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ORIGINAL ARTICLE

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Five-year results of Amaze: a randomized controlled trial of adjunct surgery for atrial fibrillation

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Key question

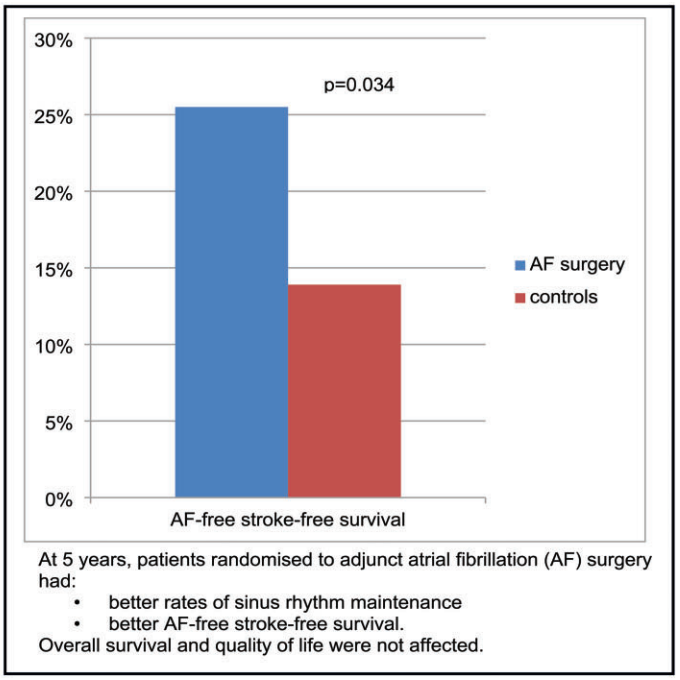
Does adjunct atrial fibrillation surgery have an impact on outcomes that matter to patients at 5 years?

Key finding(s)

Sinus rhythm rate and survival free of stroke or atrial fibrillation were better after atrial fibrillation surgery.

Take-home message

These are encouraging results, but more research is needed to determine the impact on overall survival and quality of life.



At 5 years, patients randomised to adjunct atrial fibrillation (AF) surgery had:

- better rates of sinus rhythm maintenance
- better AF-free stroke-free survival.

Overall survival and quality of life were not affected.

Abstract

OBJECTIVES: The Amaze trial showed that adding atrial fibrillation (AF) surgery to cardiac operations increased return to sinus rhythm (SR) without impact on quality of life or survival at 2 years. We report outcomes to 5 years.

METHODS: In a multicentre, phase III, pragmatic, double-blind, randomized controlled superiority trial, cardiac surgery patients with >3 months of AF were randomized 1:1 to adjunct AF surgery or control. Primary outcomes of 1-year SR restoration and 2-year quality-adjusted survival were already reported. This study reports on rhythm, survival, quality-adjusted survival, stroke, medication and safety to 5 years.

RESULTS: Between 2009 and 2014, 352 patients were randomized. By 5 years 79 died, 58 withdrew, 34 were lost to follow-up and the remaining 182 provided data. AF surgery significantly increased the odds of remaining in SR at 5 years {odds ratio = 2.98 [95% confidence interval (CI) 1.23, 7.17], $P = 0.015$}. There was a non-significant decrease in stroke incidence [odds ratio = 0.605 (95% CI 0.284, 1.287), $P = 0.19$], but no improved survival [5-year survival: AF surgery 77.3% (95% CI 71.1%, 83.5%), controls 77.8% (95% CI 71.7%, 84.0%), $P = 0.85$]. Quality-adjusted survival difference was negligible (-0.03; 95% CI -0.33, 0.27, $P = 0.85$). The composite of survival free of stroke and AF was better in the AF surgery group [odds ratio = 2.34 (95% CI 1.03, 5.31)]. There were no other differences.

CONCLUSIONS: Adjunct AF surgery confers a higher rate of SR to 5 years and a better composite outcome of survival free of stroke and AF but has no impact on overall or quality-adjusted survival or other clinical outcomes.

Clinical trial registration number: ISRCTN82731440.

Keywords: Randomised trial • Atrial fibrillation • Ablation • Cardiac surgery • Long term • Effectiveness

ABBREVIATIONS

AF	Atrial fibrillation
CI	Confidence interval
NYHA	New York Heart Association
OR	Odds ratio
QoL	Quality of life
QALYs	Quality-adjusted life years
SR	Sinus rhythm

BACKGROUND

Atrial fibrillation (AF) is the most prevalent arrhythmia in patients undergoing cardiac surgery [1]. In addition, patients with AF are at increased risk of stroke and are treated with anti-coagulants, with associated increase in the risk of bleeding, including bleeds related to cerebrovascular events [2]. AF surgery using radiofrequency, cryotherapy and other energy sources is increasingly used during cardiac surgery to block abnormal electrical signals and correct AF [3, 4].

