Amaze: a randomised controlled trial of adjunct surgery for atrial fibrillation

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Abstract

Objectives

Atrial fibrillation (AF) reduces survival and quality of life (QoL). It can be treated at the time of major cardiac surgery by ablation procedures ranging from simple pulmonary vein isolation to a full maze procedure. The aim of this study is to evaluate the impact of adjunct AF surgery as currently performed on sinus rhythm (SR) restoration, survival, QoL and cost-effectiveness.

Methods

In a multicentre, phase III, pragmatic, double-blind, parallel-arm randomised controlled trial, 352 cardiac surgery patients with >3 months of documented AF were randomised to surgery with or without adjunct maze or similar AF ablation between 2009 and 2014. Primary outcomes were SR restoration at 1 year and quality-adjusted life years (QALYs) at 2 years. Secondary outcomes included SR at 2 years, overall and stroke-free survival, medication, QoL, cost-effectiveness and safety.

Results

More maze patients were in SR at 1 year (odds ratio (OR) 2.06; 95% confidence interval (CI) 1.20-3.54; p=0.009). At 2 years the OR increased to 3.24 (95%CI 1.76-5.96). QALYs were similar at 2 years (maze – control: -0.025, p=0.6319). Significantly fewer maze patients were anticoagulated from 6 months postoperatively. Stroke rates were 5.7% (maze) and 9.1% (controls) (p=0.3083). There was no significant difference in stroke-free survival (HR=0.99, 95%CI 0.64, 1.53, p= 0.949), nor in serious adverse events, operative or overall survival, cardioversion, pacemaker implantation, NYHA, EQ-5D-3L and SF-36. Mean additional maze cost per patient was £3533 (95% CI: £1321 - £5746). Cost-effectiveness was not demonstrated at 2 years.

Conclusion

Adjunct AF surgery is safe and increases SR restoration and costs, but not survival or QoL up to 2 years. Continued follow-up will provide information these outcomes in the longer term.

Introduction

The prevalence of atrial fibrillation (AF) is 1-2% in the developed world , rising with age and comorbidity[1]. UK prevalence is 7.2% after age 65 and 10.3% after 75 [2] and will rise further with life expectancy. Symptoms include palpitations, chest pain, dizziness and breathlessness. Loss of atrial contractility increases the risk of thromboembolic stroke [3]. Anticoagulation reduces stroke but increases bleeding risk [4]. Atrial function loss may cause or exacerbate heart failure. AF has substantial impact on care and resources.

AF pathophysiology is now better understood: triggered most often by pulmonary vein foci, it is maintained through macro-re-entry circuits of 4-5 cm in diameter[5], leading to the development of the Cox-maze procedure in the 1980s [6]: through median sternotomy with cardiopulmonary bypass, the atria are cut and sutured to achieve pulmonary vein electrical isolation and interruption of macro-re-entry circuits. Despite success in restoring sinus rhythm (SR)[7], this challenging procedure is usually reserved for severely symptomatic patients. Worldwide, the number of cut-and-sew Cox-maze procedures is extremely small in relation to AF prevalence.

Less demanding methods for achieving some or all of the electrical blocks of the Cox-maze procedure use energy sources (heat, cold or radiofrequency) to ablate atrial tissue: easier, quicker and safer, but costly. Many cardiac surgery patients have AF. Whether they should routinely have adjunct AF surgery is unknown. Current practice varies widely between surgeons and hospitals. AF surgery increases SR restoration rate and decreases anti-arrhythmic medication use[8-10]. However, the impact on patient-relevant outcomes, such as survival and health-related QoL (HRQoL) is uncertain. Cost-effectiveness analyses have mixed results [11, 12], are limited by lack of HRQoL evidence in the short and medium term (1-5 years) and economic models are not robust. Amaze aimed to evaluate clinical and HRQoL outcomes and cost-effectiveness of this technology by comparing AF surgery as an adjunct to cardiac surgery with cardiac surgery alone.

Methods

Amaze was a phase III, pragmatic, multicentre, double blind, parallel arm, randomised controlled superiority trial (RCT) in 11 cardiac surgical centres. Thirty surgeons participated with at least 2 years' experience in AF surgery.

Patient recruitment

Consecutive cardiac surgery patients with a history of AF were screened. Inclusion criteria were: age ≥18, elective or urgent cardiac surgery (coronary, valve, combined, other surgery requiring cardiopulmonary bypass), documented history (>3 months) of AF (non-paroxyxmal or paroxysmal). Exclusion criteria were: previous cardiac operations, emergency or salvage operations, off-pump surgery, unavailability for follow-up and inability to consent.

Randomisation

Group allocation (1:1) was computer-generated by the trial statistician, using permuted block randomisation (sizes 6 and 8), stratified by surgeon and planned procedure. Randomisation to planned cardiac surgery (control arm) or planned cardiac surgery with additional maze or similar ablation procedure (maze arm) was on operation day.

Blinding

Operating room staff could not be blinded to treatment allocation. After surgery, procedure details were kept in sealed envelopes in patient notes and only retrieved in a clinical emergency. Patients, cardiologists assessing ECG results and researchers collecting HRQoL outcomes were unaware of treatment arm.

Clinical management

Operative and perioperative management followed local protocols and were identical in both arms. AF surgery in the intervention arm was conducted by an experienced surgeon. Amaze was a pragmatic trial evaluating AF ablation *as currently performed*, so ablation methods and lesion sets were left to the surgeon: any device in clinical use was permitted, including bipolar and unipolar radio-frequency, 'cut-and-sew', cautery, cryotherapy, ultrasound, laser and microwave. Lesion sets and devices used were recorded.

