Long-term outcomes of mini-sternotomy versus conventional sternotomy for aortic valve replacement: a randomised controlled trial.

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Visual abstract

Key question:

What are the long-term outcomes of mini-sternotomy AVR?

Key findings:

135 patients: mini-sternotomy group

135 patients: conventional group

Median FU: 6.1 years

Take-home message:

Mini-sternotomy AVR demonstrates comparable long-term mortality, re-operation and MACE outcomes to conventional sternotomy AVR

ABSTRACT

Objectives: Aortic valve replacement (AVR) for severe symptomatic aortic stenosis is one of the most common cardiac surgical procedures with excellent long-term outcomes. Multiple previous studies have compared short-term outcomes of AVR with mini-sternotomy versus AVR with conventional sternotomy. We have previously reported the results of the randomised MAVRIC trial, which aimed to evaluate early post-operative morbidity among patients undergoing mini-sternotomy and conventional sternotomy AVR. We now report the long-term all-cause mortality, re-operation, MACE outcomes and echocardiographic data from this trial.

Methods: The prospective, randomised, single-centre, single-blind MAVRIC trial compared manubrium limited mini-sternotomy and conventional median sternotomy for treatment of patients with severe aortic stenosis. The previously reported primary outcome was the proportion of patients receiving red cell transfusion postoperatively and within 7 days of the index procedure. Currently reported exploratory analyses of a combined long-term all-cause mortality and re-operation were compared between groups via the log-rank test. Sensitivity analyses reviewed individual components of the combined endpoint. The primary analysis and long-term exploratory analyses were based on an intention-to-treat principle.

Results: Between March 2014 and June 2016, 270 patients were enrolled and randomised in a 1:1 fashion to undergo mini-sternotomy AVR (n=135) or conventional median sternotomy AVR (n=135). At the median follow-up of 6.1 years, the composite outcome of all-cause mortality and re-operation occurred in 18.5% (25/135) of patients in conventional sternotomy group and in 17% (23/135) of patients in mini-sternotomy group. The incidence of chronic kidney disease, CVA, myocardial infarction was not significantly different between two groups. Follow up echocardiographic data suggested no difference in peak and mean gradients or incidence of aortic regurgitation between two approaches.

Conclusions: This exploratory long-term analysis demonstrated that in patients with severe aortic stenosis undergoing isolated AVR, there was no significant difference between manubrium limited mini-sternotomy and conventional sternotomy with respect to all-cause mortality, rate of reoperation, MACE events and echocardiographic data at the median of 6.1 years follow-up.

Central message

In current exploratory analysis mini-sternotomy AVR demonstrates similar long-term all-cause mortality, reoperation and MACE outcomes when compared to conventional AVR.

Abbreviated legend

Long-term mortality, reoperation and MACE outcomes of MAVRIC trial

Perspective statement

In this paper, we report the long-term exploratory outcomes of MAVRIC trial, which studied Manubrium-limited mini-sternotomy versus conventional sternotomy for aortic valve replacement.

Abbreviations

AVR – Aortic Valve Replacement

CI – Confidence Interval

CVA – Cerebrovascular Accident

HR – Hazard Ratio

IQR – Interquartile Range

ISRCTN - International Standard Randomised Controlled Trial Number

MACE – Major Adverse Cardiovascular Events

MAVRIC – Manubrium-limited Mini-sternotomy versus Conventional Sternotomy for Aortic Valve Replacement

