

LONDON  
SCHOOL of  
HYGIENE  
& TROPICAL  
MEDICINE



LSHTM Research Online

Nashef, SAM; Fynn, S; Abu-Omar, Y; Spyt, TJ; Mills, C; Everett, CC; Fox-Rushby, J; Singh, J; Dalrymple-Hay, M; Sudarshan, C; +4 more... Codispoti, M; Braidley, P; Wells, FC; Sharples, LD; (2018) Amaze: a randomized controlled trial of adjunct surgery for atrial fibrillation. European journal of cardio-thoracic surgery. ISSN 1010-7940 DOI: <https://doi.org/10.1093/ejcts/ezy165>

Downloaded from: <http://researchonline.lshtm.ac.uk/4647434/>

DOI: <https://doi.org/10.1093/ejcts/ezy165>

**Usage Guidelines:**

Please refer to usage guidelines at <https://researchonline.lshtm.ac.uk/policies.html> or alternatively contact [researchonline@lshtm.ac.uk](mailto:researchonline@lshtm.ac.uk).

Available under license: <http://creativecommons.org/licenses/by-nc-nd/2.5/>

<https://researchonline.lshtm.ac.uk>

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

1	Samer A M Nashef <sup>a</sup>	Consultant Surgeon, Papworth Hospital
2	Simon Fynn <sup>b</sup>	Consultant Cardiologist, Papworth Hospital
3	Yasir Abu-Omar <sup>a</sup>	Consultant Surgeon, Papworth Hospital
4	Tomasz J Spyt <sup>c</sup>	Consultant Surgeon, Glenfield Hospital
5	Christine Mills <sup>d</sup>	Clinical Project Manager, Papworth Hospital
6	Colin C Everett <sup>e</sup>	Senior Medical Statistician, University of Leeds
7	Julia Fox-Rushby <sup>f</sup>	Professor of Health Economics, Brunel University
8	Jeshika Singh <sup>f</sup>	Research Fellow, Brunel University
9	Malcolm Dalrymple-Hay <sup>g</sup>	Consultant Surgeon, Derriford Hospital
10	Catherine Sudarshan <sup>a</sup>	Consultant Surgeon, Papworth Hospital
11	Massimiliano Codispoti <sup>a</sup>	Consultant Surgeon, Papworth Hospital
12	Peter Braidley <sup>h</sup>	Consultant Surgeon, Northern General Hospital
13	Francis C Wells <sup>a</sup>	Consultant Surgeon, Papworth Hospital
14	Linda D Sharples <sup>i</sup>	Professor, London School of Hygiene & Tropical Medicine

15  
16 a: Department of Surgery, Papworth Hospital; b: Department of Cardiology, Papworth Hospital; c:  
17 Department of Cardiothoracic Surgery, Glenfield Hospital; d: Research and Development, Papworth  
18 Hospital; e: Clinical Trials Unit, Leeds University; f: Department of Health Economics, Brunel University;  
19 g: Department of Cardiothoracic Surgery, Plymouth Hospital; h: Department of Cardiothoracic Surgery,  
20 Sheffield Northern General Hospital; i: Department of Medical Statistics, London School of Hygiene and  
21 Tropical Medicine

22  
23 Trial institutions (all United Kingdom): Papworth Hospital, Cambridge; Glenfield Hospital, Leicester;  
24 University of Leeds, Leeds; Brunel University, London; Derriford Hospital, Plymouth; Northern General  
25 Hospital, Sheffield; London School of Hygiene and Tropical Medicine, London; Freeman Hospital,  
26 Newcastle; , Wythenshawe Hospital, Manchester; Royal Sussex County Hospital, Brighton; University  
27 Hospital, Coventry; Royal Brompton Hospital, London; Guy's & St Thomas's Hospital, London; Victoria  
28 Hospital, Blackpool

29  
30 Funded by the NIHR Health Technology Assessment programme

31 Study registration. ISRCTN82731440 (project number 07/01/34)

32  
33 correspondence to: S A M Nashef  
34 Papworth Hospital  
35 Cambridge  
36 CB23 3RE, UK  
37 [sam.nashef@nhs.net](mailto:sam.nashef@nhs.net)  
38 +44 1480 364807  
39 fax +44 1480 364744  
40  
41

42 **manuscript data:** word count: abstract 243, manuscript 3065 + 22 references + 3 tables + 5 figures

43 **Key words:** randomised trial, atrial fibrillation, ablation, maze procedure, cardiac surgery,  
44 cost-effectiveness

## 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.

## 69 **Introduction**

70 The prevalence of atrial fibrillation (AF) is 1-2% in the developed world , rising with age and comorbidity<sup>1</sup>.

71 UK prevalence is 7.2% after age 65 and 10.3% after 75<sup>2</sup> and will rise further with life expectancy.

72 Symptoms include palpitations, chest pain, dizziness and breathlessness. Loss of atrial contractility increases

73 the risk of thromboembolic stroke<sup>3</sup>. Anticoagulation reduces stroke but increases bleeding risk<sup>4</sup>. Atrial

74 function loss may cause or exacerbate heart failure. AF has substantial impact on care and resources.

75

76 AF pathophysiology is now better understood: triggered most often by pulmonary vein foci, it is maintained

77 through macro-re-entry circuits of 4-5 cm in diameter<sup>5</sup>, leading to the development of the Cox-maze

78 procedure in the 1980s<sup>6</sup>: through median sternotomy with cardiopulmonary bypass, the atria are cut and

79 sutured to achieve pulmonary vein electrical isolation and interruption of macro-re-entry circuits. Despite

80 success in restoring sinus rhythm (SR)<sup>7</sup>, this challenging procedure is usually reserved for severely

81 symptomatic patients. Worldwide, the number of cut-and-sew Cox-maze procedures is extremely small in

82 relation to AF prevalence.