Outcomes

SR restoration at one year after surgery and quality-adjusted life years (QALYs) over 2 years were joint primary outcomes. SR restoration required absence of any AF on 4-day continuous ECG analysed by

cardiologists unaware of patient identity or treatment arm. QALYs over 2 years were estimated from serial utility measurements from the UK population valuation of the EuroQoL EQ-5D-3L at randomisation, discharge, 6 weeks, 6, 12 and 24 months postoperatively. Secondary outcomes were 2-year SR restoration, overall survival, stroke-free survival, hospital admission for haemorrhage, antiarrhythmic and anticoagulant drug usage, NYHA, HRQoL (SF-36), resource use and cost-effectiveness at 2 years. Pre-specified subgroup analyses explored outcome differences by AF type, surgeons, and cardiac procedure. Outcome by lesion sets and method of ablation were compared within the maze arm.

Sample size

AF surgery was considered effective if there was a significant impact on either 1-year SR rates or 2-year quality-adjusted survival. The target (200 patients per arm) was based on detecting a of 15% difference in the proportion of patients in SR at 1 year (45% versus 30%) or 1 additional month of quality-adjusted life (0.083 QALYs, standard deviation 0.3) over 2 years, with approximately 80% power, two-sided significance of 5% and up to 15% death/loss to follow-up. Because of slower-than-expected accrual, recruitment stopped at 352 patients (88% target) reducing the power to detect the proposed treatment effects to over 70% for primary outcomes. In order to guard against over-interpretation of hypothesis tests due to multiple testing we recommend that p-values between 0.025 and 0.05 are considered of borderline significance.

Statistical analysis

Primary outcome analysis was by intention to treat. SR restoration was analysed by logistic regression, including surgeon (random intercepts), baseline rhythm and planned procedure (fixed effects). For QALYs, linear regression, including surgeon (random intercepts), baseline utility and treatment arm (fixed effects), was fitted to utilities post-treatment. For survivors with missing EuroQoL measurements, multiple imputation was used and QALY difference confidence interval estimated using non-parametric bootstrapping. No primary outcome discounting was applied and no adjustment made for multiplicity. Sensitivity to assumptions surrounding missing data mechanisms were explored with no changes in results. For primary outcomes, pre-specified subgroup effects were explored by including interaction terms, except

for surgeon where a random effect was applied to the treatment coefficient. Lesions set effects were assessed in the maze arm against a reference category. Adverse events by intervention were categorised by severity and relationship to procedure. Survival and stroke-free survival were analysed using Kaplan-Meier and Cox regression. SF-36 score analysis used linear regression, including time point, treatment arm, time-by-treatment arm interaction, baseline scores (fixed effects), with random intercepts for patients. Anti-arrhythmic and anti-coagulant use was tabulated by time and category and analysed by logistic regression.

Economic Analysis

Resource use data from primary admission (time in theatre, intensive care and wards, hospital transfer, diagnostics and antiarrhythmic, antiplatelet, anticoagulant and cardiac drugs) were extracted from records, supplemented by patient-reported post-discharge health service use. Resources were valued using national estimates (https://www.evidence.nhs.uk/formulary/bnf/current ; http://www.drugtariff.nhsbsa.nhs.uk/ ; http://www.pssru.ac.uk/project-pages/unit-costs/2015/ ; https://www.gov.uk/government/publications/nhs-reference-costs-2014-to-2015 /) literature (blood pressure monitoring and radiology)[13, 14] and data from Papworth Hospital (operating room and device cost). High intensity focussed ultrasound was costed at £3000 and other methods at £1250. Type missingness was examined and replaced with mean or imputed values. Missing resource and utility data were imputed jointly using chained equations with predictive mean matching. Costs and QALYs were discounted at 3.5% in year two. Incremental cost-effectiveness ratios (ICERs) relied on seemingly unrelated regression, controlling for baseline differences in age, gender, EQ-5D-3L, AF and (for QALYs) the primary surgery. Probabilistic sensitivity analysis used bootstrapping. Cost-effectiveness planes, acceptability curve and incremental net monetary benefit were estimated. Deterministic sensitivity analysis explored the impact of using of SF-6D QALYs, complete case analysis, truncating costs and discharge QALYs, excluding outliers and alternative imputation strategies.

Results

Between February 2009 and March 2014, 1013 patients were screened by 30 surgeons in 11 centres: 352 were randomised (176 each) to control or maze arms. Thirteen patients (3.7%) did not receive allocated treatment: 11 maze (6.3%) due to technical issues; 2 control (1.1%) due to surgeon-perceived benefit after

randomisation (figure 1). One-year SR status was available for 141 maze (80%) and 145 control patients (82%), 2-year QALYs were known for 160 patients in each arm (91%). Loss-to-follow-up reasons were similar for the two groups (figure 1), which were also similar in demographics, symptomatic status, cardiovascular profile and operations performed (tables 1-2). The left atrial (LA) appendage was resected or excluded in 97 maze arm patients (55.1%) and in 53 control patients (30.1%)

Primary outcome: sinus rhythm at 1 year

Among cases with complete ECG data, 87 of 141 maze patients (61.7%) were in SR at 1 year versus 68 of 145 (46.9%) controls (figure 2). In intention-to-treat analysis, the odds ratio (95%CI) for 1-year SR restoration for the maze arm was 2.06 (1.20, 3.54), p=0.0091. This increased from 1.6 (0.6, 4.0) for the first 120 randomised patients to 2.9 (0.9, 9.6) for the final 71 patients randomised in the last 18 months.

