# Mini-Stern Trial: A randomised trial comparing mini-sternotomy to full median sternotomy for aortic valve replacement

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## Glossary of Abbreviations

| | |
|---|---|
| AVR | aortic valve replacement |
| mAVR | minimal access aortic valve replacement |
| BMI | body mass index |
| CI | 95% confidence interval |
| COPD | chronic obstructive pulmonary disease |
| CPB | cardiopulmonary bypass |
| $FEV_1$ | forced expiratory volume in one second |
| FS | full median sternotomy |
| HR | hazard ratio |
| HRQoL | health-related quality of life |
| ICER | incremental cost-effectiveness ratio |
| LVEF | left ventricular ejection fraction |
| MS | mini-sternotomy |
| NHS | National Health Service |
| OR | odds ratio |
| QALY | quality-adjusted life year |
| RCT | randomised control trial |
| SAE | serious adverse event |
| SD | standard deviation |
| TLCO | transfer factor of the lung for carbon monoxide |
| TOE | transoesophageal echocardiogram |
| UK | United Kingdom |

**Central Message**

In the UK NHS, compared to conventional median sternotomy approach for surgical AVR, mini-sternotomy did not hasten recovery or hospital discharge, and was not cost-effective.

**Perspective Statement**

Minimal access surgery is appealing for its perceived advantages including better patient recovery, satisfaction and cost-effectiveness. This RCT conducted within the UK NHS setting did not demonstrate quicker patient recovery or cost-effectiveness associated with mini-sternotomy compared to full median sternotomy approach. These findings are relevant to physicians, patients and health care funders.

**Structured Abstract**

**Objective:** Aortic valve replacement (AVR) can be performed either through full median sternotomy (FS) or upper mini-sternotomy (MS). The Mini-Stern trial aimed to establish whether MS leads to quicker postoperative recovery and shorter hospital stay after first-time isolated AVR.

**Methods:** This pragmatic, open-label, parallel RCT compared MS with FS for first-time isolated AVR in two UK NHS hospitals. Primary endpoints were duration of postoperative hospital stay and the time to fitness for discharge from hospital after AVR, analysed in the intent-to-treat population.

**Results:** In this RCT, 222 patients were recruited and randomised (118 MS, 104 FS). Compared to FS patients, MS patients had longer hospital stay (mean 9.5 vs. 8.6 days) and took longer to achieve fitness for discharge home (mean 8.5 vs. 7.5 days). Adjusting for valve type, sex and surgeon, hazard ratios (HR) from Cox models did not show a statistically significant effect of MS (relative to FS) on either hospital stay (HR 0.874, 95% CI 0.668-1.143, p-value 0.3246) or time to fitness for discharge (HR 0.907, 95% CI 0.688-1.197, p-value 0.4914). During mean follow up of 760 days (MS:745 and FS:777 days), 12 (10%) MS and 7 (7%) FS patients died (HR 1.871, 95% CI 0.723-4.844, p-value 0.1966). Average extra cost for MS was £1,714, during the first 12 months after AVR.

**Conclusions:** Compared to FS for AVR, MS did not result in shorter hospital stay, faster recovery or improved survival and was not cost-effective. MS approach is not superior to FS for performing AVR.

**Word count for Abstract:** 248

## Introduction

Aortic valve replacement (AVR) is the second commonest cardiac surgery in the UK [1] with an increasing proportion of older patients [1, 2]. Minimal access AVR (mAVR) might shorten hospital stay and postoperative recovery period and could be beneficial if offered safely and cost-effectively.

Currently, most AVRs are performed safely through full median sternotomy (FS) [2-6]. However, mAVR may be associated with less postoperative pain, blood loss, pulmonary and wound complications and shorter hospital stay [2]. The most commonly practised mAVR involves mini-sternotomy (MS), which could potentially hasten postoperative recovery, shorten hospital stay and improve patient satisfaction [2-10].

Most studies comparing MS and FS for AVR are non-randomised. Although systematic reviews with meta-analyses [11, 12] have been conducted, inadequate statistical power and heterogeneity of studies calls for prospective, randomised control trials (RCTs) to assess benefits and risks of mAVR. Published evidence on cost-effectiveness comparing MS to FS is sparse and weak. A recent review comparing cost-effectiveness of FS and MS called for a well-designed RCT to evaluate cost-effectiveness of mAVR up to at least a year after surgery [13]. Recently, a propensity-matched study from the UK national data concluded that mAVR is safe and was associated with shorter postoperative hospital stay [14]. The authors concluded that although general clinical equipoise exists between FS and MS, it is essential to have a well-constructed and adequately powered RCT before widespread adoption of MS. This retrospective study did not analyse cost-effectiveness of either surgical approach.