N - Number

NYHA – New York Heart Association Classification

RBC – Red Blood Cell

SD – Standard Deviation

TIA- Transient ischaemic attack

Introduction

Severe symptomatic aortic stenosis carries poor prognosis and intervention is recommended by ESC/EACTS guidelines[1]. Given developments of different techniques for aortic valve intervention, Heart Team approach is advised to evaluate clinical, anatomical and procedural factors for each patient weighing the risks and benefits of each intervention. Aortic valve replacement (AVR) surgery, however, remains the mainstay of treatment for the majority of patients with aortic valve disease, with excellent long-term outcomes[2]. Several previous studies have reported that minimally invasive aortic valve surgery via limited upper sternotomy can be performed at least as safely as conventional surgery via a full sternotomy[3]. However, most of the studies conducted short-to mid-term follow-up and mainly looked at cardiopulmonary bypass time, perioperative and postoperative blood loss, length of hospital stay, pain scores, cost effectiveness analysis and quality of life assessments. The prospective long-term mortality, re-operation, MACE and echocardiographic data comparing mini sternotomy to conventional sternotomy is lacking. One previously reported randomised clinical trial involving 222 patients analysed all-cause mortality at a mean follow-up of 2 years and found no statistically significant difference in the events[4]. We have previously reported outcomes of the MAVRIC (Manubrium-limited mini-sternotomy versus conventional sternotomy for aortic valve replacement) trial, which compared AVR via manubrium limited mini-sternotomy and AVR via conventional sternotomy. The primary outcome was the proportion of patients receiving a red cell transfusion postoperatively and within 7 days of index surgery. MAVRIC demonstrated no additional clinical benefit in terms of red blood cell transfusion rates with minimally invasive AVR[5]. To further characterise the long-term outcomes of mini-sternotomy AVR and conventional AVR, we now report exploratory long-term mortality, re-operation, MACE and echocardiographic outcomes.

Methods

Ethical statement

The trial was approved by NHS Research and Ethics committee (March 2014, IRAS 137295, Reference Number PB-PG-1112-29035) and Health Research Authority (North East – Newcastle & North Tyneside, March 2014, REC Reference 14/NE/0005). ISRCTN

(International Standard Randomised Controlled Trial Number) registration: ISRCTN29567910. All patients provided written informed consent for publication of coded study data.

Trial design

The design of the MAVRIC trial has been described previously[5]. In brief, MAVRIC was a prospective, randomised, single-centre trial comparing manubrium limited mini-sternotomy and conventional median sternotomy for the treatment of severe aortic stenosis. The full trial protocol was designed by the chief investigator and trial committee and was published previously[6]. The trial was sponsored by South Tees NHS Foundation Trust which was also the single recruiting centre for the study.

Enrolment, randomisation and follow-up

Patients were eligible to participate in the trial if they were 18 years of age or over, requiring first-time, non-emergency, isolated AVR surgery. Randomisation was performed by the members of research team using central, secure, web-based randomisation system with concealed allocation. Eligible participants were randomised in a 1:1 fashion to manubrium limited mini-sternotomy group or conventional sternotomy group, stratified by baseline EuroSCORE and Hb value. In the intervention arm manubrium limited mini-sternotomy was performed with a 5-7cm midline incision from the sternal notch to 1cm below the manubrium-sternal junction. In the conventional arm sternotomy was performed using a midline incision from the sternal notch to the xiphisternum. No other minimally invasive access points were used in the intervention arm. Patients were followed up at 6- and 12-weeks following discharge from hospital. Long-term follow-up was enabled through multiple types of electronic medical records review including patient summary care records, cardiothoracic clinical review database, South Tees Trust mortality database and electronic clinical and management information system. The data was checked by two independent assessors. CONSORT recommendations were followed in this report.

Outcomes

The primary outcome reported previously was the number of patients receiving red blood cell (RBC) transfusion postoperatively and within 7 days of index surgery. The long-term,

currently reported exploratory outcomes were the combined incidence of all-cause mortality and re-do AVR, individual components of combined outcome, incidence of stroke, myocardial infarction, chronic kidney disease and echocardiographic data.

Statistical analysis

The MAVRIC trial was powered to detect reduction in proportion of patients receiving RBC transfusion. The long-term exploratory outcomes were not explicitly powered. The long-term analysis was performed on an intention-to-treat principle. Continuous baseline variables were expressed as mean (SD), follow-up time was expressed as median (IQR). The log-rank test, X^2 test and Mann-Whitney U test were used to evaluate significant difference in events between mini and conventional sternotomy group. Fisher's exact test was used to compare the proportions of myocardial infarction given low incidence of events. The proportions of patients with the event in each group was estimated with Kaplan-Meier method. A Cox proportional-hazards model was used to evaluate all-cause mortality and investigate the association between events and variables. All Cox models included EuroSCORE and sternotomy type. Statistical significance was expressed as P value of <0.05. All statistical analyses were performed in Stata (16.0, College Station, Texas, USA).

