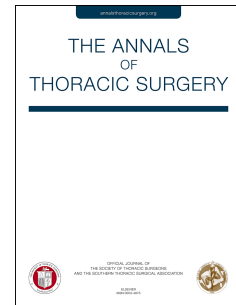


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Minimally Invasive Vs. Conventional Aortic Valve Replacement With Rapid-Deployment Bioprostheses

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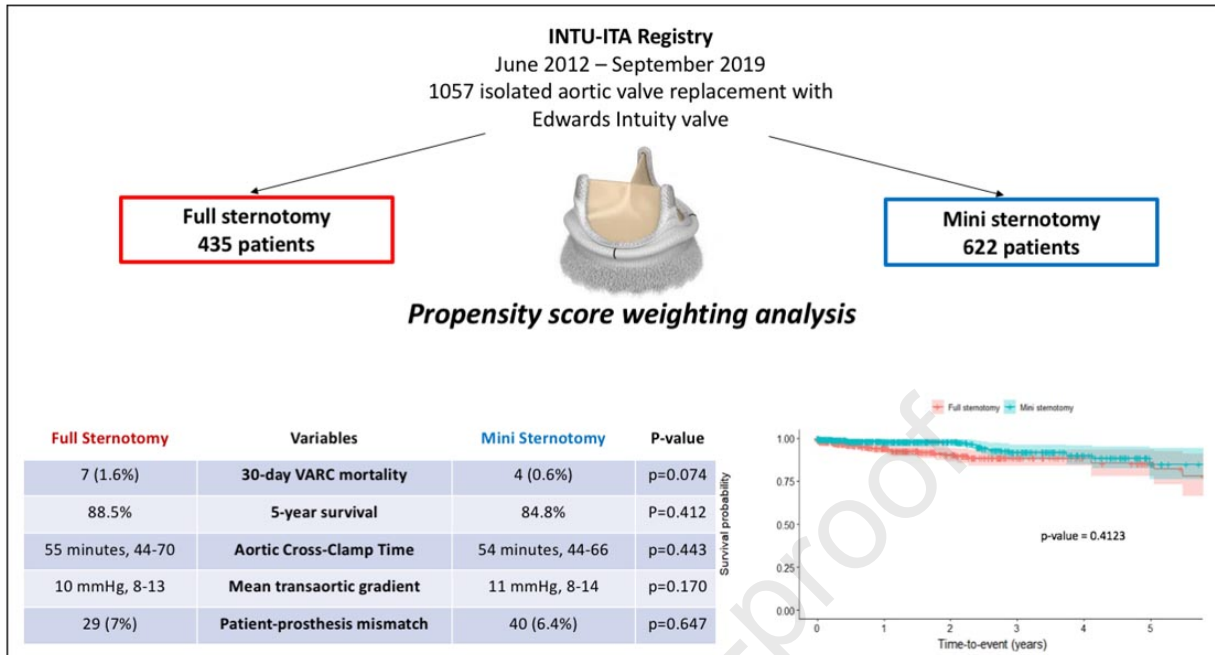
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Minimally Invasive Vs. Conventional Aortic Valve Replacement With Rapid-Deployment Bioprostheses

Running head: Rapid-deployment bioprostheses

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Abstract

Background: Aim of this multicenter retrospective study was to compare early and mid-term clinical and hemodynamic results of aortic valve replacement (AVR) with rapid-deployment bioprostheses (RDB) performed through conventional full-sternotomy versus mini-sternotomy.

Methods: Data from the Italian multicenter registry of AVR with RDB (INTU-ITA registry) were analyzed. Patients were divided into two groups: full sternotomy (FS) and mini-sternotomy (MS). Primary endpoint was the comparison of early and mid-term mortality. Secondary endpoints were: comparison of intra-operative variables, complications and hemodynamic performance. A propensity score weighting approach was employed for data analysis.

Results: A total of 1057 patients were analyzed: 435 (41.2%) and 622 (58.8%) in Group FS and MS, respectively. Thirty-day mortality was 1.6% and 0.6% in FS and MS groups, respectively ($p=0.074$). CPB time was 78.5 minutes and 83 minutes in FS and MS group, respectively ($p=0.414$). In the overall cohort, the incidence of intraoperative complications and of device success was 3.8% (40 patients) and 95.9% (1014 patients), respectively with no significant differences between groups. Survival at 1, 3, 5 years was 94.1% and 98.1%, 88.5% and 91.8%, 85.2% and 84.8% in FS and MS groups, respectively ($p=0.412$). The two groups showed similar postoperative gradients (Median mean gradient, FS: 10.0 mmHg, MS: 11.0 mmHg; $p=0.170$) and also similar incidence of patient-prosthesis mismatch (FS: 7%, MS: 6.4%, $p=0.647$).