The Mini-Stern trial assessed whether MS is superior to FS in shortening postoperative recovery time and improving patient outcomes without compromising patient safety. It also assessed cost-effectiveness of MS from the perspective of the UK NHS as a health care provider.

## Materials and Methods

Mini-Stern was a two-centre, pragmatic, open-label RCT conducted in the UK. Patients were randomised (1:1) to AVR either by MS or FS.

### Sample Size

Considering four published RCTs [5, 6, 9, 10] and two cohort studies [7, 8], a 20% reduction in hospital stay from 11.7 to 9.36 days was considered clinically significant. Based on an internal audit of 252 first-time elective AVRs performed at Papworth Hospital in 2007/08 (mean hospital stay 11.7 days, SD 6.2), to detect this change with 80% power and 2-sided significance of 5%, 110 patients per group were required. As randomisation was performed on the day of surgery after induction of anaesthesia and introduction of the transoesophageal echocardiogram (TOE) probe, no subjects dropped out between randomisation and surgery thereby making the total trial recruitment target, 220 patients.

### Recruitment

Adult patients undergoing first-time isolated AVR were included. Exclusion criteria included emergency AVR, LVEF$\leq$ 30%, chest wall deformities, severe COPD ($FEV_1$ or TLCO < 40% predicted), BMI > 35kg/$m^2$, concomitant cardiac surgery, redo-surgery and inability to perform TOE. Details of patient enrolment are given in the online protocol.

## Randomisation

Randomisation (1:1) used random permuted blocks of variable lengths (6 or 8), stratified by surgeon and valve prosthesis (bio-prosthetic or mechanical). Random allocations were pre-generated, held in secure files by Papworth Trials Unit. During early days of the trial, TOE probe could not be passed in four patients due to technical reasons. These patients underwent the allocated procedure and were included in the trial. Later the Trial Steering Committee decided that under such circumstances, MS would be unsafe and patients should be excluded from the trial to FS. Since eligibility for MS required TOE, in order to avoid post-randomisation drop-out, group allocation for the study subjects was retrieved via telephone by theatre staff soon after anaesthesia and introduction of the TOE probe. Due to the nature of interventions, this trial could not be blinded.

## Outcomes

**Primary endpoints**: Two closely related primary endpoints were measured. Firstly, length of postoperative hospital stay (days between surgery and actual hospital discharge) which is easily measured, a surrogate for early postoperative events and sensitive to outcomes that affect health-related quality of life (HRQoL). Secondly, the interval in days between surgery and the patient being medically fit for discharge. To reduce investigator bias, standard discharge criteria were followed to decide the day of fitness for discharge. This endpoint was chosen to address exogenous effects (social factors, lack of transport, non-availability of space in nursing homes etc.) that commonly delay hospital discharge in the UK.

**Clinical secondary endpoints:** duration of surgery, total theatre time, aortic cross-clamp and cardiopulmonary bypass (CPB) times, blood loss in the first 12 hours after surgery, transfusion of blood and clotting products in the first 48 hours (blood transfusion trigger was

haemoglobin level < 80g/L), frequency of re-intubation, time to initial extubation, mediastinal drain removal and first independent mobilisation, daily pain scores at rest and on deep breath (over the first ten days or until hospital discharge) on a scale of 0 to 10, LVEF and severity of para-prosthetic regurgitation at hospital discharge and at 6 months, and time to all-cause death. Definitions of adverse events and details of their reporting are in the online protocol. To exclude bias, clinical outcome data were collected by research team who were not involved in routine care of subjects, following standardised protocols.

**Non-clinical secondary endpoints**: Health-related Quality of Life and Healthcare resource use.

**HRQoL:** Patients completed EQ-5D-3L [15] and SF-36 [16, 17] questionnaires at baseline, 6 weeks, 6 months and 12 months following surgery. EQ-5D-3L was repeated on fourth postoperative day and at discharge.

