal AF, surgical centres (as a random effect), cardiac surgical procedures and surgeons. Within the maze arm, the analysis explored differences between ablation devices and lesion sets treated.

The HESTER substudy objective was to assess whether or not patients in SR at least 1 year after an adjunct maze procedure had equivalent active left atrial ejection fraction (ALAEF) to control patients who had undergone cardiac surgery and were in SR both before and after surgery.

Methods

Amaze was a Phase III, pragmatic, multicentre, double-blind, parallel-arm randomised controlled trial to compare clinical, patient and cost outcomes for patients with pre-existing AF who underwent routine cardiac surgery either with or without an adjunct device-based ablation procedure.

Setting

Eleven acute NHS specialist cardiac surgical centres, co-ordinated by the Papworth Trials Unit Collaboration. Participating surgeons had at least 2 years' experience in the use of ablation devices.

Patient recruitment

Consecutive cardiac surgery patients with a history of AF were screened for eligibility. Trial inclusion criteria were as follows: patients aged $\geq$ 18 years, scheduled for elective or in-house urgent cardiac surgery (coronary, valve, combined coronary and valve or any other cardiac surgery requiring cardiopulmonary bypass), with a documented history (> 3 months) of AF (chronic, persistent or paroxysmal). Exclusion criteria included patients who had had previous cardiac operations, emergency or salvage operations surgery without cardiopulmonary bypass and patients who were unlikely to be available for the 2-year follow-up or who were unable to consent.

Randomisation

On the day of surgery, in the anaesthetic room, eligible patients were randomised (1 : 1) to either planned cardiac surgery (control arm) or planned cardiac surgery with additional device-based AF ablation (experimental arm). The allocation sequence was computer generated using permuted blocks (sizes 6 and 8), stratified by surgeon and planned procedure.

Blinding

Although theatre staff could not be blinded to treatment allocation, patients, researchers collecting HRQoL outcomes and cardiologists assessing the 4-day electrocardiography (ECG) results were unaware of treatment allocation.

Treatment arms

In this pragmatic trial, cardiac surgery and postoperative management in the control arm was completed in accordance with standardised hospital protocols.

For patients randomised to maze, the surgeon also administered ablation. The lesion set was at the discretion of the treating surgeon. Any AF ablation device routinely used within the NHS was permitted, including bipolar and unipolar radiofrequency, 'cut-and-sew', cautery, cryotherapy, ultrasound, laser and microwave energy. Postoperative management, subsequent follow-up and data collection were identical to the control arm.

Outcomes

Return to SR at 12 months after surgery and quality-adjusted survival over 2 years were joint primary outcomes. Return to SR was defined as absence of any AF on 4-day continuous ECG recordings,

analysed centrally at Papworth Hospital, by cardiologists unaware of patient identity or treatment arm. Quality-adjusted survival over 2 years was estimated using serial utility measurements from the UK population valuation of the EuroQol-5 Dimensions, three-level version (EQ-5D-3L), administered at randomisation and discharge, and at 6 weeks and 6, 12 and 24 months after the procedure. Quality-adjusted life-years (QALYs) over 2 years were estimated using the area under the curve method.

Secondary outcomes were return to SR at 2 years after surgery, overall survival, stroke-free survival, incidence of hospital admission for haemorrhage, anticoagulant and antiarrhythmic drug usage, HRQoL [measured by the EQ-5D-3L, the Short Form questionnaire-36 items (SF-36) and the New York Heart Association (NYHA)], resource use and trial-based cost-effectiveness of the adjunct maze procedure up to 2 years after randomisation.

Sample size

The maze procedure was considered effective if there was a significant effect for either return to SR at 12 months or QALYs over 2 years. The planned recruitment target of 200 patients per arm was based on detecting a target difference of 15% in the return to SR rate (45% for maze and 30% for control) or 1 additional month of quality-adjusted life (0.083 QALYs, standard deviation 0.3), with approximately 80% power, a two-sided significance of 5% and up to 15% death/loss to follow-up.

Owing to slower than expected accrual, recruitment was terminated in September 2014, when 352 patients had been randomised.

Statistical analysis

The primary analysis used intention to treat, with multiple imputation for missing primary outcomes. For AEs, patients were included in the arm corresponding to the intervention received (maze procedure completed vs. no maze procedure).