Conclusions: According to our data, RDB allow to perform minimally-invasive AVR with similar surgical times and similar clinical and hemodynamic outcomes than conventional surgery and should be considered the first choice in these procedures.

Abstract word count: 250

The treatment of aortic valve stenosis has been rapidly evolving in the last decades. Surgical aortic valve replacement (SAVR) through full sternotomy is a well-established procedure that has demonstrated excellent long-term event-free survival and quality of life in patients of nearly all risk-profile^{1,2}. Alternatively, transcatheter aortic valve replacement (TAVR) is a microinvasive procedure³ that allows to prevent cardiopulmonary bypass (CPB) and aortic cross-clamping (ACC), but its long-term results are still not available and this is a matter of concern for its widespread application^{4,5}. Minimally invasive aortic valve replacement (MI-AVR) allows to perform SAVR with low postoperative morbidity and high patient satisfaction⁶⁻⁸. However, MI-AVR requires a more complex surgical set up as well as a longer learning curve and it is associated with longer CPB and ACC times⁹⁻¹¹. Rapid-deployment bioprostheses (RDB) have been introduced into clinical practice with the aim to reduce surgical times and, at the same time, to facilitate minimally invasive approaches. Based on transcatheter valve technology, RDB substitute pledgeted or continuous annular suturing with a sealing frame that anchors the prosthesis into the left ventricular outflow tract (LVOT) after resection of the diseased native aortic valve and annular decalcification. Our hypothesis is that RDB might reduce the technical complexity of MI-AVR through mini-sternotomy (MS) making it similar to full-sternotomy SAVR. The aim of this multicenter retrospective study was to compare, with a propensity score analysis, early and mid-term results of AVR with RDB through conventional full sternotomy versus a minimally invasive approach through MS.

Patients and Methods

Patients

Data from 23 Italian cardiac surgery centers were included in the INTU-ITA registry, a “real-world” “all-comers” independent multicenter registry, that includes patients who underwent SAVR with the RDB Intuity and its evolution Intuity Elite (Edwards Lifesciences, Irvine, CA) valve. Details about the INTU-ITA registry have been already described¹². The registry includes 1698 patients operated on in a period from June 2012 to September 2019. For this analysis, only patients who received first-time isolated AVR through full-sternotomy or minimally invasive approach through upper mini-sternotomy (MS) (inverted T- or J- shape) were considered. Only 60 patients (3.5%) underwent

SAVR through a right anterior mini-thoracotomy and were excluded from the analysis. Patients were divided in two groups according to the surgical access: full sternotomy (Group FS) or mini-sternotomy (Group MS). Data were collected at each study site and then anonymously sent to the University of Padova (coordinating center) for storage and analysis. The study was approved by the ethic committee and patients' informed consent for the procedure and for data collection for scientific purposes was always collected.

Surgical Procedure

The choice to implant a RDB as well as the choice of the surgical access (full or mini-sternotomy) was based on surgeon's preference and on the policy of each center. Patients with aortic insufficiency, bicuspid aortic valves and infective endocarditis were not considered eligible for RDB implantation and therefore they were not included in the INTU-ITA registry. The implantation of the Edwards Intuity valve was performed according to the manufacturer's instructions for use and described in details elsewhere¹³. Briefly, after ACC and aortotomy, the native valve leaflets were excised and debridement of the annulus was done as for conventional AVR. Then, the annulus was sized and three guiding sutures were passed at the nadir of each sinus and subsequently on the valve sewing ring. If there was a doubt between two sizes the smaller was generally chosen in order to avoid oversizing that carries the risk of valve pop-up leading to severe regurgitation. Then, the valve was parachuted into the aortic annulus and stabilized with three tourniquets. The balloon was inflated for 10 seconds under a pre-determined pressure (4.5 atmospheres for sizes 19 and 21; 5 atmospheres for sizes 23, 25 and 27), subsequently the delivery system was removed and the guiding sutures were tied before closing the aorta in the usual fashion.

Definitions and Follow-up

Preoperative variables were defined according to the EuroSCORE definitions¹⁴ and postoperative outcomes were defined according to the updated Valve Academic Research Consortium (VARC-2) definitions¹⁵. Clinical and echocardiographic follow-up was performed according to the following time-points: before the operation, at hospital discharge or within the first 30 postoperative days,

and then on a yearly basis (according to each center protocol) with follow-up visits at the study site or by means of telephone interviews.

Endpoints

Primary endpoint of this study was the comparison of early and mid-term mortality in the two groups. Secondary endpoints were: comparison of the two groups in terms of intra-operative variables, major complications and hemodynamic performance.