83

84 Less demanding methods for achieving some or all of the electrical blocks of the Cox-maze procedure use

85 energy sources (heat, cold or radiofrequency) to ablate atrial tissue: easier, quicker and safer, but costly.

86 Many cardiac surgery patients have AF. Whether they should routinely have adjunct AF surgery is unknown.

87 Current practice varies widely between surgeons and hospitals. AF surgery increases SR restoration rate and

88 decreases anti-arrhythmic medication use<sup>8-10</sup>. However, the impact on patient-relevant outcomes, such as

89 survival and health-related QoL (HRQoL) is uncertain. Cost-effectiveness analyses have mixed results<sup>11,12</sup>,

90 are limited by lack of HRQoL evidence in the short and medium term (1-5 years) and economic models are

91 not robust. Amaze aimed to evaluate clinical and HRQoL outcomes and cost-effectiveness of this technology

92 by comparing AF surgery as an adjunct to cardiac surgery with cardiac surgery alone.

## 93 **Methods**

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

### 97 *Patient recruitment*

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

### 103 *Randomisation*

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

### 108 *Blinding*

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

### 112 *Clinical management*

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

### 118 *Outcomes*

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

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

### 128 *Sample size*

129 AF surgery was considered effective if there was a significant impact on either 1-year SR rates or 2-year  
130 quality-adjusted survival. The target (200 patients per arm) was based on detecting a of 15% difference in  
131 the proportion of patients in SR at 1 year (45% versus 30%) or 1 additional month of quality-adjusted life  
132 (0.083 QALYs, standard deviation 0.3) over 2 years, with approximately 80% power, two-sided significance  
133 of 5% and up to 15% death/loss to follow-up. Because of slower-than-expected accrual, recruitment stopped  
134 at 352 patients (88% target) reducing the power to detect the proposed treatment effects to over 70% for  
135 primary outcomes. In order to guard against over-interpretation of hypothesis tests due to multiple  
136 testing we recommend that p-values between 0.025 and 0.05 are considered of borderline  
137 significance.

### 138 139 *Statistical analysis*

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

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

### 155 *Economic Analysis*

156 Resource use data from primary admission (time in theatre, intensive care and wards, hospital transfer,  
157 diagnostics and antiarrhythmic, antiplatelet, anticoagulant and cardiac drugs) were extracted from records,  
158 supplemented by patient-reported post-discharge health service use. Resources were valued using national  
159 estimates (<https://www.evidence.nhs.uk/formulary/bnf/current> ; <http://www.drugtariff.nhsbsa.nhs.uk> ;  
160 <http://www.pssru.ac.uk/project-pages/unit-costs/2015/> ; [https://www.gov.uk/government/publications/nhs-  
161 reference-costs-2014-to-2015/](https://www.gov.uk/government/publications/nhs-reference-costs-2014-to-2015/) ) literature (blood pressure monitoring and radiology)<sup>13, 14</sup> and data from  
162 Papworth Hospital (operating room and device cost). High intensity focussed ultrasound was costed at £3000  
163 and other methods at £1250. Type missingness was examined and replaced with mean or imputed values.  
164 Missing resource and utility data were imputed jointly using chained equations with predictive mean  
165 matching. Costs and QALYs were discounted at 3.5% in year two. Incremental cost-effectiveness ratios  
166 (ICERs) relied on seemingly unrelated regression, controlling for baseline differences in age, gender, EQ-  
167 5D-3L, AF and (for QALYs) the primary surgery. Probabilistic sensitivity analysis used bootstrapping. Cost-  
168 effectiveness planes, acceptability curve and incremental net monetary benefit were estimated. Deterministic  
169 sensitivity analysis explored the impact of using of SF-6D QALYs, complete case analysis, truncating costs  
170 and discharge QALYs, excluding outliers and alternative imputation strategies.

### 172 **Results**

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

176 randomisation (figure 1). One-year SR status was available for 141 maze (80%) and 145 control patients  
177 (82%), 2-year QALYs were known for 160 patients in each arm (91%). Loss-to-follow-up reasons were  
178 similar for the two groups (figure 1), which were also similar in demographics, symptomatic status,  
179 cardiovascular profile and operations performed (tables 1-2). The left atrial (LA) appendage was resected or  
180 excluded in 97 maze arm patients (55.1%) and in 53 control patients (30.1%)

181 *Primary outcome: sinus rhythm at 1 year*

182 Among cases with complete ECG data, 87 of 141 maze patients (61.7%) were in SR at 1 year versus 68 of  
183 145 (46.9%) controls (figure 2). In intention-to-treat analysis, the odds ratio (95%CI) for 1-year SR  
184 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  
185 120 randomised patients to 2.9 (0.9, 9.6) for the final 71 patients randomised in the last 18 months.

186 *Primary outcome: quality-adjusted life years*

187 The unadjusted, undiscounted mean (95%CI) QALY over 2 years was 1.489 (1.416, 1.558) for the maze arm  
188 and 1.485 (1.403, 1.559) in the control arm. In intention-to-treat analysis, the adjusted mean difference  
189 (95%CI) in QALYs at 2 years (maze – control) was  $-0.025$  ( $-0.129, 0.078$ ,  $p=0.6319$ ).