Return to SR rates were analysed using binary logistic regression, including surgeon (random effect), baseline heart rhythm and planned surgical procedure (fixed effects). For QALYs > 2 years, linear regression was fitted to utilities post treatment, including surgeon (random effect), baseline utility and treatment arm (fixed effects). For surviving patients with missing EuroQoL measurements, multiple imputation was used, and a confidence interval (CI) for the QALY difference was estimated using non-parametric bootstrapping. No discounting of QALY estimates was applied for the primary outcome. For both primary outcomes, subgroup effects were investigated by including interaction terms.

Overall survival and stroke-free survival were analysed using Kaplan–Meier and Cox regression methods. SF-36 scores were analysed using linear regression, including time point, treatment arm, time-by-treatment-arm interaction and baseline SF-36 scores (all fixed effects), with random intercepts for patients. Drug use was tabulated and analysed using logistic regression, including drug category, time period using drug, baseline drug usage and treatment arm.

Economic analysis

NHS resource use covered the primary admission (operation, time in intensive care, cardiac and acute care wards, transfers to rehabilitation centres or other hospitals), follow-up (including readmissions, diagnostic tests and health-care visits) and drugs (antiarrhythmic, anticoagulant, antiplatelet and cardiac drugs). Resource use was costed using national estimates of unit prices [Department of Health and Social Care (DHSC). *NHS Reference Costs 2014–15*. London: DHSC; 2015], literature (e.g. 24-hour blood pressure monitoring and chest radiography) or information from Papworth Hospital (e.g. theatre cost and cost of device). The ablation device was costed at £3000 per patient for high-intensity focused ultrasound, and at £1250 per patient for all other methods. Both costs and QALYs were discounted at 3.5% in year 2 for the cost-effectiveness analysis [National Institute for Health and Care Excellence. *Guide to the Methods of Technology Appraisal 2013: Process and Methods*. URL: www.nice.org.uk/process/pmg9/chapter/the-reference-case#discounting (accessed 10 January 2018)].

Costs and QALYs were analysed using seemingly unrelated regression, including age, sex, baseline EQ-5D-3L score, baseline AF and, for QALYs only, specific procedure; regression coefficients were used to estimate incremental cost-effectiveness ratios (ICERs). Probabilistic sensitivity analysis used bootstrapping. Cost-effectiveness planes, the cost-effectiveness acceptability curve and incremental net monetary benefit were estimated. Deterministic sensitivity analysis explored the impact of using Short Form questionnaire-6 Dimensions QALYs, complete-case analysis, truncating costs and QALYs at discharge, excluding outliers and alternative imputation strategies.

The 'Has Electrical Sinus Translated into Effective Remodelling?' substudy

To assess whether or not contractile function after maze procedure was equivalent to that for non-AF patients, 22 maze procedure patients who were in SR at least 1 year postoperatively, were matched (1 : 1) to non-trial control patients who were in SR before, and at least 1 year after, routine cardiac surgery. Matching criteria were time since procedure, age, sex, procedure, preoperative left ventricular ejection fraction and logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE).

Eligible patients underwent ECG to confirm SR, transthoracic two- and three-dimensional echocardiography and cardiac magnetic resonance imaging (MRI). The primary outcome was ALAEF; left atrial volumes and an ECG marker of left ventricular function (E/A ratio) were secondary end points.

Sample size

The minimum clinically important difference in ALAEF was set at 18.2%. Equivalence was concluded if the two-sided 95% CI of the estimated treatment effect (maze–control) was entirely in the interval (95% CI –18.2% to 18.2%). Twenty-two matched pairs provided 80% power to demonstrate equivalence.

Statistical analyses

For the primary end point, the linear regression model, including treatment, matching variables (fixed effects) and matched pairs (random effect), was fitted.

Results

Between 25 February 2009 and 6 March 2014, 1013 patients were screened in 11 UK specialist cardiac surgery centres and 352 patients were randomised to the control ($n = 176$) or experimental ($n = 176$) arms. Thirty surgeons participated in the trial. The SR status of patients at 12 months was available for 141 maze procedure and 145 control patients (80% and 82%, respectively); QALYs up to 2 years were available for 160 patients in each arm (91%).