Primary outcome: quality-adjusted life years

The unadjusted, undiscounted mean (95%CI) QALY over 2 years was 1.489 (1.416, 1.558) for the maze arm and 1.485 (1.403, 1.559) in the control arm. In intention-to-treat analysis, the adjusted mean difference (95%CI) in QALYs at 2 years (maze – control) was – 0.025 (- 0.129, 0.078, p=0.6319).

Secondary outcomes

At 2 years, 69 of 118 (58.5%) maze completers were in SR compared with 47 of 129 (36.4%) controls (figure 2). The adjusted odds ratio for SR at 2 years was 3.24 (95%CI 1.76, 5.96). Significantly fewer maze patients received anticoagulants from 6 months (appendix table A2) without a higher stroke rate: 13 strokes in 10 (5.7%) maze patients and 19 in 16 (9.1%) control patients; the difference of -3.4% (95%CI -14.1%, 7.3%) was not significant (Fisher's Exact Test p=0.3083), nor was the difference in stroke events between the two groups (log-linear model relative rate 0.68 (95%CI: 0.34, 1.39, p=0.292). Stroke-free survival was similar in the two arms (HR=0.99, 95%CI 0.64, 1.53, p= 0·949, figure 4). Fifteen patients (7 maze, 8 control) already had permanent pacemakers at surgery. Maze did not increase the need for permanent pacemaker implantation after surgery (maze 15, control 17). Sixty (34.1%) maze patients required 65 cardioversions and 67 (38.1%) control patients required 72 cardioversions. Immediate cardioversion success rates were similar (48/65 (73.8%) maze and 54/72 (75.0%) control). There was no significant difference in anti-arrhythmic drug use throughout follow-up (appendix table A2). There were no significant differences between the two arms in any of the following outcomes at any time point: NYHA, EQ-5D-3L and SF-36.

Safety

Mean (SD) cross-clamp time was 5.1 minutes longer in the maze group (82.2 (37.2) versus 77.2 (48.6)) and bypass time 18.9 minutes longer (118.1 (43.4) versus 99.3 (41.8)). There were 5 (2.8%) operative deaths in the maze group and 9 (5.1%) among controls (p=0.414). Over the trial course there were 30 maze and 25 control deaths (hazard ratio (95%CI): 1.23 (0.73, 2.10) p=0.437), so that adding AF surgery did not significantly affect early or late mortality (figure 3).

There were 330 adverse events in 100 AF surgery patients and 333 in 111 controls (each 60%). Of these 71 (42.5%) maze and 84 (45.5%) control patients had at least one moderately severe event and 31 (18.6%) maze and 38 (20.5%) control patients had a severe event. Few events were 'possibly related' to treatment: 23 in 17 maze patients (10.2%) and 28 in 19 control patients (10.3%); one patient admitted to hospital for atrial flutter (classed as 'definitely related' to treatment) was subsequently found to be in the control group.

Subgroup analysis

Pre-planned subgroup analysis showed no significant interaction between 1-year SR restoration and type of AF (paroxysmal or non-paroxysmal) or planned cardiac procedure (figure 5). Random intercepts analysis showed that SR restoration rates varied by surgeon across both arms, with an intra-class correlation coefficient of 0.089. In the maze arm, the highest odds for 1-year SR restoration occurred with a comprehensive LA lesion set including the mitral isthmus lesion. Adding right atrial (RA) lesions conveyed no further increase in SR restoration odds (to be interpreted cautiously because of confounding associations between lesion sets and surgeons). Post hoc analysis of LA appendage excision showed a significant interaction, being increasingly used as the trial progressed for the maze group but not controls.

Cost-effectiveness

Higher maze costs resulted from the ablation device, length of stay in critical care and readmissions (table 3). The adjusted mean incremental maze cost was £3533 (95% CI: £1321 to £5746), significantly higher than control (p<0·01). The adjusted mean QALY difference was not significant (-0022, 95% CI: -01231 to 00791, p=0.67, appendix table A3). No analyses suggested that maze was cost-effective at 2 years at £30,000

per QALY. The smallest ICER was £53,538/QALY from an unplanned analysis limited to patients randomised in the second half of the trial (appendix figures A2-5).

Discussion

In this pragmatic, multicentre trial, 1-year and 2-year SR restoration rates were significantly higher for maze patients than controls and slightly higher than reported in a recent RCT meta-analysis[15]. SR restoration rate in the control group was higher than any previously reported through cardiac surgery alone [16, 17]. Control patients received the same postoperative care as trial patients including postoperative cardioversion suggesting that, with a determined effort, cardiac surgery *alone* can restore SR in a third of patients at 2 years, an outcome worth pursuing in the absence of adjunct AF surgery.

The optimal lesion set remains controversial. The full Cox-maze lesion set is established [18], and if there is a 'dose-response' relationship, SR restoration rates should be better with a more complete lesion. One RCT of AF surgery in mitral patients found no significant difference in SR restoration between the complete lesion set and pulmonary vein isolation alone [16], although it was probably insufficiently powered to detect such a difference. Many surgeons carry out only parts of the full Cox-maze, and there is a wide range of lesion sets used. Terminology is unhelpful with such procedures variously described as maze, mini-maze, left atrial maze or simply AF ablation. Amaze showed higher SR restoration rates with a complete LA lesion set including the mitral annulus or 'isthmus' lesion, but did demonstrate the benefit of adding RA lesions, although the power to detect these differences was low and adding such lesions has little impact on operative time or complexity above a full LA lesion set.