190 *Secondary outcomes*

191 At 2 years, 69 of 118 (58.5%) maze completers were in SR compared with 47 of 129 (36.4%) controls  
192 (figure 2). The adjusted odds ratio for SR at 2 years was 3.24 (95%CI 1.76, 5.96). Significantly fewer maze  
193 patients received anticoagulants from 6 months (appendix table A2) without a higher stroke rate: 13 strokes  
194 in 10 (5.7%) maze patients and 19 in 16 (9.1%) control patients; the difference of  $-3.4\%$  (95%CI  $-14.1\%$ ,  
195  $7.3\%$ ) was not significant (Fisher's Exact Test  $p=0.3083$ ), nor was the difference in stroke events between  
196 the two groups (log-linear model relative rate 0.68 (95%CI: 0.34, 1.39,  $p=0.292$ ). Stroke-free survival was  
197 similar in the two arms (HR=0.99, 95%CI 0.64, 1.53,  $p=0.949$ , figure 4). Fifteen patients (7 maze, 8  
198 control) already had permanent pacemakers at surgery. Maze did not increase the need for permanent  
199 pacemaker implantation after surgery (maze 15, control 17). Sixty (34.1%) maze patients required 65  
200 cardioversions and 67 (38.1%) control patients required 72 cardioversions. Immediate cardioversion success  
201 rates were similar (48/65 (73.8%) maze and 54/72 (75.0%) control). There was no significant difference in  
202 anti-arrhythmic drug use throughout follow-up (appendix table A2). There were no significant differences  
203 between the two arms in any of the following outcomes at any time point: NYHA, EQ-5D-3L and SF-36.



204 *Safety*

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

210 There were 330 adverse events in 100 AF surgery patients and 333 in 111 controls (each 60%). Of these 71  
211 (42.5%) maze and 84 (45.5%) control patients had at least one moderately severe event and 31 (18.6%)  
212 maze and 38 (20.5%) control patients had a severe event. Few events were 'possibly related' to treatment: 23  
213 in 17 maze patients (10.2%) and 28 in 19 control patients (10.3%); one patient admitted to hospital for atrial  
214 flutter (classified as 'definitely related' to treatment) was subsequently found to be in the control group.

215

216 *Subgroup analysis*

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

225

226 *Cost-effectiveness*

227 Higher maze costs resulted from the ablation device, length of stay in critical care and readmissions (table  
228 3). The adjusted mean incremental maze cost was £3533 (95% CI: £1321 to £5746), significantly higher  
229 than control (p<0.01). The adjusted mean QALY difference was not significant (-0.022, 95% CI: -0.1231 to  
230 0.0791, p=0.67, appendix table A3). No analyses suggested that maze was cost-effective at 2 years at £30,000

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

## 234 Discussion

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

241  
242 The optimal lesion set remains controversial. The full Cox-maze lesion set is established<sup>18</sup>, and if there is a  
243 ‘dose-response’ relationship, SR restoration rates should be better with a more complete lesion. One RCT of  
244 AF surgery in mitral patients found no significant difference in SR restoration between the complete lesion  
245 set and pulmonary vein isolation alone<sup>16</sup>, although it was probably insufficiently powered to detect such a  
246 difference. Many surgeons carry out only parts of the full Cox-maze, and there is a wide range of lesion sets  
247 used. Terminology is unhelpful with such procedures variously described as maze, mini-maze, left atrial  
248 maze or simply AF ablation. Amaze showed higher SR restoration rates with a complete LA lesion set  
249 including the mitral annulus or ‘isthmus’ lesion, but did demonstrate the benefit of adding RA lesions,  
250 although the power to detect these differences was low and adding such lesions has little impact on operative  
251 time or complexity above a full LA lesion set.

252  
253 We found no QoL impact at 2 years, but this is relatively short follow-up, and cardiac surgery alone achieves  
254 such an increase in QoL<sup>19</sup> that it may be difficult to discern additional benefits from AF surgery at this  
255 stage. Two factors may modify this conclusion in future: there was significantly less anticoagulation of maze  
256 patients postoperatively with no increase in stroke rate, and the HESTER study<sup>20</sup> showed LA contractile  
257 recovery in most but not all patients when maze restores SR. These results lend support to anticoagulation  
258 withdrawal when SR is restored after maze but the varying extent of LA contractile recovery suggests LA

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

261  
262 The per-patient cost over 2 years was higher in the maze arm with no significant impact on discounted  
263 QALYs. Deterministic and probabilistic sensitivity analyses confirmed this and the probability that maze  
264 would be cost-effective at 2 years was less than 5% and alternative assumptions do not alter this conclusion.

### 265 266 *Strengths and limitations*

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

274  
275 Recruitment is a widespread RCT problem. Logistic delays, activity overestimation and rising awareness of  
276 AF surgery among patients and clinicians affected recruitment rate. Infrequent follow-up (6, 12, 24 months)  
277 is associated with underreporting of frequent events, illness severity, and intensive service use, but there is  
278 no recommended interval between follow-ups<sup>21,22</sup>. In Amaze, 95% of the difference in follow-up costs  
279 related to re-admissions (infrequent major events) making cost underestimation unlikely. The cost-  
280 effectiveness analysis was limited to 2 years and may not reflect long-term benefits.

### 281 282 *Conclusion*

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

287

288

**289 Acknowledgements**

290 We are grateful to the NIHR Health Technology assessment programme for funding the trial. We  
291 acknowledge the work of Fay Cafferty, Mark Schulpher and Derek Todd who formed the data monitoring  
292 committee chaired by James Roxburgh. We thank Brian Elliott and Paul Kinnersley who participated in the  
293 Trial Steering Committee chaired by Dai Rowlands. We thank surgeons Haitham Abunasra, Simon Allen,  
294 Benjamin Bridgewater, Pedro Catarino, Stephen Clarke, John Dark, John Dunning, Leonidas Hadjinikolao,  
295 Jonathan Hyde, David Jenkins, Anthony de Souza, Stephen Large, Michael Lewis, Neil Moat, Narain  
296 Moorjani Suku Nair, Choo Ng, Rajesh Patel, Jacek Szostek, Augustine Tang, Graham Venn, John Wallwork,  
297 and Nizar Yonan who also recruited to the trial. The Papworth Trials Unit staff supported the design,  
298 recruitment, co-ordination, conduct, data management, analysis and quality assurance. We also thank Dr  
299 Hester Goddard for the trial set-up and grant application and Donna Alexander, for continuous support  
300 throughout.