**Healthcare resource use:** Patient-specific resource use collected from hospital records and patient interviews during the primary admission included phases of care including operative surgery, critical care, post-surgical ward care and medications. Post-discharge resource use included attending wound clinics, community nurse visits, physiotherapy sessions, occupational therapy services, medical tests, cost of analgesics and other drugs and further hospitalisation within the first year after AVR.

**Surgical details**

All participating surgeons were consultants experienced in performing AVR by both FS and MS. They followed the operative surgical protocol as described below.

**MS approach:** With the patient anaesthetised as per standard protocol, skin was incised from half-way between the suprasternal notch and the sternal angle to the level of the fourth

intercostal space, measuring approximately 8cm. The manubrium was divided in the midline from the suprasternal notch inferiorly and then into the right 4th intercostal space. Thymus was divided and pericardium opened exposing the ascending aorta, aortic root and right atrial appendage. A loading dose of unfractionated heparin 300U/kg followed by boluses of 5000U was administered to achieve activated clotting time above 450 seconds. Aorta was cannulated using a wired flexible aortic cannula. Right atrial appendage was cannulated using a flat venous cannula and CPB commenced. The ascending aorta was cross-clamped and intermittent, antegrade, cold blood cardioplegia administered. The aorta was then incised open in an oblique or transverse fashion, the diseased valve excised and annulus decalcified. A suitably sized aortic valve prosthesis was inserted using either horizontal mattress, 2-0 Ethibond sutures or semi-continuous, 2-0 Prolene sutures. Surgeons adopted either of these suture techniques and adhered to the same technique irrespective of the type of valve prosthesis or the surgical approach. Aortotomy was then closed, heart de-aired, right atrial and ventricular epicardial pacing wires inserted and patient weaned off CPB. After confirming satisfactory functioning of the aortic valve prosthesis by TOE, heparin was reversed with protamine (1mg/100U of heparin). Chest drains were inserted into the anterior mediastinum, posterior pericardial space and pleural space if necessary. Sternal wires were inserted and incision closed in layers. Conversion to FS was performed to ensure patient safety if access was difficult or if intraoperative complications occurred.

**FS approach:** Anaesthesia and positioning of patients was the same as for MS approach. The skin incision was made between the suprasternal notch and the xiphoid process and sternum divided in the midline from the suprasternal notch to the xiphoid process. A two-stage venous cannula was used for atrial cannulation. Remaining steps were similar to MS approach.

## Statistical analysis

Analyses of primary and secondary endpoints used intention-to-treat and included all randomised patients. Unless stated otherwise, statistical models included treatment (MS vs. FS), valve (mechanical vs. bio-prosthetic) and sex as fixed effects, and surgeons as random effects. Hypothesis testing was two-sided at the 5% significance level, with no adjustments for multiple testing. All confidence intervals (CI) were estimated at the 95% confidence level.

Distributions of time-to-event endpoints were compared between study groups using Kaplan-Meier curves and log-rank tests (stratified by sex, valve and surgeon). Hazard ratios (HR) for MS relative to FS were estimated from a Cox model. The null hypothesis of no treatment effect (HR = 1) was tested. Patients who were lost to follow-up, withdrew or died before the event were censored at the latest time they were known to be event-free. Models were checked by plotting Schoenfeld and deviance residuals. For primary endpoints, Cox models were re-fitted using the per-protocol population and in sensitivity analyses (Appendix A. Table A4).

Need for reintubation and other dichotomous endpoints were compared between groups by estimating a MS/FS odds ratio (OR) via logistic regression. EQ-5D, SF-36 and pain scores were modelled using repeated measures linear regression. Where possible, random intercepts and random time coefficients for patients were included. For EQ-5D and SF-36, fixed effects for baseline scores were included. Models were fitted using complete cases, then re-fitted with multiple imputation of missing scores via chained equations.

Serious adverse events (SAEs) were analysed in the safety population according to intervention received. Patients randomised to MS who crossed over to FS prior to surgery were considered to have received FS; those who crossed over after MS had commenced were

considered to have received MS. Rates of SAEs were explored using Poisson regression with a random patient effect.

CONSORT guidelines [18] were followed. Analyses were performed in SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). No interim analyses were undertaken but reports were presented annually to the Data Monitoring and Ethics Committee.