Statistical Analysis

Descriptive statistics was reported as first quartile/median/third quartile for continuous variables and absolute number (percentages) for categorical variables. A propensity score weighting approach was employed to account for potential confounding related to the non-random allocation of the patients into the two groups. Propensity scores were estimated using Generalized Boosted Models algorithm and a trimming of the weights was performed at 90° quartile. The effect of each surgical approach on the postoperative outcomes of interest was assessed using a weighted regression approach with Linear Mixed-Effects Models, including a random effect on the center. The trend of echocardiographic parameters was evaluated using a weighted regression approach, with Linear Mixed-Effects Models, including a random effect on the center. The significance of the trend was assessed using a sequential decomposition of the deviance based on contributions of the fixed effects. The survival distribution in the two groups was evaluated using a weighted Kaplan-Meier approach, and the distribution of the cardiovascular mortality in the two groups was evaluated using weighted cumulative incidence function. The analysis was performed using R software (version 3.6.1)¹⁶, with the packages Twang and WeightIt (propensity score estimation and weighting implementation), lm4 (model estimation), survey, and rms.

Results

A total of 1057 patients who underwent isolated SAVR with the study device were included in the analysis. Patients were divided into two groups, FS: 435 patients (41.2%), and MS: 622 patients

(58.8%). Baseline characteristics of the overall population and of the two groups is shown in Table 1. Patients undergoing MS were more likely to suffer from chronic obstructive pulmonary disease (18% vs 11%, $p=0.005$) while FS patients were more likely to have associated coronary artery disease (19% vs. 13%, $p=0.020$) as well as mitral valve regurgitation ($p<0.001$). However, the overall risk profile, assessed by STS-PROM score, was low and similar between groups (overall 1.80%, FS: 1.81%, MS: 1.79%; $p=0.254$). Operative variables are shown in Table 2. Median CPB and ACC times were 80 and 55 minutes, respectively, in the overall population. CPB time was 78.5 minutes and 83 minutes in FS and MS group, respectively ($p=0.414$) while ACC time was 55 minutes and 54 minutes in FS and MS group, respectively ($p=0.443$). In the overall cohort, the incidence of intraoperative complications and of device failure (according to VARC) was 3.8% (40 patients) and 95.9% (1014 patients), respectively with no significant differences between groups. In particular, there were 11 (2.5%) conversions from mini-sternotomy to full-sternotomy in the MS group for bleeding-related problems discovered intraoperatively. Postoperative outcomes are depicted in Table 3. VARC mortality was 1% (11 patients) in the overall population and it was 1.6% (7 patients) and 0.6% (4 patients) in FS and MS groups, respectively ($p=0.074$). Causes of death were cardiovascular in 6 patients (3 major arrhythmias, 2 myocardial infarctions, 1 aortic dissection) and non-cardiovascular in the remaining 5 patients (3 pneumonias and 2 septic shocks). We did not observe significant differences in terms of myocardial infarction, stroke, bleeding, vascular complications, patient-prosthesis mismatch and paravalvular leak. Furthermore, intensive care (FS: 45 hours, MS: 46 hours; $p=0.468$) and hospital stay (FS: 8 days, MS: 7 days; $p=0.461$) were similar between groups. Median follow-up was 337 days (52-814). Kaplan-Meier survival in the overall population and in the two groups is shown in Figure 1. Survival at 1, 3, 5 years was 94.1% and 98.1%, 88.5% and 91.8%, 85.2% and 84.8% in FS and MS groups, respectively ($p=0.412$). Valve size distribution was similar between groups, as shown in Figure 2. As far as prosthesis hemodynamics is concerned, the two groups showed similar postoperative gradients (Overall median mean gradient 10.0 mmHg; FS: 10.0 mmHg, MS: 11.0 mmHg; $p=0.170$) and also similar incidence of patient-prosthesis mismatch (overall: 6.5%. FS: 7%, MS: 6.4%,

$p=0.647$). The two groups showed good prosthesis hemodynamic performance over time with no differences between groups (Figure 3).