In the Amaze multicentre randomized controlled trial, 352 non-emergency cardiac surgery patients were randomized to either planned cardiac surgery with adjunct AF surgery or planned cardiac surgery alone, to assess whether treating AF in this way increased the probability of restoring sinus rhythm (SR), improved long-term survival and quality of life (QoL) and increased cost-effectiveness [5]. The trial showed that adding AF surgery significantly increased the probability of SR restoration but did not significantly affect survival, QoL or stroke incidence at 2 years after surgery [5, 6]. However, the associated HESTER study showed that most people for whom SR was restored had good recovery of atrial contractile function, suggesting that survival, QoL and other clinical benefits may accrue over time [7]. This study presents the results of 5-year follow-up of Amaze trial participants to assess whether the early increase in SR restoration was maintained and whether it resulted in longer-term survival and QoL improvements.

METHODS

Ethics statement

This study was approved by the NHS Health Research Authority (reference number 08/H0301/98) and written informed consent was obtained from all participants. Amaze was a phase III, pragmatic, multicentre, double-blind, parallel-arm, randomized controlled superiority trial in 11 UK cardiac surgical centres, coordinated by Papworth Hospital. Thirty participating consultant cardiac surgeons had at least 2 years' prior experience in AF surgery. Full details of trial methods and results up to 2 years follow-up have been published [5, 6], as has the HESTER study, which looked at atrial contractility after SR restoration [7].

Briefly, adult elective or urgent cardiac surgery patients with >3-month documented AF were randomized on the day of surgery to either the planned cardiac procedure alone (control arm) or planned cardiac procedure with adjunct AF surgery (experimental arm). All major cardiac surgery requiring cardiopulmonary bypass was included (valve, coronary, combined and others). Patients, cardiologists assessing ECG results and researchers collecting QoL outcomes were unaware of the treatment arm. Surgeons followed local surgery and perioperative management protocols and decided on the ablation method and lesion set. Subsequent management, including follow-on cardioversion, was identical in both arms.

In the Amaze trial, SR restoration at 1 year after surgery and quality-adjusted life years (QALYs) over 2 years were joint primary outcomes [6]. In the trial analysis to 2 years, 93.2% of patients were either wholly in SR or wholly in AF during 4-day continuous ECG recordings and most others were close to these extremes, suggesting that the predominant cardiac rhythm, be it SR or AF, was stable in the overwhelming majority of patients [5]. Therefore, SR restoration at 5 years was assessed by single ECG read by cardiologists unaware of the treatment arm. Five-year QALYs were calculated from serial utility measurements from the UK population valuation of the EuroQoL EQ-5D-3 l, completed at randomization, discharge, 6 weeks, 6 months and 1, 2 and 5 years postoperatively. QALYs were estimated using the area under the curve method.

Secondary outcomes were survival, stroke incidence, antiarrhythmic and anticoagulant drug usage, permanent pacemaker implantation and cardioversion and New York Heart Association (NYHA) dyspnoea index at 5 years. Definitions of these outcomes have been published [5, 6]. We also analysed beneficial outcome (at each time point) defined as the composite of alive, in SR and stroke free as follows:

- zero if the patient died or had a stroke before the follow-up time, or if the ECG identified AF, atrial flutter or atrial tachycardia;
- one if the patient survived and was stroke-free up to the follow-up time, and if the ECG demonstrated SR (including 1 patient with 'Junctional rhythm' recorded); and
- missing if a patient withdrew or was lost to follow-up and did not have stroke or recorded AF prior to the assessment time point.

All participating patients gave informed consent to the follow-up study and were free to withdraw at any time.

Statistical analysis

Analysis was by intention to treat, with patients analysed according to the original random allocation. Repeated measurement of return to SR was summarized as frequencies in each of the 2 treatment arms (AF surgery and control). These longitudinal measurements were analysed using generalized linear mixed

models with a logistic link, with SR status (1 if in SR and 0 if in AF) taken as the response variable [8, 9]. We included trial arm, baseline covariates used to stratify randomization (SR on pre-operative ECG and procedure type), follow-up time and treatment-by-time interaction as fixed effects, and participants and surgeon as random effects. The adjusted effect of adjunct AF surgery on rhythm at each time point was extracted from this model. Initially, only patients and follow-up times with an assessment were included, referred to as 'Complete Case' analysis. Analyses were repeated using multivariate imputation by chained equation for missing data [10, 11]. The composite beneficial outcome was analysed using the same methods.