Results

Between March 2014 and July 2016 271 consecutive eligible participants were enrolled in the study and randomised to receive AVR via conventional sternotomy (135 patients) or to receive AVR via mini-sternotomy (135 patients). One patient was inoperable and randomised in error, 16 patients in mini group were converted to conventional sternotomy due to anaesthetic emergency, difficult intravascular access and intraoperative complications. Baseline characteristics were well balanced between the two groups and were published previously (Table 1). Briefly, the mean age in the mini-sternotomy group was 69.3(9.3) years and in the conventional group was 68.7(8.4) years. The mean EuroSCORE 2 was 1.5(1.1) in mini-sternotomy group and 1.5(1.2) in the conventional group. The valve types used were broadly similar across both groups.

All 270 patients who received surgery as part of MAVRIC trial were enrolled in the long-term analysis. Electronic record review was completed and cross checked for 270 patients. Median follow-up analysis for mini-sternotomy group was at 6.1 years (interquartile range

5.6-6.8), median follow-up for conventional sternotomy group was at 6.1 years (5.5-6.8). The composite outcome of all-cause mortality and re-operation occurred in 18.5% (25/135) of patients in conventional sternotomy group and in 17% (23/135) of patients in mini-sternotomy group (P value= 0.70) (Figure 1). No difference in mortality and re-operation outcomes were observed based on valve type by sternotomy group (P > 0.05).

Figure 1

All-cause mortality had occurred in 17.8% (24/135) in conventional sternotomy group and in 16.3% (22/135) in manubrium limited mini-sternotomy group (P=0.72) (Figure 2). The factor influencing primary outcome and all-cause mortality was higher EuroSCORE (HR, 1.10; 95% CI, 1.03-1.18, P=0.01).

Figure 2

Rates of reoperation were also not statistically significant in both groups: three patients underwent re-do surgical AVR in conventional group and one patient had re-do AVR in mini group (P= 0.31). In conventional group two patients underwent re-do AVR within 9 months of original procedure due to severe paravalvular aortic regurgitation and one patient developed staphylococcus aureus prosthetic valve endocarditis and aortic root abscess requiring pericardial patch to aorto-mitral curtain and re-do mechanical AVR within 2 months of initial intervention. In mini-sternotomy group severe paravalvular aortic regurgitation was the reason for re-do AVR within 5 months of initial intervention. Two patients required sternal wound debridement and sternal wires removal: one in each group. One patient in mini-sternotomy group underwent sternal manubrial plating.

Incidence of CVA (11% in mini-sternotomy group vs 8% in conventional group, P=0.59), myocardial infarction (3% vs 0%, P=0.23) and chronic renal failure (25% vs 23%, P=0.70) was not significantly different between two groups at the median of 6.1 years follow-up (Table 2). Echocardiography data demonstrated similar peak and mean gradients across mini-sternotomy and conventional sternotomy groups (P=0.31 and P=0.16 respectively). Incidence of aortic regurgitation was also not significantly different (P=0.86) between two groups.

Discussion

Our centre has previously reported early- to medium-term outcomes of MAVRIC trial which demonstrated no reduction in RBC transfusions in mini-sternotomy group. Evaluation of adverse events which included mortality, stroke, TIA, renal failure and atrial arrhythmias were broadly similar across both groups at 12 weeks follow up, there was also no significant difference in quality of life up to 12 weeks. We now present the long-term follow-up results. The findings are summarised in Figure 3.