301

**References**

1. Kannel WB, Wolf PA, Benjamin EJ, Levy D. Prevalence, incidence, prognosis, and predisposing conditions for atrial fibrillation: population-based estimates. *Am J Cardiol.* 1998;82(8A):2N-9N.
2. Hobbs FD, Fitzmaurice DA, Mant J, Murray E, Jowett S, Bryan S, Raftery J, Davies M, Lip G. A randomised controlled trial and cost-effectiveness study of systematic screening (targeted and total population screening) versus routine practice for the detection of atrial fibrillation in people aged 65 and over. The SAFE study. *Health technology assessment.* 2005;9(40):iii-iv, ix-x, 1-74. Epub 2005/10/06.
3. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke.* 1991;22(8):983-8. Epub 08/01.
4. Friberg L, Rosenqvist M, Lip GY. Evaluation of risk stratification schemes for ischaemic stroke and bleeding in 182 678 patients with atrial fibrillation: the Swedish Atrial Fibrillation cohort study. *Eur Heart J.* 2012;33(12):1500-10. Epub 2012/01/13.
5. Haïssaguerre M, Jaïs P, Shah DC, Takahashi A, Hocini M, Quiniou G, Garrique S, LeMouroux A, Le Métayer P, Clémenty J. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. *N Engl J Med.* 1998;339(10):659-66.
6. Cox JL, Schuessler RB, Cain ME, Corr PB, Stone CM, D'Agostino HJ, Harada A, Chang BC, Smith PK, Boineau JP. Surgery for atrial fibrillation. *Semin Thorac Cardiovasc Surg.* 1989;1(1):67-73.
7. Cox JL, Boineau JP, Schuessler RB, Kater KM, Lappas DG. Five-year experience with the maze procedure for atrial fibrillation. *Ann Thorac Surg.* 1993;56(4):814-23; discussion 23-4.
8. Damiano RJ, Schwartz FH, Bailey MS, Maniar HS, Munfakh NA, Moon MR, Schuessler RB. The Cox maze IV procedure: predictors of late recurrence. *J Thorac Cardiovasc Surg.* 2011;141(1):113-21.
9. Weimar T, Bailey MS, Watanabe Y, Marin D, Maniar HS, Schuessler RB, Damiano RJ Jr. The Cox-maze IV procedure for lone atrial fibrillation: a single center experience in 100 consecutive patients. *J Interv Card Electrophysiol.* 2011;31(1):47-54. Epub 2011/02/22.
10. Ware JE. SF-36 health survey : manual and interpretation guide. Lincoln, R.I.: QualityMetric Inc.; 2000.

- 328 11. Van Breugel HN, Nieman FH, Accord RE, Van Mastrigt GA, Nijs JF, Severens JL, Vrakking R,  
329 Maessen JG. A prospective randomized multicenter comparison on health-related quality of life: the value of  
330 add-on arrhythmia surgery in patients with paroxysmal, permanent or persistent atrial fibrillation undergoing  
331 valvular and/or coronary bypass surgery. *J Cardiovasc Electrophysiol*. 2010;21(5):511-20. Epub  
332 2009/11/17.
- 333 12. Gillinov AM, Argenziano M, Blackstone EH, Iribarne A, DeRose JJ, Ailawadi G, Russo MJ,  
334 Ascheim DD, Parides MK, Rodriguez E, Bouchard D, Taddei-Peters WC, Geller NL, Acker MA, Gelijns  
335 AC. Designing comparative effectiveness trials of surgical ablation for atrial fibrillation: experience of the  
336 Cardiothoracic Surgical Trials Network. *J Thorac Cardiovasc Surg*. 2011;142(2):257-64.e2. Epub  
337 2011/05/25.
- 338 13. Lovibond K, Jowett S, Barton P, Caulfield M, Heneghan C, Hobbs FD, Hodgkinson J, Mant J,  
339 Martin U, Wonderling D, McManus RJ. Cost-effectiveness of options for the diagnosis of high blood  
340 pressure in primary care: a modelling study. *Lancet*. 2011;378(9798):1219-30.
- 341 14. Auguste P, Barton P, Hyde C, Roberts TE. An economic evaluation of positron emission  
342 tomography (PET) and positron emission tomography/computed tomography (PET/CT) for the diagnosis of  
343 breast cancer recurrence. *Health Technol Assess*. 2011;15(18):iii-iv, 1-54.
- 344 15. Huffman MD, Karmali KN, Berendsen MA, Andrei AC, Kruse J, McCarthy PM, Malaisrie SC.  
345 Concomitant atrial fibrillation surgery for people undergoing cardiac surgery. *Cochrane Database Syst Rev*.  
346 2016(8):CD011814.
- 347 16. Gillinov AM, Gelijns AC, Parides MK, DeRose JJ, Moskowitz AJ, Voisine P, Ailawadi G,  
348 Bouchard D, Smith PK, Mack MJ, Acker MA, Mullen JC, Rose EA, Chang HL, Puskas JD, Couderc JP,  
349 Gardner TJ, Varghese R, Horvath KA, Bolling SF, Michler RE, Geller NL, Ascheim DD, Miller MA,  
350 Bagiella E, Moquete EG, Williams P, Taddei-Peters WC, O'Gara PT, Blackstone EH, Argenziano M; CTSN  
351 Investigators.. Surgical ablation of atrial fibrillation during mitral-valve surgery. *N Engl J Med*.  
352 2015;372(15):1399-409.
- 353 17. Yoo JS, Kim JB, Ro SK, Jung Y, Jung SH, Choo SJ, Lee JW, Chung CH. Impact of concomitant  
354 surgical atrial fibrillation ablation in patients undergoing aortic valve replacement. *Circ J*. 2014;78(6):1364-  
355 71. Epub 2014/03/26.