Responses from EQ-5D-3 l questionnaire were converted to utility scores for the UK population [12]. Analysis was completed for (i) patients who were alive at each time point only and (ii) after zeroes were imputed for people who died and missing utilities were multiply imputed using multivariate imputation by chained equation for survivors. Five-year QALYs were estimated by the area under the curve method. Patients who did not complete baseline EQ-5D-3 l questionnaires, or only completed 1 post-surgery questionnaire were excluded from this analysis (7%). Comparisons between AF surgery and control arms were taken from linear mixed models for QoL, analogous to those for SR.

Survival analysis used Kaplan–Meier curves, the log-rank test and Cox proportional hazards models (adjusted for age, baseline utility score and procedure). Censoring time was either the date of completing 5-year follow-up, the date of death, the date of withdrawal or the date of loss to follow-up.

Stroke incidence was summarized as total number of events during follow-up divided by the total follow-up time in each group. Groups were compared using negative binomial regression models. For other secondary outcome comparisons, Fisher's exact test was used.

We used the R version 3.6.3 for all analyses [13].

RESULTS

Patient recruitment and retention

Between February 2009 and March 2014, 352 patients were randomized (176 each) to AF surgery or control arms (Fig. 1). The mean (standard deviation) age was 71.9 (7.7) years, and 232 (65.9%) were men. As previously reported, 11 AF surgery patients did not receive their allocated treatment and 2 controls did have AF surgery [5, 6].

By November 2019, 182 patients completed the 5-year follow-up visit (AF surgery 92; control 90). Of these, 139 (39.4%) and 182 (51.7%) had data on the primary outcomes of return to SR and QoL, respectively. The other 170 patients either died (79), withdrew (57) or were lost to follow-up (34). In total, AF surgery patients had 728.7 patient-years of follow-up and control patients had 758.4 patient-years.

Primary outcome: sinus rhythm

Although all patients had a history of AF, 62 (18.1%) were in SR at the baseline ECG (Table 1), of whom 55 (88.7%) had paroxysmal AF. This compares with 34 (12.1%) paroxysmal patients in 280 patients with AF on the baseline ECG. The proportion returning to SR increased after the procedure but decreased over time thereafter. Of the patients with ECGs available at 5 years, 28/72 (38.9%) in the AF surgery group and 15/67 (22.4%) in the control group were in SR ($P = 0.044$, Fisher's exact test, Fig. 2). Unadjusted odds ratio (OR) for return to SR at 5 years for AF surgery patients (relative to controls) was 2.21 [95% confidence interval (CI) 1.048, 4.645, $P = 0.037$].

Composite (beneficial) outcome: freedom from atrial fibrillation, *death or stroke*

Of the patients with a composite outcome assessment, 28/110 (25.5%) AF surgery patients and 15/108 (13.9%) control patients had a beneficial outcome at 5 years ($P = 0.041$ Fisher's exact test). Unadjusted OR for a beneficial outcome at 5 years for AF surgery patients (relative to controls) was 2.12 (95% CI 1.058, 4.237, $P = 0.034$).

Over the 5-year follow-up, the number of patients with available measurements dropped by almost 20 per year for SR and 12 per year for the composite outcome. Compared to controls, AF surgery patients had ∼3 times the odds of being in SR and twice the odds of a beneficial outcome at 5 years (Table 2). The increase in odds of return to SR and for a beneficial composite outcome for AF surgery was significant at all time points and for both complete case and missing data analyses. Full adjusted models are in Supplementary Material, Tables S1–S4.

Intra-class correlation coefficient estimates the proportion of variation in outcomes related to differences between surgeons, which is not accounted for by other variables in the analysis. This indicated that around 18–20% of the total variation in SR maintenance at 5 years resulted from surgeon differences.

Primary outcome: quality-adjusted life years

At least 2 measures of QoL were available for 93.7% of AF surgery and 93.2% of control patients. There were no significant differences in QoL at any point during follow-up and this applies to survivors and after imputing missing data, including zero for patients who died (Fig. 3 and Supplementary Material, Table S5).

In the imputed data, the mean (standard deviation) QALYs over 5 years were estimated as 3.37 (1.52) for AF surgery patients and 3.42 (1.53) for controls. Adjusted for baseline utility, procedure and surgeon effects, AF surgery and control QALYs were not significantly different (mean difference -0.03; 95% CI -0.33, 0.27), $P = 0.8498$). Full model results are in Supplementary Material, Table S6.