The exploratory analysis of long-term all-cause mortality, re-operations, MACE and echocardiography outcomes of MAVRIC trial demonstrates similar event rates when comparing mini-sternotomy and conventional sternotomy AVR. To our knowledge, there is no prior randomised data comparing these treatment strategies prospectively beyond 24 months follow-up. Retrospective observational data comparing both techniques is conflicting. Previously published meta-analysis comparing upper sternotomy AVR and conventional sternotomy AVR found no evidence of early- to medium-term survival benefit or increased risk with minimally invasive surgery via limited hemi-sternotomy[3]. Nair et al. previously reported all cause death of 10% in mini-sternotomy group and 7% in conventional group at a mean follow-up of 2 years[4]. Further retrospective analysis published in 2019 comparing 30-day mortality following minimally invasive AVR and conventional AVR reported survival benefit and shorter postoperative length of stay with mini-sternotomy[7]. Previously reported postoperative length of stay in MAVRIC trial was not significantly different between two groups. Propensity matched analysis published in Perfusion comparing mini- sternotomy AVR and conventional AVR demonstrated no significant difference in mortality and mid-term survival at 3 years between two groups despite longer aortic cross-clamp time and cardiopulmonary bypass time in mini group[8].

Median follow-up analysis in our study was at 6.1 years with the shortest follow-up of 5 years and longest follow-up over 7 years. All-cause death in MAVRIC follow-up was similar and not statistically different between the two groups. Re-operation outcomes were also similar across both groups. As expected, higher EuroSCORE values were the statistically significant factor influencing combined outcome of all-cause mortality and re-operation. Other exploratory outcomes reported in our analysis included MACE events, incidence of chronic kidney disease and echocardiographic data. Prior reported studies suggested higher

incidence of low cardiac output syndrome with conventional sternotomy and longer cross-clamp times with mini-sternotomy which potentially could affect renal function. In current analysis we have not detected increased incidence of chronic kidney disease. The cross-clamp time in MAVRIC was prolonged only by 9 minutes. Rates of myocardial infarctions were low in our analysis likely due to strict MAVRIC enrolment criteria excluding patients with significant coronary artery disease on angiogram. Incidence of MI and stroke were similar between two groups. Overall, the results of long-term analysis of MAVRIC trial support previously published evidence of the early- to medium-term safety of mini-sternotomy AVR.

Mini-sternotomy AVR in MAVRIC trial was performed using a 5-7cm midline incision extending 1cm below the manubrium sternal junction. This technique is extensively used and has been described previously[9]. Alternative J or L shaped incisions can be used when mini-sternotomy incision extends to the 3rd or 4th intercostal space. We reasoned that if major difference was to be found between sternotomy and mini-sternotomy, it would be observed when the sternum was least disrupted. Another technique using right anterior thoracotomy access can be utilised to perform AVR with minimally invasive approach. Previously published observational analyses suggest comparable outcomes of minimally invasive AVR via anterior right thoracotomy to conventional sternotomy with regards to early to medium term morbidity and mortality[10]. Retrospective data from Italy analysed 1130 patients undergoing mini-sternotomy and right mini-thoracotomy approach. The analysis suggested safety and efficacy of both approaches with a signal towards higher rates of reoperation for bleeding in right mini-thoracotomy group[11]. Further recently reported data on endoscopic approach for AVR suggested low mortality and comparable morbidity outcomes[12]. Long-term outcomes of randomised control trials are, however, lacking.

Current analysis has several limitations. First, the MAVRIC trial wasn't specifically powered to detect long-term MACE outcomes, the original power calculation was based on clinically significant bleeding events and not survival outcome. Given current sample size, the study is underpowered for all-cause mortality outcome. If we consider the event rate in the conventional sternotomy group (18.5%) and a target 20% relative difference in death/reoperation for the 6.1 years study period, then the event rate in the mini-sternotomy group will be 15.4%. Based on the observed sample sizes for experimental

subjects (135) and control subjects (135), we will be able to reject the null hypothesis that the failure rates for experimental and control subjects are equal with probability (power) 0.104. The Type I error probability associated with the test of this null hypothesis is 0.05. At alpha=0.05 and 80% power, 2299 patients would be needed in each arm to detect 20% relative difference. Current exploratory analysis, however, is based on the largest, randomised clinical trial to date comparing mini-sternotomy and conventional sternotomy. Second, the long-term analysis was conducted through electronic records review as opposed to clinical follow-up. This could potentially exclude patients who have recently relocated. The electronic follow-up, however, was completed for all patients and cross checked by two independent assessors from multiple sources. All 270 patients originally recruited into MAVRIC trial were involved in the long-term analysis. Third, echocardiography data was not available for all study participants given various echocardiographic follow up rules amongst cardiologists in different centres.