- 356 18. Badhwar V, Rankin JS, Damiano RJ, Gillinov AM, Bakaeen FG, Edgerton JR, Philpott  
357 JM, McCarthy PM, Bolling SF, Roberts HG, Thourani VH, Suri RM, Shemin RJ, Firestone S, Ad N. The  
358 Society of Thoracic Surgeons 2017 Clinical Practice Guidelines for the Surgical Treatment of Atrial  
359 Fibrillation. *Ann Thorac Surg.* 2017;103(1):329-41.
- 360 19. Grady KL, Lee R, Subačius H, Malaisrie SC, McGee EC, Kruse J, Goldberger JJ, McCarthy PM.  
361 Improvements in health-related quality of life before and after isolated cardiac operations. *Ann Thorac Surg.*  
362 2011;91(3):777-83.
- 363 20. Abu-Omar Y, Thorpe, BS, Freeman C, Mills C, Stoneman VEA, Gopalan D, Rana B, Spt TJ,  
364 Sharples LD, Nashef SAM. Recovery of left atrial contractile function after maze surgery in persistent  
365 longstanding atrial fibrillation. *J Am Coll Cardiol* 2017; 70:2309-11  
366
- 367 21. Johnston K, Buxton MJ, Jones DR, Fitzpatrick R. Assessing the costs of healthcare technologies in  
368 clinical trials. *Health Technol Assess.* 1999;3(6):1-76.
- 369 22. Ridyard CH, Hughes DA. Methods for the collection of resource use data within clinical trials: a  
370 systematic review of studies funded by the UK Health Technology Assessment program. *Value Health.*  
371 2010;13(8):867-72.

372

373

374

375

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.

	<b>Maze (n=176)</b>	<b>Control (n=176)</b>	<b>Total (n= 352)</b>
<b>Age (years)</b>			
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)
<b>Sex</b>			
male (%)	112 (63.6%)	120 (68.2%)	232 (65.9%)
female (%)	64 (36.4%)	56 (31.8%)	120 (34.1%)
<b>Body mass index</b>			
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)
<b>Logistic EuroSCORE (%)</b>			
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)
<b>CCS Class</b>			
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%)
<b>NYHA classification</b>			
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%)

379

380



381 **Table 2.** Cardiovascular status at baseline of patients randomised in the Amaze trial  
 382 (LVEF: left ventricular ejection fraction, MI: myocardial infarction, PCI: percutaneous coronary intervention, MVR:  
 383 mitral valve repair or replacement; CABG: coronary artery bypass grafting; AVR: aortic valve replacement

	<b>Maze</b> <b>(n=176)</b>	<b>Control</b> <b>(n=176)</b>	<b>Total</b> <b>(n=352)</b>
<b>Left ventricular function</b>			
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%)
<b>Previous PCI</b>	16 (9.1%)	14 (8.0%)	30 (8.5%)
<b>Congestive Cardiac Failure</b>	5 (2.8%)	1 (0.6%)	6 (1.7%)
<b>Diabetes</b>			
Insulin-dependent	5 (2.8%)	7 (4.0%)	12 (3.4%)
Non-insulin-dependent	27 (15.3%)	17 (9.7%)	44 (12.5%)
<b>Hyperlipidaemia</b>	70 (39.8%)	63 (35.8%)	133 (37.8%)
<b>Atrial fibrillation class</b>			
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%)
<b>Atrial fibrillation history</b>			
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%)
<b>Permanent pacemaker</b>	7 (4.0%)	8 (4.5%)	15 (4.3%)
<b>Previous cardioversion</b>	24 (13.6%)	23 (13.1%)	47 (13.4%)
<b>Previous ablation</b>	3 (1.7%)	1 (0.6%)	4 (1.1%)
<b>Other arrhythmias</b>	2 (1.1%)	2 (1.1%)	4 (1.1%)
<b>Anticoagulants</b>	137 (77.8%)	137 (77.3%)	274 (77.6%)
<b>Anti-arrhythmics</b>	145 (82.4%)	148 (84.1%)	293 (83.2%)
<b>Actual procedure category</b>			
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
	<i>Sub total</i>	<i>£14,847</i>	<i>£12,474</i>	<i>£11,404</i>	<i>£7194</i>	<i>£3,443</i>
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
	<i>Sub total</i>	<i>£3,217</i>	<i>£5,629</i>	<i>£2,757</i>	<i>£4,329</i>	<i>£460</i>
Grand Total		£18,681	£13,340	£14,842	£8,295	£3,839

385

386

387

**Figure legends**

388

**Figure 1.**

389 Patient flow through the Amaze trial

391

392

**Figure 2.**

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

395

396

**Figure 3.**

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

399

400

**Figure 4.**

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

403

404

**Figure 5.**405 Forest plot showing the odds ratio of sinus rhythm restoration at one year after randomisation for predefined  
406 subgroups in the Amaze trial