Overall survival

Forty AF surgery patients and 39 controls died during follow-up. Kaplan–Meier estimates showed high risk of death within the first 3 months after surgery, followed by more gradual decrease in survival thereafter (Fig. 4). Differences overall were not significant

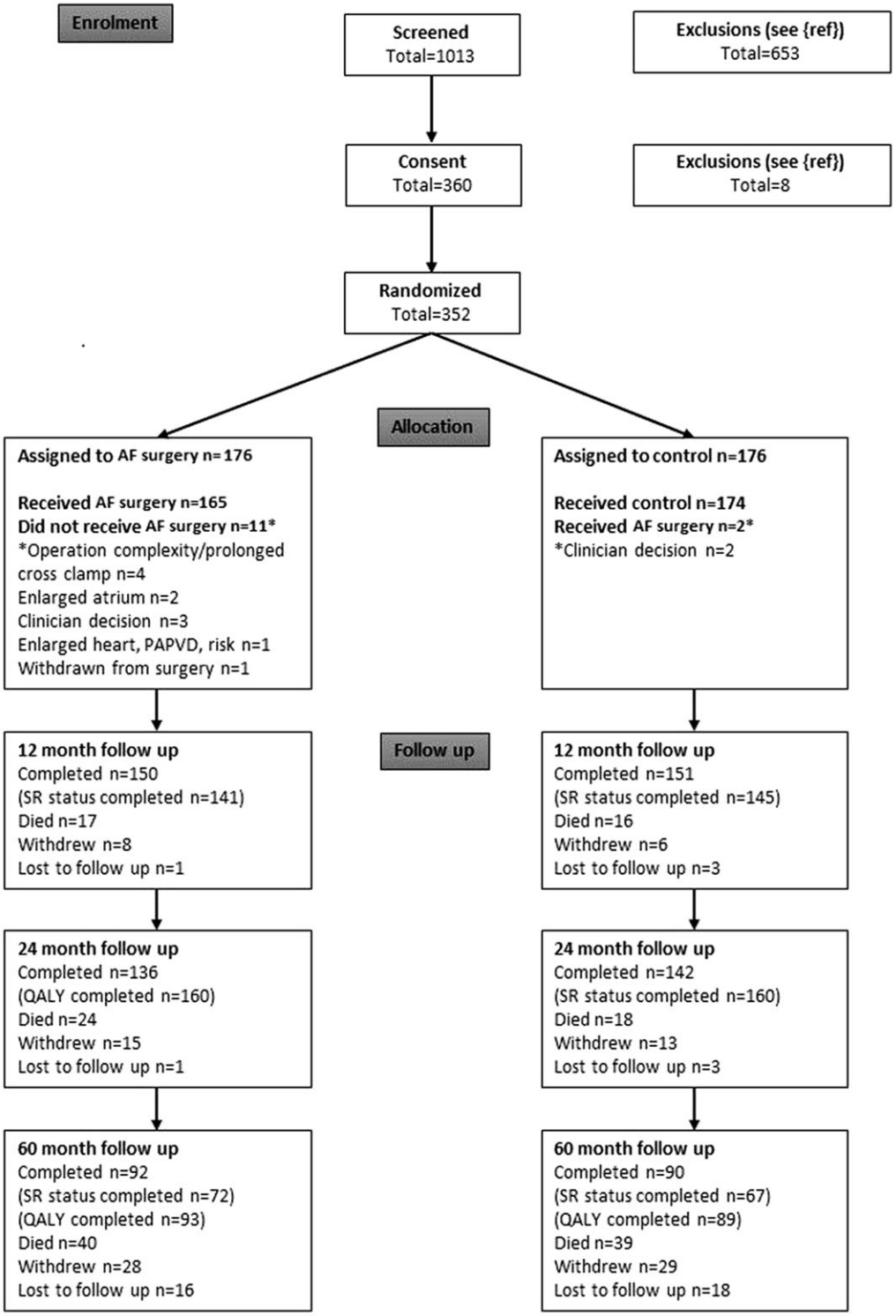


Figure 1: Patient flow through the Amaze trial up to 5 years (1 patient did not complete the follow-up study but did provide the available quality of life data before deciding on withdrawal).

(log-rank test $p = 0.85$). The percentage of survivors at 5 years was virtually identical in the 2 groups [77.3% (95% CI 71.1%, 83.5%) for AF surgery patients and 77.8% (95% CI 71.7%, 84.0%) for controls]. Adjusting for age, baseline QoL and procedures, there was no difference in survival between the groups [hazard ratio 1.048 (95% CI: 0.67, 1.64, $P = 0.84$].

Stroke

Fewer AF surgery patients than controls had strokes (12 vs 19, $P = 0.26$, Fisher's exact test). The OR for stroke in ablation patients, compared to controls, was 0.605 [95% CI 0.284, 1.287, $P = 0.19$]. Approximately half the strokes (7/12 AF surgery, 9/19 control) occurred between 2 and 5 years.