**Economic analysis**

Unit costs were obtained from nationally published sources in the UK [19, 20, 21, 22] or from the Finance department, Papworth Hospital when the former did not provide the required information. Total cost per patient was calculated by summing resource use items multiplied by unit costs across the in-patient stay and the 12-month postoperative follow-up period (Appendix B. Table B7). Health state utilities from the EQ-5D-3L and SF-36, based on UK value sets [15, 23] were used to generate quality-adjusted life years (QALYs) using the area under the curve method and assigning a value of zero from date of death. Missing values were imputed using chained predictive mean matching, stratified by treatment and conditional on age, sex and baseline EQ-5D-3L.

Differences in mean costs and QALYs were estimated using seemingly unrelated regression, controlling for age, sex, valve, baseline EQ-5D-3L and treatment, to accommodate skewness [24]. Uncertainty in cost-effectiveness was estimated by drawing 1000 bootstrapped samples and conducting probabilistic sensitivity analysis. Results are presented as incremental net monetary benefit at various thresholds of willingness to pay per QALY, cost-effectiveness planes and cost-effectiveness acceptability curves. Deterministic sensitivity analyses explored effects of using complete cases only, SF6D-based QALY estimates, the procedure inpatient

admission only, excluding patients who died and excluding additional equipment costs (Appendix B. Table B11).

## Results

Overall 1024 patients were screened between 28 January 2010 and 13 April 2015, of whom 222 were recruited and randomised to MS (118) or FS (104). One-year follow-up was completed on 23 May 2016.

Study groups were similar at baseline except for a non-significant sex imbalance (Table 1). In this trial, MS was not completed in 14 (12%) of 118 patients randomised to MS. Of these patients, 6 (5%) had conversion from MS to FS due to reasons listed in Figure 1. The remaining 8 patients underwent FS after randomisation to MS but without initial MS incision as MS was considered unsafe/impractical. The true rate of intraoperative conversion of MS to FS was therefore 5%. Four patients (2%, Table 2) were censored before discharge: one withdrawal before surgery (FS) and three deaths (all randomised to and received MS). A further thirteen (6%) were censored before fitness for discharge: six discharged to acute hospital (three MS, three FS), seven to long-term care or rehabilitation (three FS, four MS).

Mean time to hospital discharge was longer for MS than FS (9.5 vs. 8.6 days), as was mean time to fitness to discharge (8.5 vs. 7.5 days). However, distributions of these endpoints were similar in both groups (Figure 2, Table 2). The difference was not statistically significant in either primary analyses using Cox models (Figure 3), log-rank tests (Table 2) or sensitivity analyses (Appendix A. Table A4). The gamma-distributed frailty term in the Cox models was estimated to have variance 0.006675 for time to fitness and 0.000100 for time to discharge, suggesting that surgeon heterogeneity was negligible.

Time to drain removal (including drains inserted/retained to treat complications) was longer for MS, but times to extubation and independent mobilisation did not differ significantly between groups (Table 2, Figure 3), nor did numbers of patients re-intubated (six MS vs. five FS, OR 1.039, CI 0.306-3.531, p=0.9512). Statistically significant HRs indicated longer surgery, CPB, cross-clamp and theatre times for MS (Figure 3). No significant differences were seen in blood loss (Appendix A. Table A3), or in numbers of patients requiring transfusion of blood (50 MS vs. 51 FS, OR 0.797, CI 0.453-1.402, p=0.4310) or clotting products (11 MS vs 4 FS, OR 2.616, CI 0.801-8.541, p=0.1112).

Regression models for pain at rest, EQ-5D utilities and SF-36 domain scores (Appendix A. Tables A6, A7, A8) estimated greater rate of improvement over time in MS patients for three SF-36 domains (social functioning, vitality and role physical). After multiple imputation, the difference was only significant for the role physical domain (Appendix A. Table A9). Pain on deep breath was not analysed as only less than half the data were collected due to poor patient compliance.

Nine (4%) patients died within a year of surgery: seven (6%) MS, two (2%) FS. Five deaths were possibly related to treatment (four MS, one FS), none were probably or definitely related (Appendix A. Table A15). Overall, twelve (10%) MS and seven (7%) FS patients died during follow-up (mean follow-up 760 days: 745 MS, 777 FS). Time to all-cause death, adjusted for age, showed a moderately large but statistically non-significant HR (MS/FS) of 1.871 (CI 0.723-4.844, p=0.1966).