We found no QoL impact at 2 years, but this is relatively short follow-up, and cardiac surgery alone achieves such an increase in QoL [19] that it may be difficult to discern additional benefits from AF surgery at this stage. Two factors may modify this conclusion in future: there was significantly less anticoagulation of maze patients postoperatively with no increase in stroke rate, and the HESTER study[20] showed LA contractile recovery in most but not all patients when maze restores SR. These results lend support to anticoagulation withdrawal when SR is restored after maze but the varying extent of LA contractile recovery suggests LA

function should be measured before contemplating withdrawal. Continued follow-up of Amaze patients will establish whether QoL and survival advantages accrue over time.

The per-patient cost over 2 years was higher in the maze arm with no significant impact on discounted QALYs. Deterministic and probabilistic sensitivity analyses confirmed this and the probability that maze would be cost-effective at 2 years was less than 5% and alternative assumptions do not alter this conclusion.

Strengths and limitations

Amaze is the largest randomised trial to date to evaluate adjunct AF surgery. It is unique in including all cardiac (not only mitral) procedures, in having both patients and outcome assessors blinded to treatment arm and in incorporating survival, stroke-free survival and QoL as outcome measures. The pragmatic design evaluated AF surgery as currently done in clinical practice, rather than what may be achievable in specialist centres. The number of participating units and surgeons, the variety of ablation devices and lesion sets and the interaction between these variables has improved result generalisability but reduced the power to draw firm conclusions about the optimal device and lesion set.

Recruitment is a widespread RCT problem. Logistic delays, activity overestimation and rising awareness of AF surgery among patients and clinicians affected recruitment rate. Infrequent follow-up (6, 12, 24 months) is associated with underreporting of frequent events, illness severity, and intensive service use, but there is no recommended interval between follow-ups [21, 22]. In Amaze, 95% of the difference in follow-up costs related to re-admissions (infrequent major events) making cost underestimation unlikely. The cost-effectiveness analysis was limited to 2 years and may not reflect long-term benefits.

Conclusion

Adjunct AF surgery can be practised safely in a routine cardiac surgical setting and increases SR restoration up to 2 years after surgery. This electrophysiological success did not translate into better 2-year survival or QoL and the procedure is therefore not proven to be cost-effective at 2 years. Longer follow-up will determine whether AF surgery has an impact on these outcomes.

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376 ## Tables

377 **Table 1.** Baseline characteristics for patients randomised in the Amaze trial. SD: standard deviation, CCS: Canadian
378 Cardiac Society. NYHA: New York Heart Association.

	Maze (n=176)	Control (n=176)	Total (n= 352)
Age (years)			
mean (SD)	72.3 (7.53)	71.4 (7.81)	71.9 (7.67)
range	(50.0 , 86.0)	(48.0 , 89.0)	(48.0 , 89.0)
Sex			
male (%)	112 (63.6%)	120 (68.2%)	232 (65.9%)
female (%)	64 (36.4%)	56 (31.8%)	120 (34.1%)
Body mass index			
mean (SD)	28.1 (5.27)	27.6 (4.62)	27.9 (4.96)
range	(17.4 , 46.0)	(17.9 , 42.8)	(17.4 , 46.0)
Logistic EuroSCORE (%)			
mean (SD)	6.94 (5.489)	6.64 (4.869)	6.79 (5.184)
range	(0.88 , 30.41)	(1.40 , 23.85)	(0.88 , 30.41)
CCS Class			
Class 0	125 (71.0%)	133 (75.6%)	258 (73.3%)
Class 1	13 (7.4%)	17 (9.7%)	30 (8.5%)
Class 2	21 (11.9%)	16 (9.1%)	37 (10.5%)
Class 3	10 (5.7%)	8 (4.5%)	18 (5.1%)
Class 4	1 (0.6%)	1 (0.6%)	2 (0.6%)
Missing / not known	6 (3.4%)	1 (0.6%)	7 (2.0%)
NYHA classification			
I	31 (17.6%)	30 (17.0%)	61 (17.3%)
II	74 (42.0%)	68 (38.6%)	142 (40.3%)
III	59 (33.5%)	71 (40.3%)	130 (36.9%)
IV	10 (5.7%)	6 (3.4%)	16 (4.5%)
Missing / Not known	2 (1.1%)	1 (0.6%)	3 (0.9%)

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Table 2. Cardiovascular status at baseline of patients randomised in the Amaze trial

(LVEF: left ventricular ejection fraction, MI: myocardial infarction, PCI: percutaneous coronary intervention, MVR: mitral valve repair or replacement; CABG: coronary artery bypass grafting; AVR: aortic valve replacement