We believe that long-term analysis of MAVRIC trial generates hypotheses for future prospective trials comparing long-term safety and efficacy of mini-sternotomy AVR to conventional AVR.

Figure 3.

Conclusion

In this exploratory analysis, mini-sternotomy AVR demonstrates no significant difference in all-cause mortality, MACE events and reoperation outcomes to conventional AVR. The results of this analysis support previously published reviews assessing early- and medium-term outcomes of mini-sternotomy.

Table 1: Baseline characteristics of participants by group

	Mini-Sternotomy Group	Conventional Sternotomy Group
Age		
Mean (SD)	69.3 (9.3)	68.7 (8.4)
Gender n (%)		
Male	78(57.8)	87(64.4)
Female	57(42.2)	48(35.6)
Body mass index (kg/m^2)		
Mean (SD)	30.5 (5.6)	30.4 (6.1)
EuroSCORE: Mean (SD)		
Logistic	5.2 (3.5)	5.1 (3.5)
II-mean	1.5 (1.1)	1.5 (1.2)
NYHA class: n (%)		
I	24(17.8)	18(13.3)
II	68(50.4)	66(48.9)
III	40(29.6)	46(34.1)
IV	3(2.2)	5(3.7)
Valve type: n (%)		
Biological and sutureless	4(3.0)	3(2.2)
Biological prosthesis	96(71.1)	98(72.6)
Mechanical prosthesis	35(25.9)	34(25.2)

Table 2: Exploratory clinical and echocardiographic outcomes, by group

	Mini-Sternotomy Group	Conventional Sternotomy Group	P-value
Exploratory clinical outcomes			
Renal failure, n (%)	31 / 122 (25)	26 / 112 (23)	0.70
Stroke, n (%)	13 / 118 (11)	9 / 102 (8)	0.59
Myocardial infarction, n (%)	4/118 (3)	0 / 102 (0)	0.23
Echocardiographic parameters			
Peak aortic gradient, mmHg (SD)	31.1 (16.1)	33.7 (16.5)	0.31
Mean aortic gradient, mmHg (SD)	15.6 (8.6)	17.7 (9.2)	0.16
Aortic regurgitation severity			
None, n (%)	48 / 68 (71)	34 / 50 (68)	0.86
Mild, n (%)	14 / 68 (21)	10 / 50 (20)	
Moderate, n (%)	5 / 68 (7)	4 / 50 (8)	
Severe, n (%)	1 / 68 (2)	2 / 50 (4)	

Figure legends.

Figure 1. Comparison of the composite outcome of all-cause mortality and re-do AVR for patients undergoing conventional sternotomy and manubrium limited sternotomy. No statistically significant difference in composite outcome was seen across both groups.

Figure 2. Comparison of all-cause mortality in patients undergoing isolated AVR via full sternotomy versus manubrium limited mini-sternotomy. No significant difference was seen in all-cause mortality between two groups at the median follow-up of 6.1 years.

Figure 3. Isolated AVR for severe aortic stenosis via mini-sternotomy demonstrates comparable outcomes to AVR via full sternotomy at the median follow-up of 6.1 years.

Data availability statement: Anonymised data from this study maybe available to the scientific community subject to appropriate ethical approval. Requests for data should be directed to the senior author.