Safety analyses excluded one patient who was withdrawn before surgery. There were significantly more SAEs in MS recipients (rate ratio 1.615, CI 1.070-2.437, p=0.0225) (Appendix A. Table A11). The numbers of patients experiencing SAEs were not significantly different (OR 1.559, CI 0.895-2.715, p=0.1161). Incidence of para-prosthetic

regurgitation did not differ significantly between groups (Appendix A. Table A13). Seven patients developed pericardial collection (three MS vs four FS, OR 0.680, CI 0.146-3.178, p=0.6229). Wound infections (including superficial and deep infections) were more common in FS recipients (thirteen FS vs four MS, OR 0.312, CI 0.097-1.005, p=0.0511). Deep sternal wound infection developed in one MS and one FS recipient, neither of whom required plastic surgical repair.

Economic analyses are summarised in Table 4. There was additional cost for MS relative to FS (£1,714 per patient, p=0.0765) in the first year following surgery. MS patients had (non-significant) better EQ-5D-based QALYs (0.03 per patient, p=0.1509). The incremental cost per QALY gained was £61,379, but after adjusting for baseline characteristics, MS had higher costs and lower QALYs (i.e. was dominated). In deterministic and probabilistic sensitivity analyses, MS was either dominated or had a very large cost per QALY, except for the complete case analysis (Appendix B. Tables B11, B12).

## Discussion

The UK NHS is a free for patient at point-of-delivery healthcare system. Apart from good recovery, hospital discharge of a significant proportion of elderly patients depends on the timely availability of social care services in the community. The Mini-Stern trial is the first RCT comparing FS and MS for isolated AVR when performed for UK NHS patients.

In this prospective, pragmatic, open-label RCT, MS did not reduce the total duration of hospital stay after AVR. As hospital discharge is sometimes delayed due to social factors, we included time until fit for discharge as a second primary endpoint. This was also not reduced by MS. These endpoints were recorded by physiotherapists based on a common discharge

protocol with specific clinical milestones to achieve, thereby excluding physician-induced bias.

In this study operation, total theatre, aortic cross-clamp and CPB times were significantly prolonged with MS. This was expected as in general, minimal access valve operations take longer [5, 9]. This is justifiable if MS resulted in either faster recovery, shorter postoperative stay, reduced cost of treatment or more importantly a significant reduction in adverse events and therefore superior patient safety. In this RCT, MS did not achieve these benefits and hence we feel that the prolonged operation time, total theatre, cross-clamp and CPB times are not justifiable for performing AVR through MS.

Previously, two meta-analyses [11, 12] concluded that mAVR approaches are superior in certain aspects of postoperative recovery. However, both included studies on mini-thoracotomy approach for AVR, and therefore inferences drawn cannot be extrapolated to MS. A retrospective propensity-matched analysis of data from a UK national database concluded that MS is safe and comparable to conventional AVR [14]. The authors found thatMS resulted in a shorter postoperative hospital stay, which disagrees with our findings. However, a propensity-matched study can suffer from selection bias if its matching algorithm produces treatment groups that are unbalanced in some unobserved characteristics. Recently, a retrospective study demonstrated safety of right thoracotomy minimally invasive isolated and concomitant AVR in patients of all age groups [25]. As randomisation balances study groups in known and unknown characteristics, results of the Mini-Stern trial should be more reliable than non-randomised studies.

Previous studies investigating cost-effectiveness provided unclear answers. A report analysing registry data from patients who underwent isolated primary AVR [26] reported lower hospital cost when AVR was performed through right anterior thoracotomy compared to sternotomy-based approaches with no significant differences in outcome. The main reasons attributed to lower costs were earlier hospital discharge and reduced use of blood products. Ghanta et al [27] noted that exclusion of rehabilitation costs could alter this finding. A review by Glauber et al [13], based on uncontrolled studies, noted that higher cost of instruments and devices in mAVR could be offset by economic advantage gained by shorter hospital stay and lower complication rates. The Mini-Stern trial assessed cost-effectiveness using a range of sensitivity analyses, but only the complete case analysis showed MS to be cost-effective, suggesting lower costs but slightly worse outcomes with MS. However, this analysis used a potentially unrepresentative sample of just 90 patients. Our analysis was restricted to the first year following operation without long-term analysis beyond 1 year.