	Maze (n=176)	Control (n=176)	Total (n=352)
Left ventricular function			
poor (LVEF <30%)	4 (2.3%)	8 (4.5%)	12 (3.4%)
moderate (LVEF 30 - 50%)	50 (28.4%)	56 (31.8%)	106 (30.1%)
good (LVEF > 50%)	122 (69.3%)	112 (63.6%)	234 (66.5%)
Previous PCI	16 (9.1%)	14 (8.0%)	30 (8.5%)
Congestive Cardiac Failure	5 (2.8%)	1 (0.6%)	6 (1.7%)
Diabetes			
Insulin-dependent	5 (2.8%)	7 (4.0%)	12 (3.4%)
Non-insulin-dependent	27 (15.3%)	17 (9.7%)	44 (12.5%)
Hyperlipidaemia	70 (39.8%)	63 (35.8%)	133 (37.8%)
Atrial fibrillation class			
Paroxysmal	44 (25.0%)	48 (27.3%)	92 (26.1%)
Persistent	30 (17.0%)	19 (10.8%)	49 (13.9%)
Permanent	102 (58.0%)	109 (61.9%)	211 (59.9%)
Atrial fibrillation history			
0 -3 months	4 (2.3%)	2 (1.1%)	6 (1.7%)
3 - 6 months	25 (14.2%)	25 (14.2%)	50 (14.2%)
6 - 12 months	31 (17.6%)	23 (13.1%)	54 (15.3%)
> 12 months	115 (65.3%)	126 (71.6%)	241 (68.5%)
not known	1 (0.6%)	-	1 (0.3%)
Permanent pacemaker	7 (4.0%)	8 (4.5%)	15 (4.3%)
Previous cardioversion	24 (13.6%)	23 (13.1%)	47 (13.4%)
Previous ablation	3 (1.7%)	1 (0.6%)	4 (1.1%)
Other arrhythmias	2 (1.1%)	2 (1.1%)	4 (1.1%)
Anticoagulants	137 (77.8%)	137 (77.3%)	274 (77.6%)
Anti-arrhythmics	145 (82.4%)	148 (84.1%)	293 (83.2%)
Actual procedure category			
MVR	39 (22.2%)	48 (27.3%)	87 (24.7%)
CABG	35 (19.9%)	34 (19.3%)	69 (19.6%)
AVR	32 (18.2%)	23 (13.1%)	55 (15.6%)
CABG+AVR	16 (9.1%)	21 (11.9%)	37 (10.5%)
CABG+MVR	14 (8.0%)	13 (7.4%)	27 (7.7%)
All others	40 (22.7%)	37 (21.0%)	77 (21.9%)

384 **Table 3**. Mean (standard deviation) of per-patient costs of resource use, with imputation

		Maze (n=176)		Control (n=176)		Difference (Maze-Control)
Health Service Use		Mean cost / patient (£)	Std. Dev.	Mean cost / patient (£)	Std. Dev.	
Primary Admission	Theatre use	£5,225	£1,594	£4,949	£1,863	£276
	Ablation device	£1,212	£408	£14	£133	£1,197
	Adult Critical Care	£4,029	£7,600	£3,065	£5,586	£964
	Cardiac Ward	£3,397	£4,661	£3,064	£2,014	£333
	Rehabilitation	£48	£325	£148	£1,082	-£100
	Acute Trust	£937	£6,105	£165	£1,409	£772
	Sub total	*£14,847*	*£12,474*	*£11,404*	*£7194*	*£3,443*
Medication (whole trial period)		£618	£1,584	£681	£2,765	-£63
Follow-up	Readmissions	£1,650	£4,192	£1,220	£2,994	£430
	Tests	£388	£376	£344	£283	£44
	Healthcare Visits	£1,179	£1,061	£1,193	£1,052	-£14
	Sub total	*£3,217*	*£5,629*	*£2,757*	*£4,329*	*£460*
Grand Total		£18,681	£13,340	£14,842	£8,295	£3,839

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Figure legends

Figure 1.

Patient flow through the Amaze trial

Figure 2.

Percentage of patients in sinus rhythm free from atrial fibrillation at 1 year and 2 years after randomisation

Figure 3.

Six-year cumulative mortality rate after patient randomisation in the Amaze trial

Figure 4.

Six-year cumulative mortality-or-stroke rate after patient randomisation in the Amaze trial

Figure 5.

Forest plot showing the odds ratio of sinus rhythm restoration at one year after randomisation for predefined subgroups in the Amaze trial