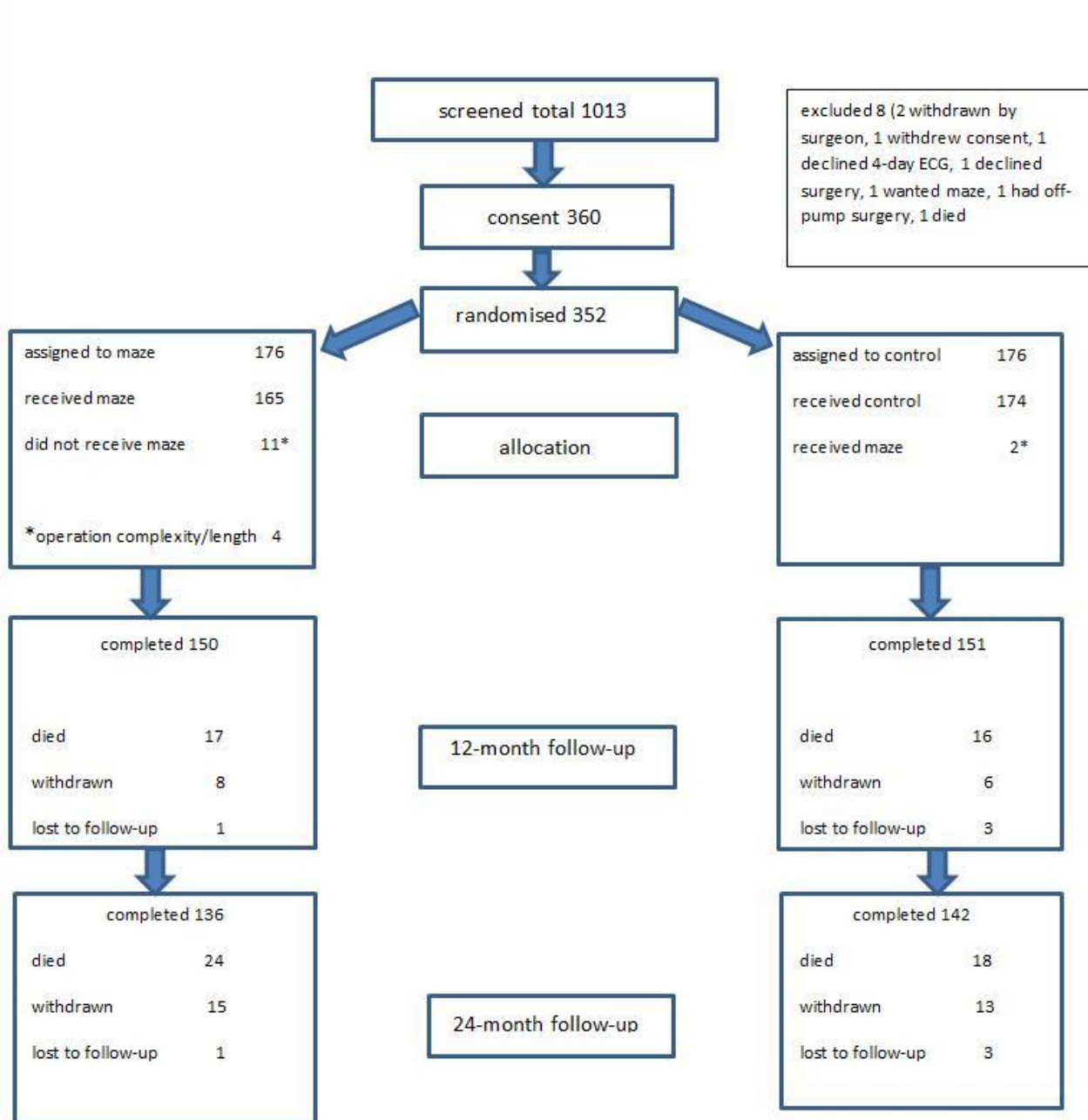
408

409

410

**Figures**

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



413

414

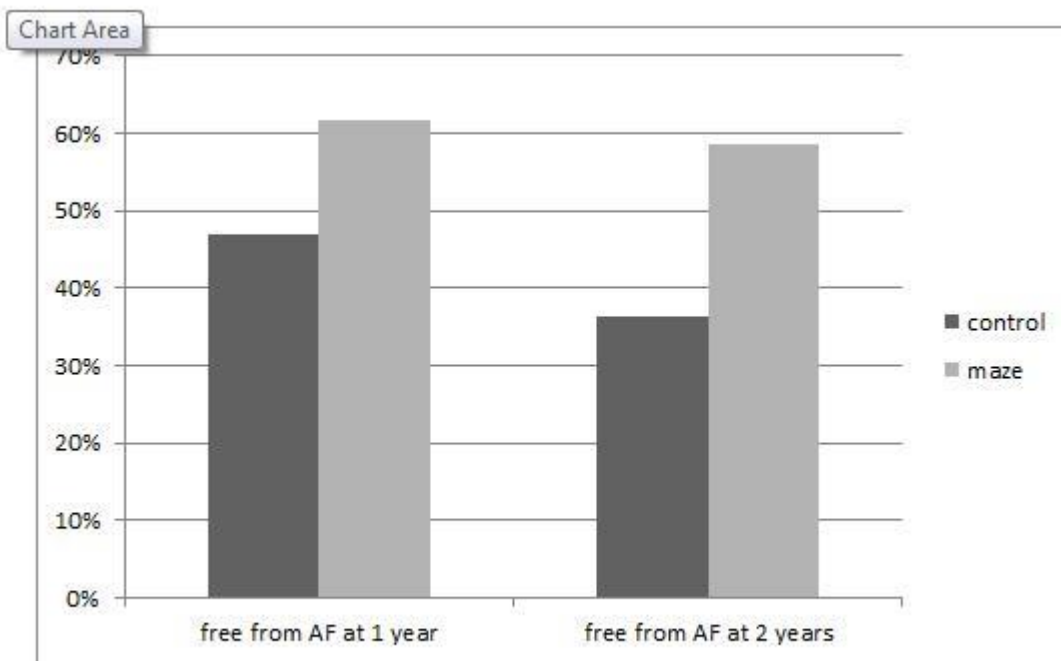
415 **Figure 2.** Percentage of patients in sinus rhythm free from atrial fibrillation at 1 year and 2 years after  
416 randomisation