This RCT is robust with many merits including on-table randomisation, comprehensive and independent outcome assessment without physician-bias, longer-term clinical assessment, HRQoL analysis and economic analysis. However there were some limitations. Although we report on secondary endpoints, this trial was powered only to address the primary endpoint. A total of 14 patients (12%) allocated to MS received FS, which could be another limitation. However, only 6 patients (5%) had true conversion after an attempted MS, while 8 patients (6.7%) went on to FS for safety reasons. Although this RCT took place in only two centres, thereby limiting generalisability, recruitment by eight surgeons improves generalisability. A total of 1024 patients were screened to recruit 222 (21.7%) patients. Although this potentially suggests selection bias, only 125 eligible patients (12.2%) failed recruitment while the remaining 667 patients (65.1%) did not meet inclusion criteria. Blinding was not

practical as sternotomy dressings were usually changed 48 hours after surgery and patients became aware of the approach. This could have caused bias in self-reported outcomes. Missing 'pain at rest' data were unlikely to be missing at random, and therefore imputation might not have addressed all potential biases. Despite having two primary outcomes, we did not adjust for multiple testing. However, as neither showed a significant difference between groups, this would not have affected our conclusions.

In conclusion, MS for AVR did not result in quicker recovery or earlier hospital discharge. MS resulted in longer operations, increased costs, and resulted in more SAEs than FS. Overall, this pragmatic RCT did not provide evidence that MS results in better clinical or quality of life outcomes, or that MS is cost-effective compared to FS in the first year after AVR.

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**Legends**

**Central Picture Legend:** Duration of hospital stay after AVR: FS versus MS.

**Video Legend:** MS approach for AVR.

**Figure 1.** Trial flow diagram.

**Figure 2**. Kaplan-Meier curves for primary endpoints. Points indicate censoring and dashed lines represent 95% confidence intervals.

**Figure 3**. Forest plot of HRs and 95% confidence intervals from Cox models.

**Figure 4**. Cost-effectiveness planes. Proportion of points below each threshold gives the probability that MS is more cost-effective than FS. This probability is 3.7% for willingness to pay £20,000/QALY and 5.1% for willingness to pay £30,000/QALY.

418 **Table 1. Baseline characteristics**

| | **MS (n = 118)** | **FS (n = 104)** |
|---|---|---|
| **Age (years) - Mean (SD)** | 71.3 (12.3) | 72.1 (10.9) |
| **BMI (kg/m$^2$) – Mean (SD)** | 26.6 (3.2) | 27.7 (3.7) |
| **Sex - frequency (%)** | | |
| Female | 53 (45%) | 57 (55%) |
| Male | 65 (55%) | 47 (45%) |
| **Valve type - frequency (%)** | | |
| Mechanical | 15 (13%) | 14 (13%) |
| Tissue | 103 (87%) | 90 (87%) |
| **EuroSCORE (%) - Mean (SD)** | 5.9 (2.1) * | 6.1 (2.1) |

419 * EuroSCORE was missing for one MS patient.

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423 **Table 2. Kaplan-Meier medians (quartiles) for time-to-event endpoints**

| | MS (n = 118) | FS (n = 104) | p-value* |
|---|---|---|---|
| **Time to discharge (days)** | 7 (6, 10) | 7 (6, 10) | 0.6924 |
| Censored | 3 | 1 | |
| **Time until fit for discharge (days)** | 6 (5, 10) | 6 (5, 9) | 0.5597 |
| Censored | 10 | 7 | |
| **Time to independent mobilisation (days)** | 4 (3, 7) | 4 (3, 6) | 0.5819 |
| Censored | 8 | 7 | |
| **Time to mediastinal drain removal (hours)** | 26.1 (20.6, 53.3) | 22.5 (19.4, 37.8) | 0.0157 |
| Censored | 2 | 2 | |
| **Time to extubation (hours)** | 9.2 (7.8, 12.1) | 8.3 (6.8, 11.7) | 0.5488 |
| Censored | 1 | 1 | |
| **Theatre time (minutes)** | 191 (172, 225) | 176 (152, 203) | < 0.0001 |
| Censored | 0 | 0 | |
| **CPB time (minutes)** | 80 (70, 95) | 66 (52, 85) | < 0.0001 |
| Censored | 0 | 0 | |
| **Cross-clamp time (minutes)** | 65 (53, 76) | 49 (39, 64) | < 0.0001 |
| Censored | 0 | 0 | |
| **Surgery duration (minutes)** | 163 (139, 190) | 149 (114, 167) | < 0.0001 |
| Censored | 3 | 4 | |

424 **Log-rank test. Seven surgery durations were not recorded and censored at 1 minute.*