411 **Figures**

412 **Figure 1.** Patient flow through the Amaze trial

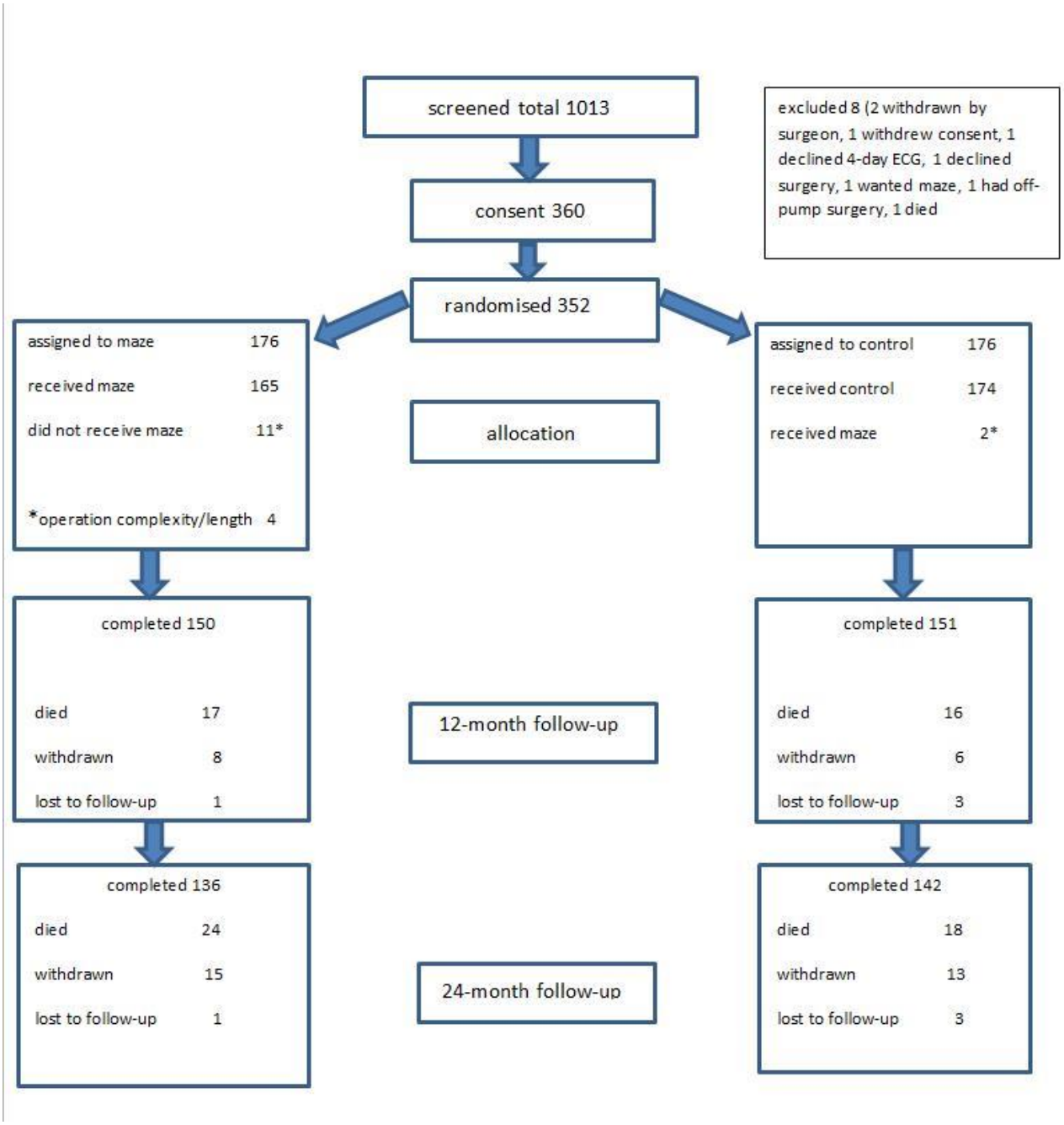

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Figure 2. Percentage of patients in sinus rhythm free from atrial fibrillation at 1 year and 2 years after randomisation

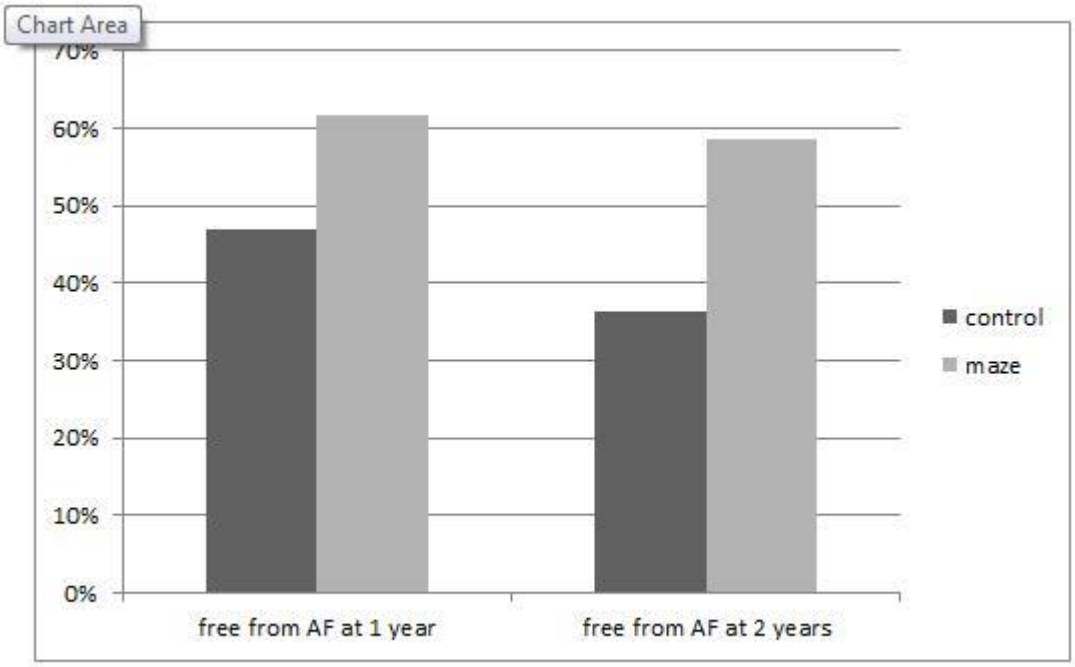


Figure 3. Six-year cumulative mortality rate after patient randomisation in the Amaze trial