Table 1: Number of patients in sinus rhythm by time period after surgery

	AF surgery ($n = 176$)	Control ($n = 176$)	Total ($n = 352$)
SR at baseline			
Yes, *n* (%)	30 (17.5)	32 (18.7)	62 (18.1)
No, *n* (%)	141 (82.5)	139 (81.3)	280 (81.9)
Missing,[a] *n*	5	5	10
SR at 1 year			
Yes, *n* (%)	87 (61.7)	68 (46.9)	155 (54.2)
No, *n* (%)	54 (38.3)	77 (53.1)	131 (45.8)
Missing, *n*	35	31	66
SR at 2 years			
Yes, *n* (%)	69 (58.5)	47 (36.4)	116 (47.0)
No, *n* (%)	49 (41.5)	82 (63.6)	131(53.0)
Missing, *n*	58	47	105
SR at 5 years			
Yes, *n* (%)	28 (38.9)	15 (22.4)	43 (30.9)
No, *n* (%)	44 (61.1)	52 (77.6)	96 (69.1)
Missing, *n*	104	109	213

[a]Ten baseline scans could not be analysed due to technical problems.
AF: atrial fibrillation; SR: sinus rhythm.

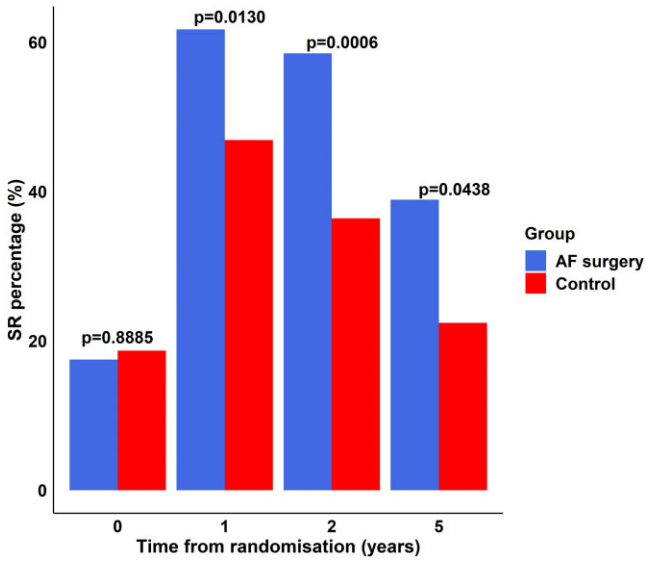


Figure 2: Patients who are in sinus rhythm at each time point, by treatment arm, as a percentage of the number of the patients with available ECG data.

The number of strokes reported during follow-up was also lower for AF surgery patients than controls (15 vs 24 strokes). Adjusting for length of follow-up, the stroke rate per year was 1.6% after AF surgery and 2.5% for controls. AF surgery patients thus had 0.625 times the rate of stroke of control patients (95% CI 0.293, 1.331, $P = 0.22$).

New York Heart Association

NYHA classification over 5 years was very similar in the 2 trial arms, with no significant differences between groups at any time point (Supplementary Material, Table S7).

Anti-arrhythmia and anticoagulant drug use

Information about anti-arrhythmic drug usage (including beta-blockers, digoxin, sotalol, amiodarone, flecainide, propafenone and 'others') and anti-coagulants (including warfarin, sinthrome, phenindione and 'others') was reported by 92 ablation and 90 control patients at 5 years. Of these, 69 (75.0%) AF surgery patients and 64 (71.1%) controls were prescribed anti-arrhythmics ($P = 0.62$), whilst 63 (68.5%) and 69 (76.7%) were prescribed anti-coagulants ($P = 0.25$).

Cardioversion and pacemaker insertion

Up to 5 years, 17 (9.7%) AF surgery patients and 23 (13.1%) controls reported implantation of a permanent pacemaker ($P = 0.40$, Fisher's exact test), whilst 60 (34.1%) and 67 (38.1%), respectively, reported cardioversion ($P = 0.51$). Because patients have varying follow-up times, these numbers may be underestimated and results should be interpreted cautiously.

DISCUSSION

Summary of results

We investigated the long-term effect on clinical outcomes and QoL of AF surgery as an adjunct to elective or urgent cardiac surgery based on 5-year follow-up data. Although the proportion of patients in SR decreased over time for both arms, AF surgery significantly increased the odds of remaining in SR up to 5 years after operation. Moreover, AF surgery significantly increased the odds of a beneficial outcome, defined as the composite of survival, in SR and free of stroke.