417

418

419

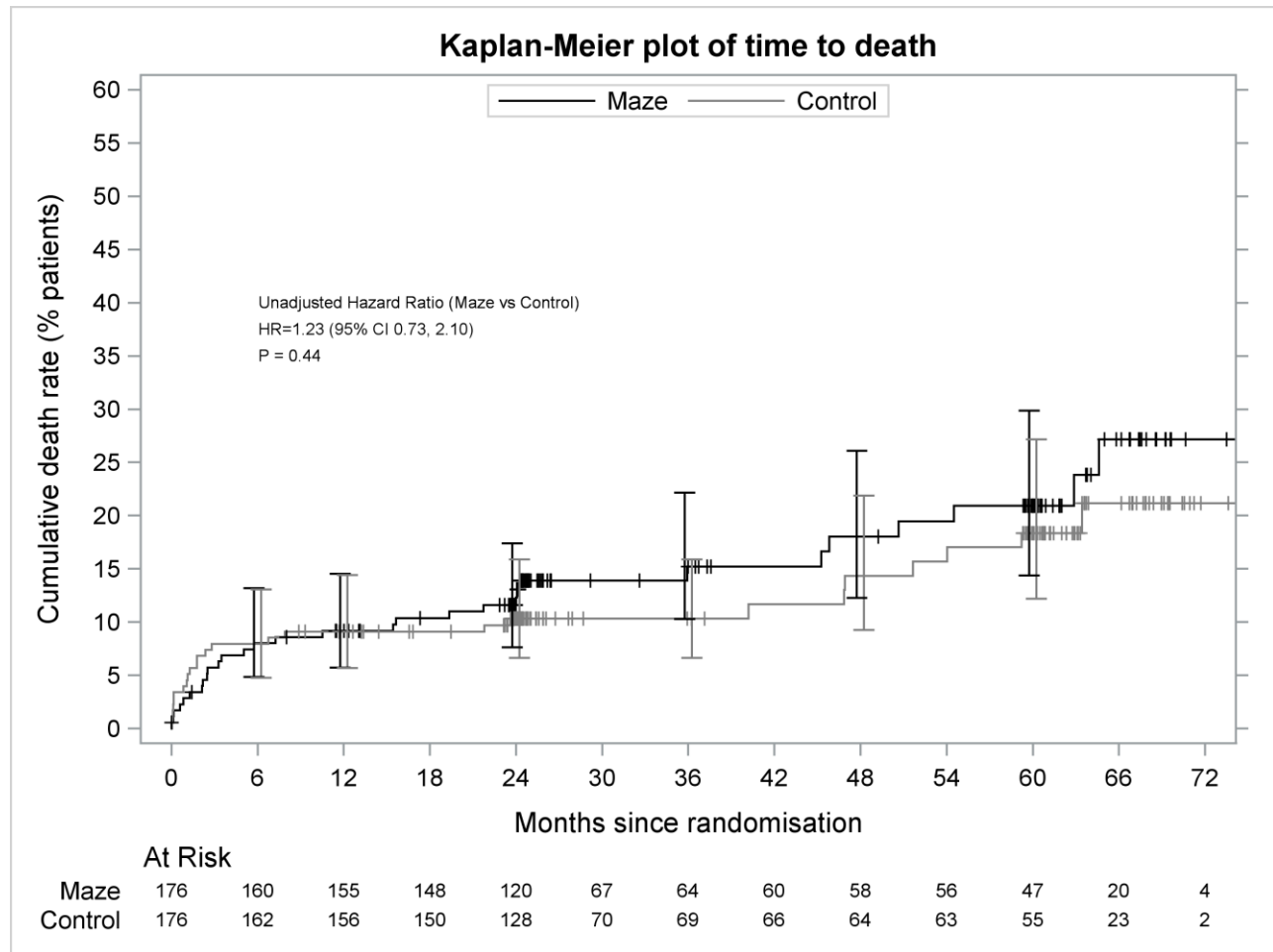
420



421

422

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

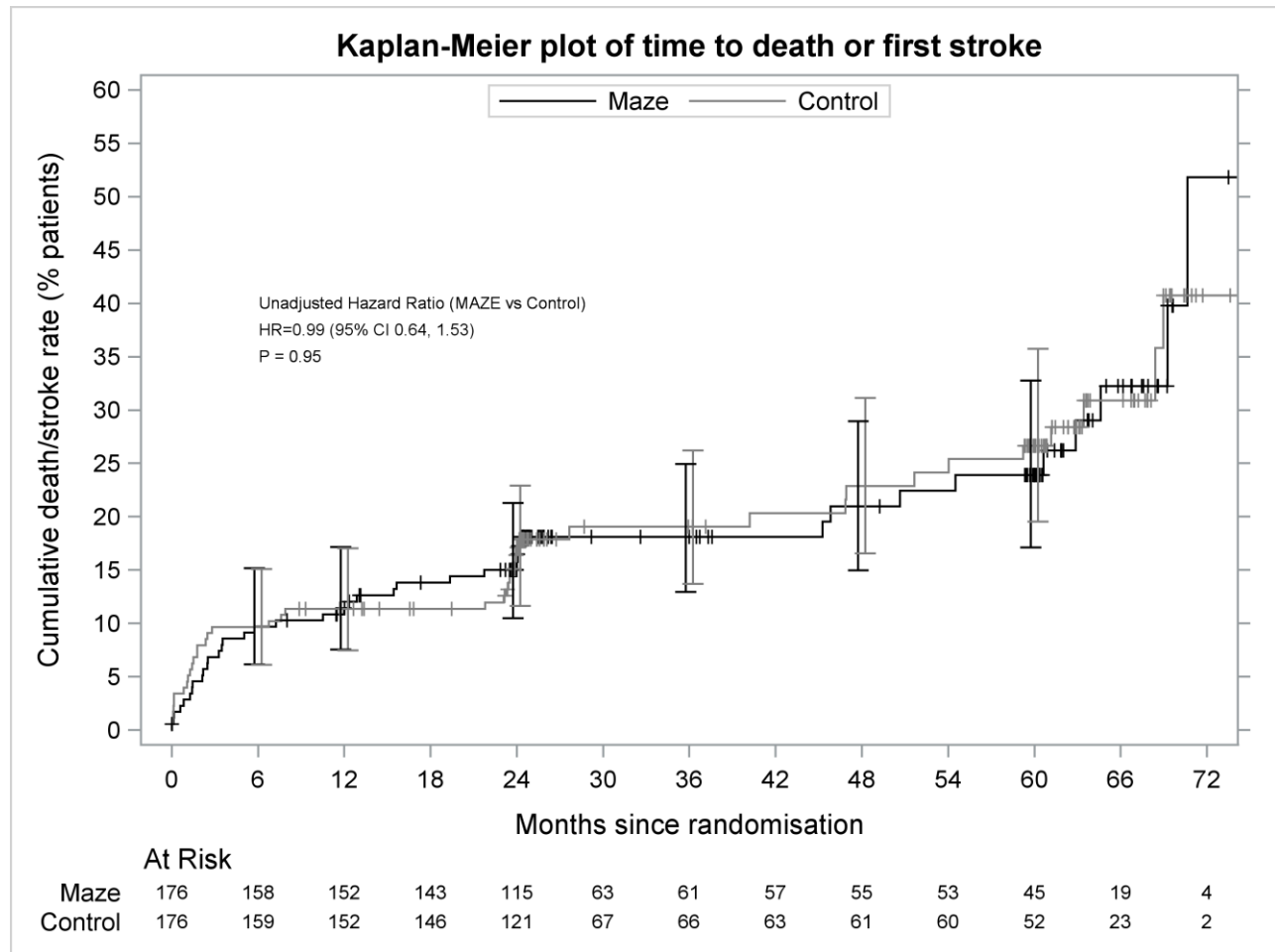


426

427

428