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426 **Table 3. Costs, QALYs and Cost-effectiveness**

| | **Cost and QALYs (with imputation)** | **FS (n = 118)** | | **MS (n = 104)** | |
|---|---|---|---|---|---|
| | | **Mean Cost per patient** | **SD** | **Mean Cost per patient** | **SD** |
| Primary Admission Costs | Theatre use | £3,824 | £1,243 | £4,422 | £2,053 |
| | Additional surgical items | £16.52 | £0.0 | £52.0 | £0.0 |
| | Critical care (ITU) | £1,834 | £3,023 | £2,934 | £5,030 |
| | Cardiac ward | £2,744 | £1,664 | £2,676 | £1,500 |
| | Physio- and Occupational Therapy | £77 | £55 | £78 | £68 |
| | Rehabilitation | £384 | £1,878 | £263 | £1,621 |
| | Acute hospital | £347 | £1,919 | £298 | £1,971 |
| | *Sub-total cost* | *£9,226* | *£6,511* | *£10,724* | *£8,850* |
| Post primary admission costs to 12 months | Hospital Re-admission | £418 | £1,475 | £575 | £1,863 |
| | Follow up tests | £224 | £258 | £282 | £279 |
| | Follow up healthcare visits | £373 | £359 | £311 | £263 |
| | *Sub-total cost* | *£1,015* | *£1,778* | *£1,168* | *£2,079* |
| | Drugs | £379 | £548 | £441 | £977 |
| | *Total cost over 12 months* | *£10,620* | *£7,624* | *£12,333* | *£9,864* |
| Incremental cost-effectiveness* (probabilistic analysis with baseline | Incremental cost at 12 months (MS-FS) | | | £2,154.0 (*SE* £36) | |
| | Incremental EQ-5D-3L QALYs (MS-FS) | | | -0.0122 (SE 0.0008) | |
| | ICER | | | MS dominated by FS | |
| | NMB (at WTP £20,000/QALY) | | | -£2,397 | |
| | NMB (at WTP £30,000/QALY) | | | -£2,519 | |

adjustment)

SD: standard deviation, SE: standard error, WTP: willingness to pay, NMB: net monetary benefit, ICER: incremental cost-effectiveness ratio. * Incremental costs and effects estimated using SUR, adjusting for baseline differences.

## References

[1] The Society for Cardiothoracic Surgery in Great Britain & Ireland. http://bluebook.scts.org/#ActivityRates

[2] Rosengart TK, Feldman T, Borger MA, Vassiliades TA Jr, Gillinov AM, Hoercher KJ, et al. Percutaneous and minimally invasive valve procedures: a scientific statement from the American Heart Association Council on Cardiovascular Surgery and Anesthesia, Council on Clinical Cardiology, Functional Genomics and Translational Biology Interdisciplinary Working Group, and Quality of Care and Outcomes Research Interdisciplinary Working Group. Circulation. 2008;117:1750-67.

[3] Merk DR, Lehmann S, Holzhey DM, Dohmen P, Candolfi P, Misfeld M, et al. Minimal invasive aortic valve replacement surgery is associated with improved survival: a propensity-matched comparison. Eur J Cardiothorac Surg. 2015;47:11-7.

[4] Furukawa N, Kuss O, Aboud A, Schönbrodt M, Renner A, Hakim MK, et al. Ministernotomy versus conventional sternotomy for aortic valve replacement: matched propensity score analysis of 808 patients. Eur J Cardiothorac Surg. 2014;46:221-6.

[5] Bonacchi M, Prifti E, Giunti G, Frati G, Sani G. Does ministernotomy improve postoperative outcome in aortic valve operation? A prospective randomized study. Ann Thorac Surg. 2002;73:460-5.

[6] Moustafa MA, Abdelsamad AA, Zakaria G, Omarah MM. Minimal vs median sternotomy for aortic valve replacement. Asian Cardiovasc Thorac Ann. 2007;15:472-5.

[7] Sharony R, Grossi EA, Saunders PC, Schwartz CF, Ribakove GH, Culliford AT, et al. Minimally invasive aortic valve surgery in the elderly: a case-control study. Circulation. 2003;108 Suppl 1:II43-7.

[8] Bakir I, Casselman FP, Wellens F, Jeanmart H, De Geest R, Degrieck I, et al. Minimally invasive versus standard approach aortic valve replacement: a study in 506 patients. Ann Thorac Surg. 2006;81:1599-604.