Surviving patients maintained a similarly high level of QoL in both groups, although estimated average utility decreased after adjusting for deaths. Survival, stroke incidence, NYHA class, anti-arrhythmic or anticoagulant drug usage, permanent pacemaker insertion and cardioversion did not differ significantly between the AF surgery and control arms at any point in the 5-year follow-up period.

Strengths and limitations

Only half of the recruited patients completed the 5-year follow-up due to patient death, withdrawal and loss to follow-up. Despite this, we demonstrated the positive effect of AF surgery on SR and the composite of SR, survival and freedom from stroke. All patients contributed to survival estimates and over 93% contributed to calculation of QoL during at least part of the follow-up. Because the proportion of patients who withdrew/were lost to follow-up was similar in the 2 groups (Fig. 1) and results were not sensitive to different ways of addressing missing data, it is unlikely that group comparisons were biased. However, there was reduced power to detect potential treatment effects on other outcomes and we cannot rule out small effects. Furthermore, subgroup analyses by different AF types were not feasible.

It is likely that a more complete lesion set, especially the LA lesions, will lead to higher rates of SR restoration. The original Amaze trial was a 'real-world' study, in which surgeons carried out AF surgery in the way they normally did it, with no restriction

Table 2: Adjusted odds ratios comparing ablation and control arms for return to sinus rhythm and for the composite outcome by time period post procedure for patients with complete data only and after multiple imputation of missing data

Analysis types[a]	Follow-up time	OR (95% CI)	*P*-Value
Complete case analysis for return to SR	One year	2.35 (1.36, 4.05)	0.002
	Two years	3.36 (1.84, 6.13)	<0.001
	Five years	2.98 (1.23, 7.17)	0.015
Missing data analysis for return to SR	One year	2.48 (1.45, 4.25)	0.001
	Two years	3.69 (2.02, 6.75)	<0.001
	Five years	3.00 (1.28, 7.03)	0.012
Complete case analysis for the composite outcome	One year	1.96 (1.19, 3.24)	0.009
	Two years	2.37 (1.37, 4.09)	0.002
	Five years	2.34 (1.03, 5.31)	0.042
Missing data analysis for the composite outcome	One year	1.89 (1.16, 3.08)	0.009
	Two years	2.29 (1.36,3.85)	0.002
	Five years	1.86 (1.01, 3.43)	0.047

[a]Analysis based on 502 and 512 ECG measurements from ablation and control patients respectively.
CI: confidence interval; OR: odds ratio; SR: sinus rhythm.

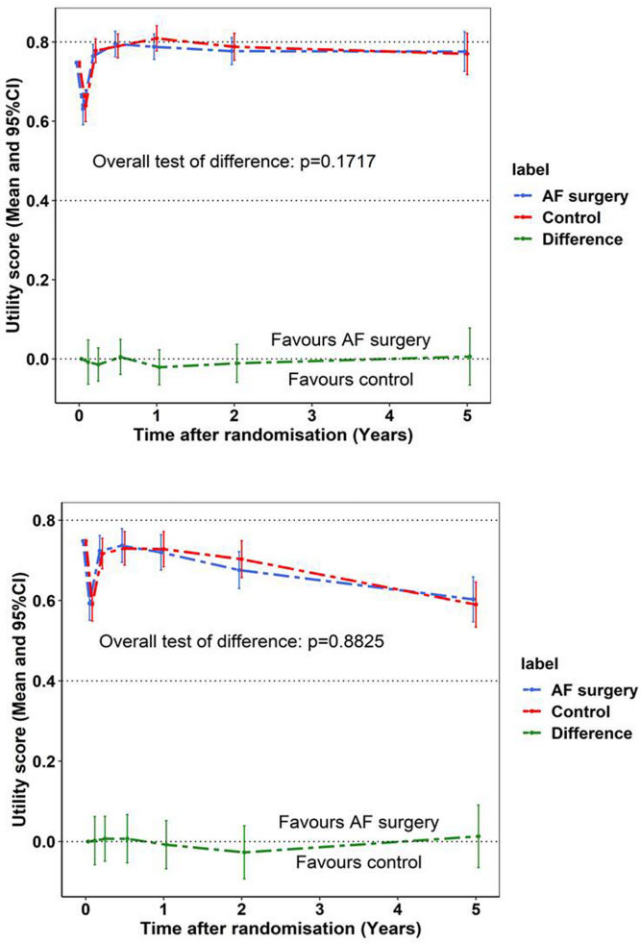


Figure 3: Mean and 95% confidence intervals for the baseline-adjusted EQ-5D-3 l utility score over time. Top panel: complete cases (survivors); bottom panel: multiply imputed data (with zero for deceased patients).