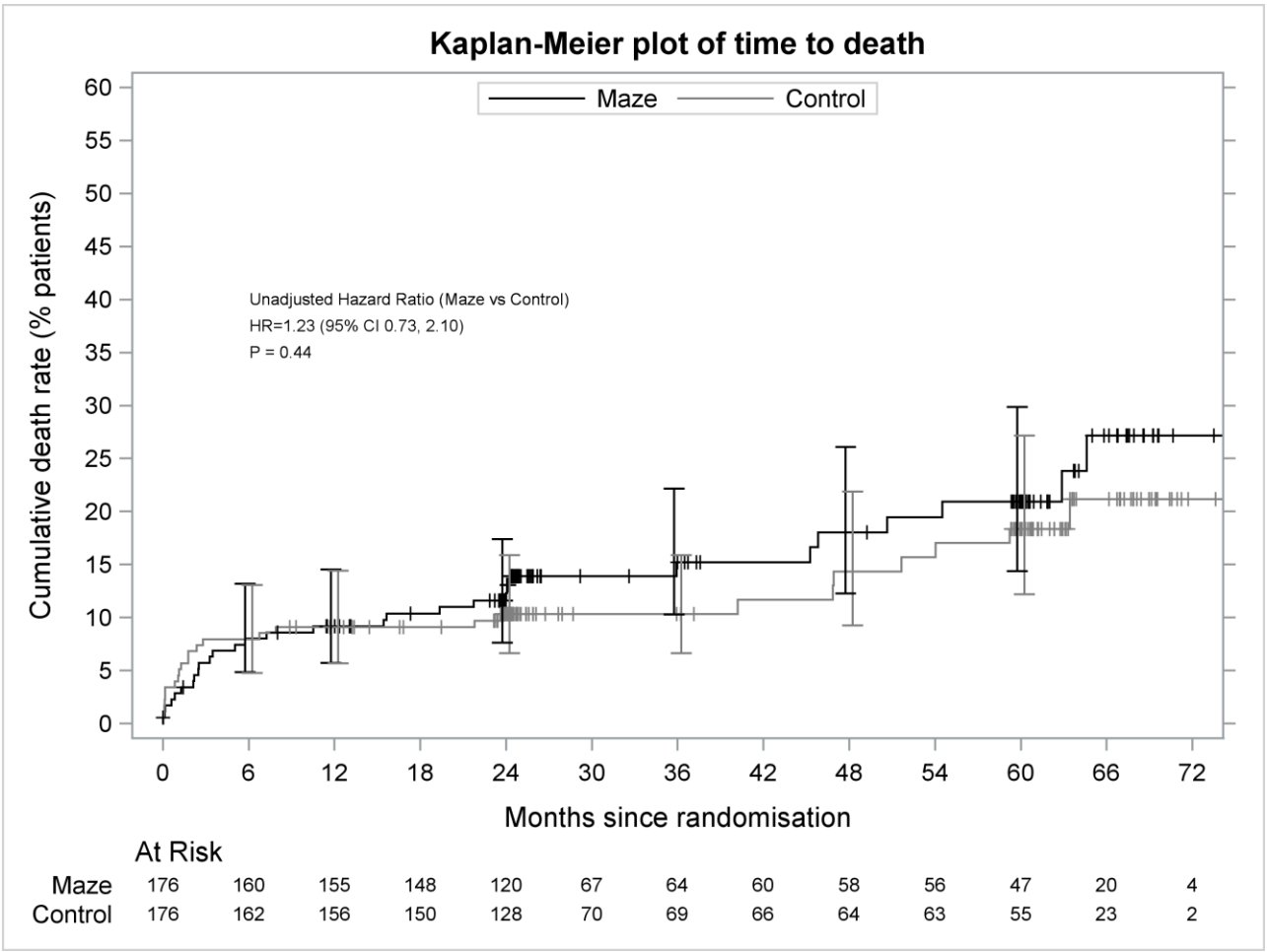
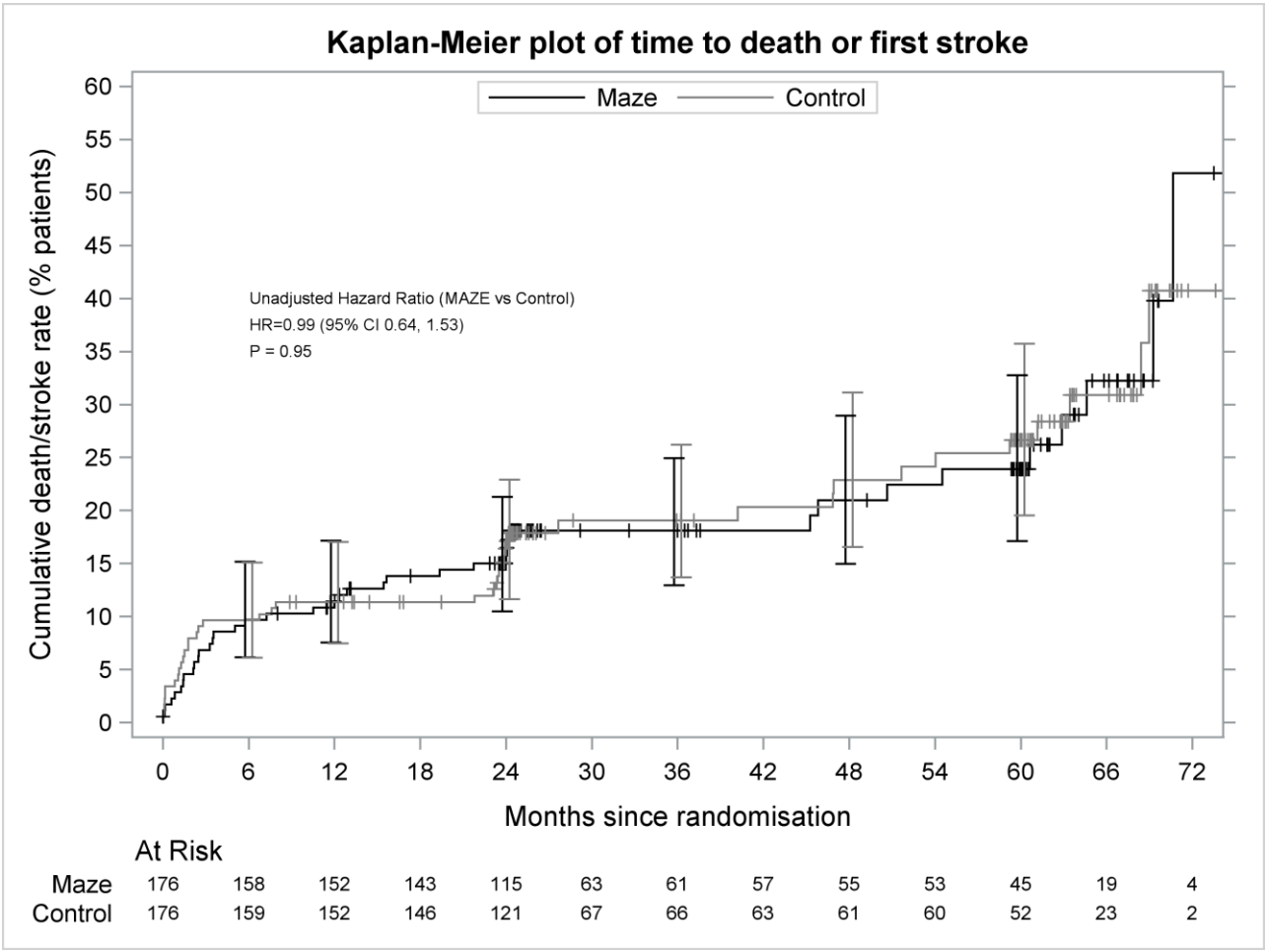