Primary outcome results

Among complete cases in the maze procedure arm, 87 out of 141 patients (61.7%) were in SR compared with 68 out of 145 (46.9%) control patients. The odds ratio (OR) (95% CI) for return to SR was 2.06 (1.20 to 3.54; $p = 0.0091$). Surgical results varied by surgeon in both groups, but the treatment effects did not. Results were broadly consistent across subgroups.

In both trial arms, QALYs could be estimated for 160 patients. Unadjusted, undiscounted mean QALYs (95% CI) over 2 years were 1.489 (1.416 to 1.558) for maze procedure patients and 1.485 (1.403 to 1.559) for control patients. The mean difference (95% CI) in QALYs at 2 years (maze–control) was –0.025 (–0.129 to 0.078; $p = 0.6319$). Results did not vary by surgeon or subgroup.

Secondary outcomes

In the maze procedure arm, 69 out of 118 (58.5%) completers were in SR compared with 47 out of 129 (36.4%) completers in the control arm. The adjusted OR for patients in SR at 2 years was 3.24 (95% CI 1.76 to 5.96). The number of patients requiring anticoagulant drug therapy was significantly lower in the

maze arm from 6 months to 2 years post procedure. Slightly more maze procedure patients required antiarrhythmic drugs throughout follow-up, but the difference was not statistically significant.

There were no significant differences between the arms for any of the following secondary outcomes at any time point: operative or overall survival, stroke-free survival, need for cardioversion or permanent pacemaker implants, NYHA score, EQ-5D-3L utility and SF-36 dimensions.

Safety

Sixty per cent of patients in each arm had a serious adverse event ($p = 1.000$); most events were mild, but 71 (42.5%) maze procedure patients and 84 (45.5%) control patients had at least one moderately severe event, and 31 (18.6%) maze procedure patients and 38 (20.5%) control patients had a severe event. Twenty-three events in 17 (10.2%) patients were possibly related to treatment in the maze procedure arm compared with 28 events in 19 (10.3%) patients in the control arm; one patient (0.5%) in the control group was admitted to hospital for investigation of atrial flutter, classed as 'definitely related' to treatment.

Cost-effectiveness

The mean additional cost of the maze procedure was £3533 (95% CI £1321 to £5746), which was statistically significant, but the mean difference in QALYs was not statistically significant (–0.022, 95% CI –0.1231 to 0.0791). None of the analyses suggested that the maze procedure was cost-effective at £30,000 per QALY over 2 years. The smallest ICER was £83,625 per QALY for the complete-case analysis.

The 'Has Electrical Sinus Translated into Effective Remodelling?' substudy

Between 24 July 2013 and 8 July 2015, 22 eligible patients were recruited for each cohort and underwent echocardiography and MRI. The mean difference (95% CI) in ALAEF between maze procedure and control patients was –8.03 (–12.43 to –3.62). The 95% CI was contained entirely in the interval (–18.2 to 18.2), so that the predefined criterion for equivalence was met. However, the mean ALAEF was significantly lower in maze procedure patients than in control patients ($p = 0.0015$).

Mean E/A ratio was significantly higher and mean left atrial ejection fraction (four-chamber view and MRI) was significantly lower for maze procedure patients than for control patients. There were no significant differences in the other end points.

Conclusions

Implications for future health care

The Amaze trial demonstrated that ablation can be practised safely in a routine NHS cardiac surgical setting and that it increases the proportion of patients who return to SR up to 2 years after surgery. Clinical effects did not translate into improved survival or QALYs, and the addition of the maze procedure was not cost-effective over 2 years.

The reduction in anticoagulant drug use and results of the substudy provide support for anticoagulant drug withdrawal, but varying rates of left atrial functional recovery after the maze procedure mean that atrial function should be measured before considering withdrawal of anticoagulant drugs.

Implications for further research

The clinical results are promising, and continued follow-up of clinical events, HRQoL and long-term clinical effectiveness and cost-effectiveness analysis is warranted.

Subgroup analyses had low power to provide robust recommendations on specific methods. Further comparison of ablation methods would inform best practice.

Trial registration

This trial is registered as ISRCTN82731440.

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