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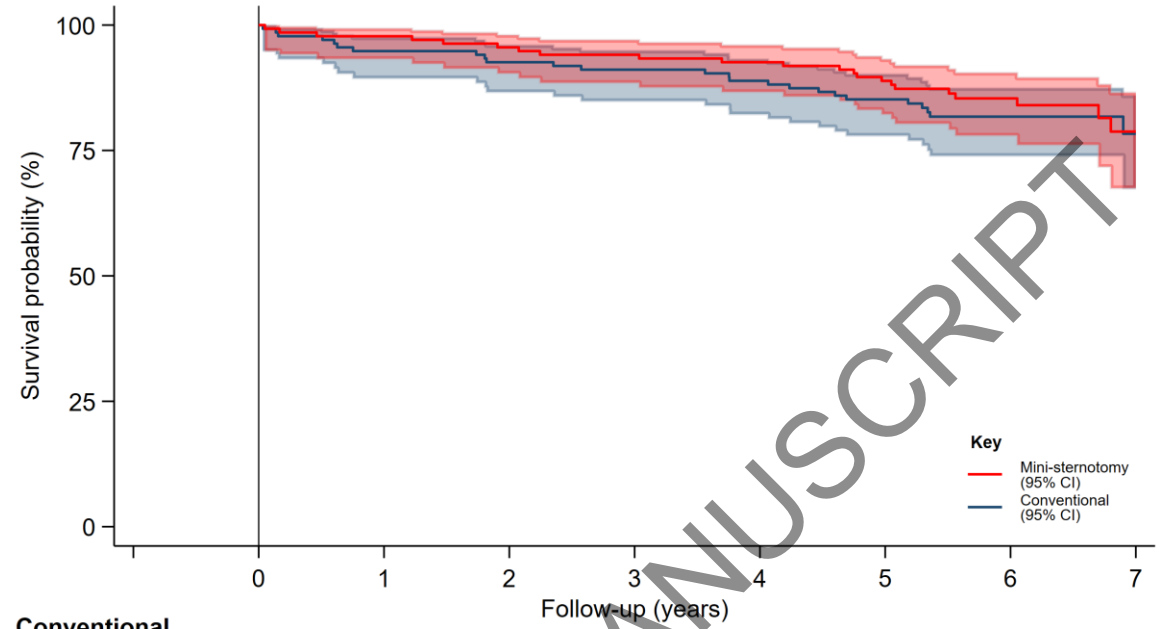
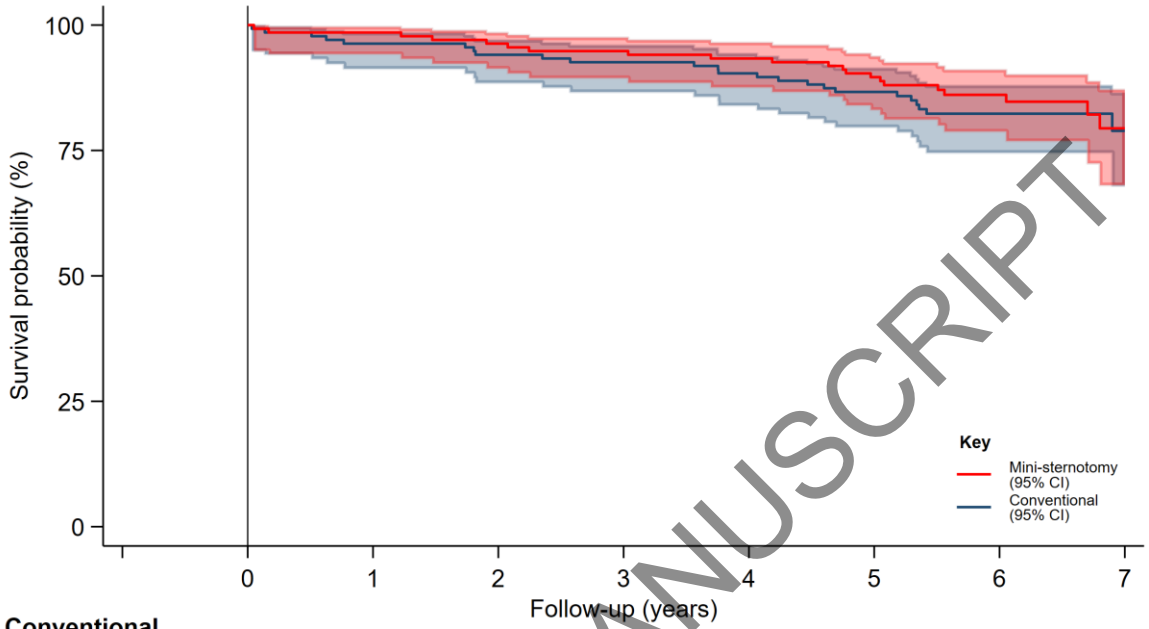
Figure 1 composite outcome