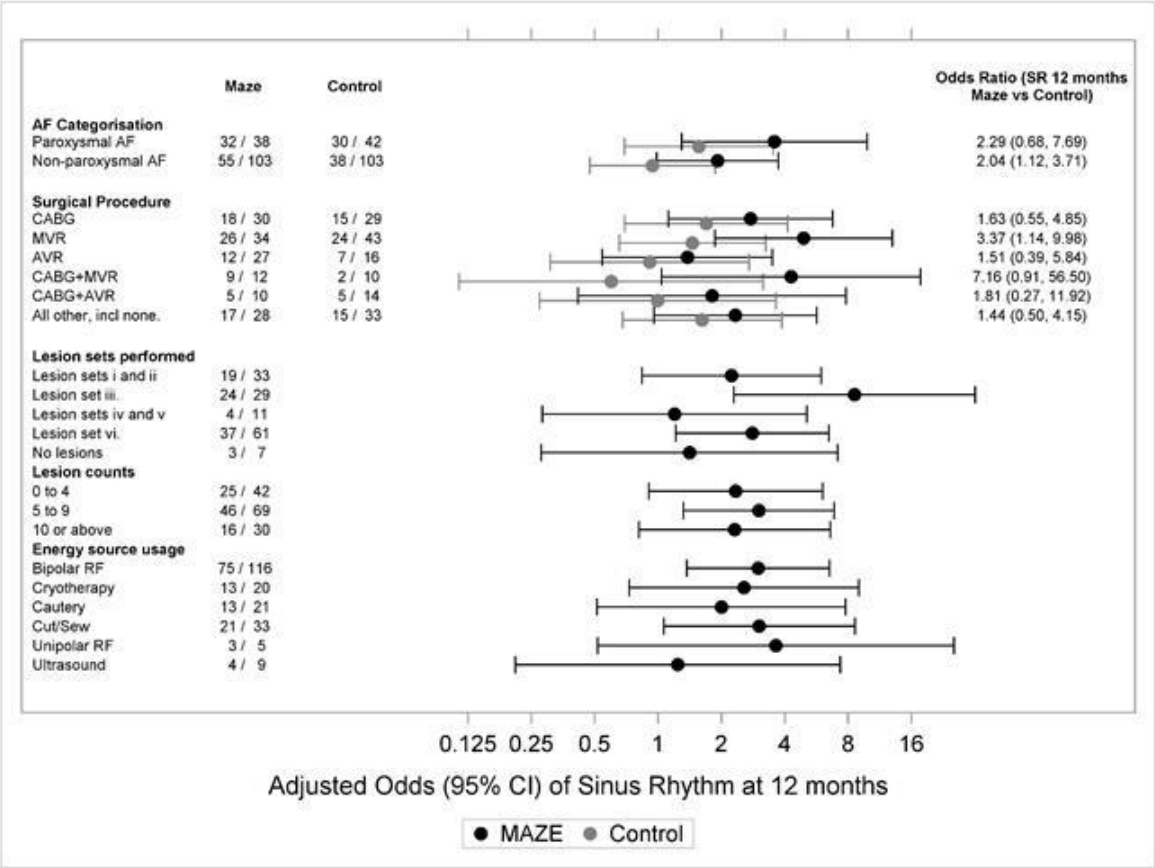
Figure 4. Six-year cumulative mortality-or-stroke rate after patient randomisation in the Amaze trial



436 **Figure 5**. Forest plot showing the odds ratio of sinus rhythm restoration at one year after randomisation for
437 predefined subgroups in the Amaze trial

Lesion set groupings below (LA left atrium, RA right atrium, PV pulmonary veins)

i: minimal LA lesion set: PV isolation only ± LA appendage line
ii: more extensive LA only lesion set excluding mitral annulus
iii: more extensive LA only lesion set including mitral annulus
iv: minimal LA lesion set and RA lesion set
v: more extensive LA lesion set excluding mitral annulus + RA lesion set
vi: more extensive LA lesion set including mitral annulus + RA lesion set



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