[9] Aris A, Camara ML, Montiel J, Delgado LJ, Galan J, Litvan H. Ministernotomy versus median sternotomy for aortic valve replacement: a prospective, randomized study. Ann Thorac Surg. 1999;67:1583-7.

[10] Dogan S, Dzemali O, Wimmer-Greinecker G, Derra P, Doss M, Khan MF, et al. Minimally invasive versus conventional aortic valve replacement: a prospective randomized trial. J Heart Valve Dis. 2003;12:76-80.

[11] Lim JY, Deo SV, Altarabsheh SE, Jung SH, Erwin PJ, Markowitz AH, et al. Conventional versus minimally invasive aortic valve replacement: pooled analysis of propensity-matched data. J Card Surg. 2015;30:125-34.

[12] Phan K, Xie A, Di EM, Yan TD. A meta-analysis of minimally invasive versus conventional sternotomy for aortic valve replacement. Ann Thorac Surg. 2014;98:1499-511.

[13] Glauber M, Ferrarini M, Miceli A. Minimally invasive aortic valve surgery: state of the art and future directions. Ann Cardiothorac Surg. 2015;4:26-32.

[14] Attia RQ, Hickey GL, Grant SW, Bridgewater B, Roxburgh JC, Kumar P, et al. Minimally invasive versus conventional aortic valve replacement. A propensity-matched study from the UK National Data. Innovations. 2016:11:15-23.

[15] Dolan P, Gudex C, Kind P. A social tariff for EuroQoL: results from a UK general population survey (1995). Discussion Paper, no 138, University of York Centre for Health Economics. https://www.york.ac.uk/che/pdf/DP138.pdf

[16] Brazier JE, Harper R, Jones NM, O'Cathain A, Thomas KJ, Usherwood T, et al. Validating The SF-36 Health Survey Questionnaire: New Outcome Measure For Primary Care. BMJ. 1992;305:160-4.

520 [17] Ware JE, Kosinski M, Gandek B. SF-36 Health Survey: Manual and Interpretation
521 Guide. Lincoln RI: Quality Metric Incorporated; 1993.
522 [18] Schulz KF, Altman DG, Moher D. CONSORT 2010 Statement: updated guidelines for
523 reporting parallel group randomised trials. BMJ. 2010;340:c332
524 [19] Joint Formulary Committee. British National Formulary (BNF).
525 https://www.evidence.nhs.uk/formulary/bnf/current (July 2016)
526 [20] Department of Health. NHS reference costs 2014 to 2015.
527 https://www.gov.uk/government/publications/nhs-reference-costs-2014-to-2015 (July 2016)
528 [21] NHS Prescription Services Electronic Drug Tariff. http://www.drugtariff.nhsbsa.nhs.uk/
529 (July 2016)
530 [22] Curtis L, Burns A. Unit Costs of Health and Social Care 2015. Canterbury: Personal
531 Social Services Research Unit, University of Kent. http://www.pssru.ac.uk (July 2016)
532 [23] Brazier J, Roberts J, Deverill M. The estimation of a preference-based measure of health
533 from the SF-36. J Health Econ. 2002; 21:271-92.
534 [24] Faria, R, Gomes, M., Epstein, D, White, IR. A guide to handling missing data in cost-
535 effectiveness analysis conducted within randomised controlled trials. Pharmacoeconomics.
536 2014;32:1157–1170.
537 [25] Lamelas J, Mawad M, Williams R, Weiss UK, Zhang Q, LaPietra A. Isolated and
538 concomitant minimally invasive minithoracotomy aortic valve surgery. J Thorac Cardiovasc
539 Surg. 2018;155:926-36.
540 [26] Rodriguez E, Malaisrie SC, Mehall JR, Moore M, Salemi A, Ailawadi G, et al.
541 Economic Workgroup on Valvular Surgery, Right anterior thoracotomy aortic valve
542 replacement is associated with less cost than sternotomy-based approaches: a multi-institution
543 analysis of 'real world' data. J Med Econ. 2014;17:846-52.

544 [27] Ghanta RK, Lapar DJ, Kern JA, Kron IL, Speir AM, Fonner E, et al. Minimally invasive
545 aortic valve replacement provides equivalent outcomes at reduced cost compared with
546 conventional aortic valve replacement: A real-world multi-institutional analysis. J Thorac
547 Cardiovasc Surg. 2015;149:1060-5.
548