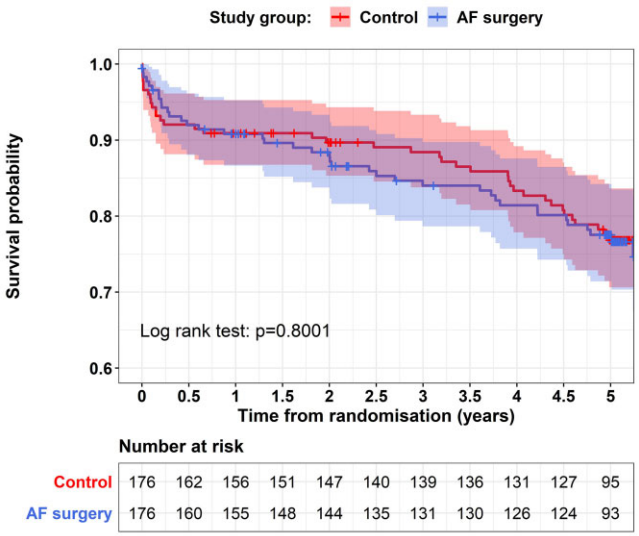


Figure 4: The Kaplan–Meier curve with 95% confidence interval for overall survival, by trial arm.

on device choice or lesion set. This is a limitation of the study in that it underestimates the success rate that can be achieved, but also a strength in that it reflects what is truly happening in real clinical practice.

At 5 years, we assessed heart rhythm by a single ECG. This was driven by data from the original study that, on 4-day Holter monitoring, virtually all patients were either wholly in AF or in SR. We therefore opted for the single ECG to improve compliance but recognize this as a limitation in that it could slightly underestimate AF detection.

Stroke incidence was elicited directly from patients and then reported strokes were verified from hospital records. Retrieval of all hospital admissions, including stroke-related admissions, directly from hospitals was not possible in the timescale of the project, in large part due to the COVID-19 pandemic. This may have resulted in an underestimate of the actual number of strokes due to patient recall, although this is likely to have been similar in the 2 arms. The likely impact is a reduction in precision of the comparison between groups, rather than a bias in the treatment effect: wider 95% CI and

higher *P*-value for the group comparison. This, and the design of the study, may contribute to our inability to confirm the significant difference in stroke rates reported by the PRAGUE-12 Study [14].

Implications for clinical service

The Amaze trial remains the largest randomized controlled study of the impact of adjunct AF surgery on the outcomes most important to the patient: survival, symptoms, QoL and freedom from strokes. In line with other studies [14, 15], Amaze showed significantly higher restoration of SR to 5 years in patients receiving adjunct AF surgery. Moreover, the more complex cardiac procedure was not associated with an increase in adverse events in the original trial report. However, we have not shown a clear impact on other key outcomes. This is important, because the outcomes that matter to patients do not relate to the ECG trace, but to QoL, long-term survival and freedom from stroke. The fewer overall strokes and smaller number of patients having a stroke in the AF surgery group were not significant but could be considered encouraging. The composite beneficial outcome of AF-free and stroke-free survival was also better in the AF surgery group, but this must be interpreted with caution as much of the contributory impact on this outcome was related to SR restoration. QoL and survival are not affected, and the crucial question 'do we save lives with AF surgery?' still remains unanswered [16].

Amaze was a pragmatic trial in which individual surgeons selected the method of AF surgery, including device, energy source and lesion set. The intra-class correlation coefficient estimates that 18–20% of the variation in the rate of SR maintenance over 5 years is related to the surgeon. This may be due in part to differences in surgical techniques, such as the choice of AF surgery method and lesion set. A previous randomized controlled trial had shown no significant difference between pulmonary vein isolation alone and a complete maze procedure in SR restoration [15], but the study may not have been powered to detect such a difference. The original Amaze trial suggested the highest rates of SR restoration were obtained when a complete left atrial lesion set was performed, including the mitral isthmus lesion. It is possible that adopting such a lesion set may reduce the observed inter-surgeon variation in outcomes to some extent, especially in patients receiving AF surgery for non-paroxysmal AF.

Implications for research

The HESTER study [7] showed that restoration of SR after AF surgery for chronic persistent AF is associated in most patients with very good recovery of left atrial function, so that we would expect that a reduction in stroke rate and, with it, better survival and QoL should follow. That our data do not conclusively show that this may be due to the size of the sample, the pragmatic trial design and the limited length of follow-up. Future meta-analyses of pooled randomized controlled trial data should be encouraged.