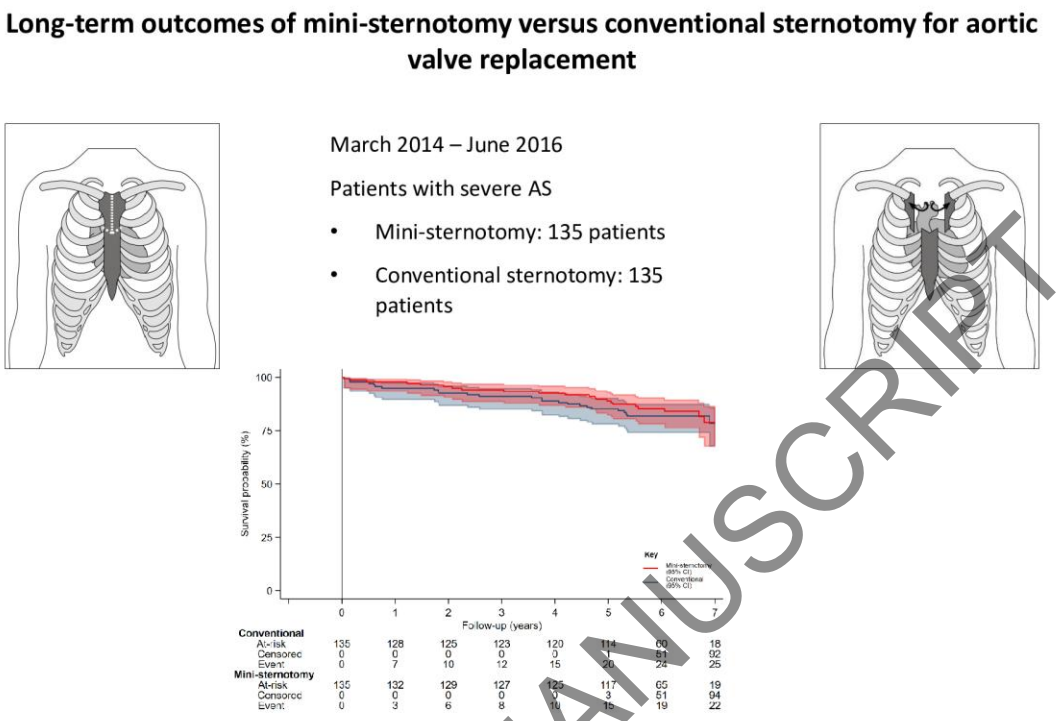
Conventional								
At-risk	135	128	125	123	120	114	60	18
Censored	0	0	0	0	0	1	51	92
Event	0	7	10	12	15	20	24	25
Mini-sternotomy								
At-risk	135	132	129	127	125	117	65	19
Censored	0	0	0	0	0	3	51	94
Event	0	3	6	8	10	15	19	22

Figure 2 mortality outcome



Conventional								
At-risk	135	130	127	125	122	116	61	18
Censored	0	0	0	0	0	1	51	93
Event	0	5	8	10	13	18	23	24
Mini-sternotomy								
At-risk	135	133	130	128	126	118	65	19
Censored	0	0	0	0	0	3	52	95
Event	0	2	5	7	9	14	18	21

Figure 3 graphic-picture (1)



Mini-sternotomy AVR demonstrates comparable long-term mortality and re-operation outcomes to conventional sternotomy AVR