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



430

431

432

433

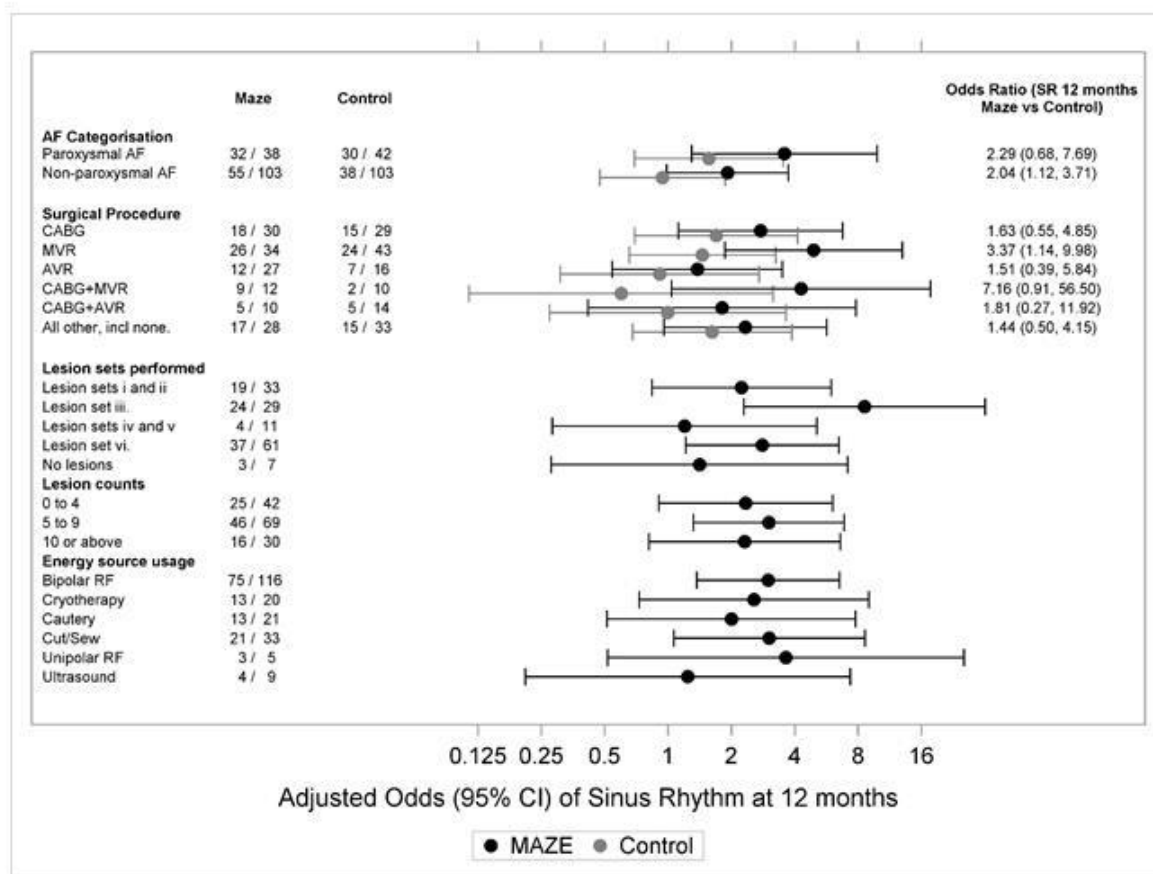
434

435

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



438