CONCLUSION

Adjunct AF surgery maintained higher rates for return to SR and a better composite outcome of survival free of AF and stroke up to 5 years after surgery compared with controls. There was no difference in pacemaker implantation. Overall survival and QoL were not affected up to 5 years after surgery.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *EJCTS* online.

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Conflict of interest: none declared.

Data Availability Statement

All relevant data are within the manuscript and its supporting information files. The data underlying this article will be shared on reasonable request to the corresponding author.

Author contributions

Linda D. Sharples: Formal analysis; Writing—original draft. **Christine Mills:** Funding acquisition; Project administration. **Yi-Da Chiu:** Formal analysis. **Simon Fynn:** Formal analysis; Investigation. **Helen M. Holcombe:** Data curation; Investigation. **Samer A.M. Nashef:** Conceptualization; Funding acquisition; Methodology; Project administration; Writing—original draft; Writing—review & editing.

Reviewer information

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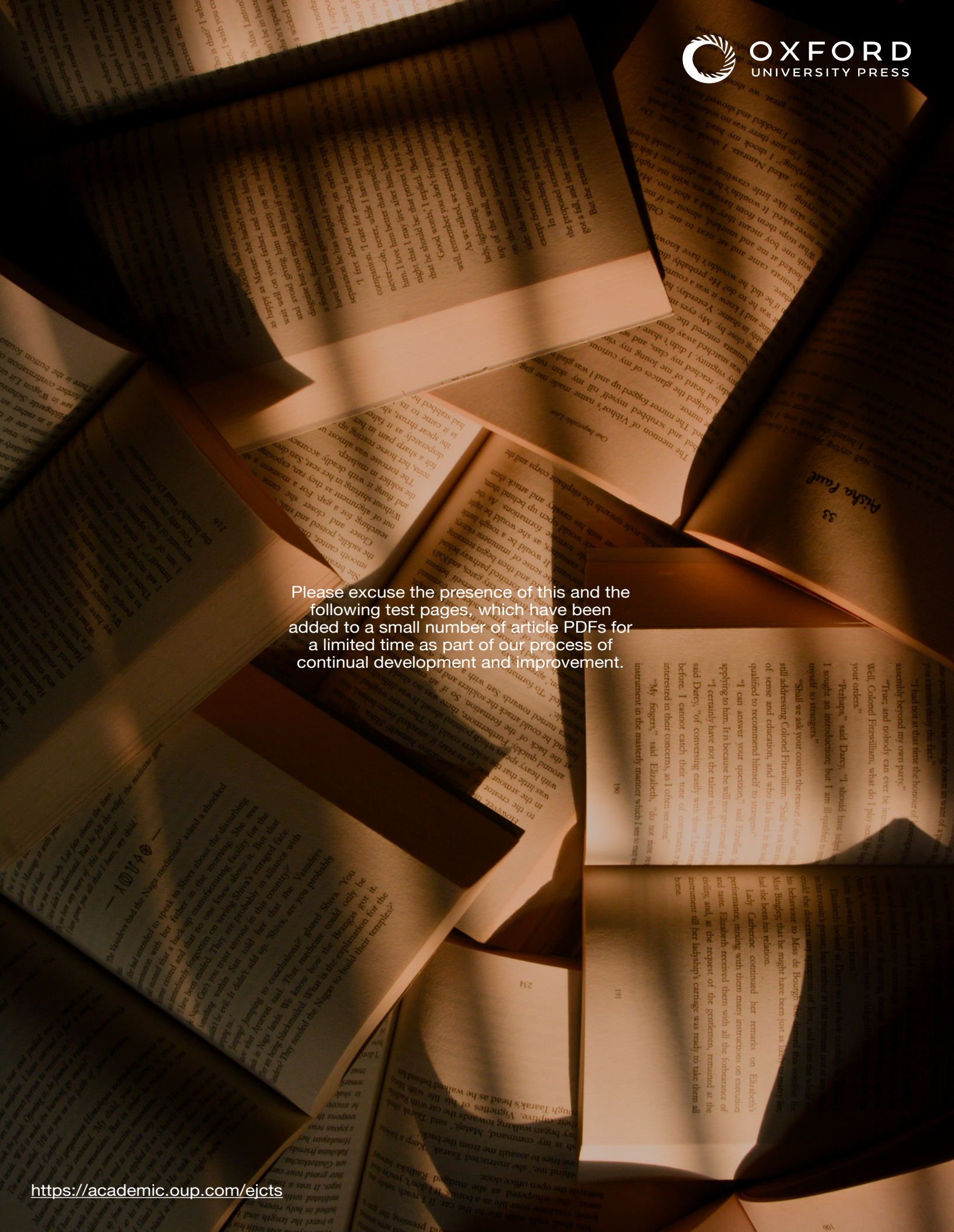

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