Comment

The main finding of this study is that rapid deployment Intuity bioprostheses allow to perform MI-AVR through MS with similar surgical times and similar clinical and hemodynamic outcomes than conventional surgery. Although several studies have demonstrated that MI-AVR has excellent results in terms of postoperative complications, blood loss, postoperative pain and length of hospital stay^{6,11,17,18}, MI-AVR is still not universally adopted since it is technically more demanding and there are concerns about prolongation of surgical times. In fact, two meta-analyses comparing conventional AVR through full sternotomy versus MI-AVR demonstrated that the latter requires longer CPB and ACC time^{6,17}. Prolonged CPB and ACC times have been associated with increased morbidity and mortality both in low- and in high-risk patients¹⁹. Furthermore, Ranucci and coll. demonstrated that ACC time was an independent predictor of severe cardiovascular morbidity, with an increased risk of 1.4% per one minute increase and that patients with a left ventricular ejection fraction <40%, and also diabetic patients, showed the most relevant clinical benefits induced by a reduction in ACC time²⁰. Therefore, the main question that arises when talking about MI-AVR is: should we really consider “minimally invasive” an approach that, although performed through a small skin incision, not only does it require CPB and ACC but also has longer surgical times? It is still debated whether the invasiveness of cardiac surgery is only related to the length of skin incision or mainly to the complexity and to the duration of the operation. In this regard, the definition of “*micro-invasive cardiac surgery*” has been recently introduced³ in order to differentiate between surgical procedures that are performed through a small skin incision but still require CPB and ACC as well as opening of the chest and general anesthesia (minimally-invasive) from those that are performed on the beating heart, with no CPB nor ACC, often percutaneously and in local anesthesia (micro-invasive; e.g. transcatheter aortic valve replacement, transapical mitral neochordae implantation, etc.). In this context, the possibility to have a device that allows to overcome the issues related to surgical times enables to optimize MI-AVR since it combines the

advantages of minimally invasive access with those of conventional surgery. Despite the mean age of 75 years, TAVI was not clearly indicated in these patients because of the low-risk profile (STS-PROM: 1.8%); furthermore, in patients belonging to the “gray zone” between TAVI and RDB, the latter showed similar outcomes but lower incidence of paravalvular leak²¹. In our series overall paravalvular leak rate was low, below 10%, with no cases of severe PVL, and similar to other series^{13,22}. Considering also that this cohort includes also the roll-in cases of all centers we believe that, as experience increases, PVL rate will decrease because all issues related to sizing, annular shape and decalcification will be better understood. Sutureless and rapid-deployment aortic bioprostheses have shown good clinical and hemodynamic results^{12,22} and there are studies that report shorter surgical times²³. There are currently two available devices: sutureless Perceval (Livanova, London, UK) and rapid-deployment Intuity. This difference in nomenclature is due to the fact that during Perceval implantation the three guiding sutures are removed while during Intuity implantation they are tied and therefore the latter is not a truly sutureless valve. A prospective study that compared MI-AVR with RDB versus conventional AVR with stented valves found shorter ACC time in the RDB group²⁴ while a recently published meta-analysis found that sutureless bioprostheses can be implanted with shorter ACC and CPB if compared to conventional devices²⁵. Although MI-AVR with conventional stented bioprostheses can be facilitated by the use of automated knot fastener device there is still no evidence to support its wide-spread use in valve surgery²⁶; further studies should compare MI-AVR with this device vs. MI-AVR with RDB/Sutureless bioprostheses. In our study, we found similar ACC and CPB times between FS and MS and this is not surprising since the technique of implant requires only three guiding sutures at the nadir of each sinus and, despite the smaller surgical field in the MS group, their positioning does not appear to be more time consuming. Given the similar surgical times and their association with outcomes it is not surprising as well that we didn't find significant differences in terms of postoperative complications; in fact, we observed similar intensive care unit and hospital length of stay and similar major complications rate between groups. In particular, permanent pace-maker implantation rate was similar to that reported in other series^{13,24,27}, with no differences between groups. Conduction disorders have been demonstrated to occur in up to one third of patients after

AVR with RDB and left bundle branch block is the most frequent. This is probably due to the compression that the balloon expandable skirt performs on the left ventricular outflow tract²⁸. Also, medium-term survival was excellent and similar between groups. Moreover, valve hemodynamics was good both at discharge and at follow-up with a remarkably low incidence of patient-prosthesis mismatch^{22,27,29}. Looking at the literature but also the data presented in this study and based on the experience from this registry we believe that patients who would benefit more from a RDB implantation are those undergoing minimally invasive surgery and/or combined procedures but also those with small aortic annuli due to the good hemodynamic performance of this device.

Limitations

Limitations of this study are related to its retrospective nature. There is no adverse event adjudication committee nor echocardiographic core-lab; adverse events were self-adjudicated by participating centers. Echocardiographic examinations were done by different physicians using different machines.

Conclusions

According to our data, there are no differences in terms of surgical times, complications, survival and hemodynamic performance in patients undergoing aortic valve replacement with rapid-deployment bioprostheses though mini-sternotomy or full-sternotomy. Therefore, we believe that, in experienced hands, rapid-deployment bioprostheses should be considered the first choice for minimally invasive aortic valve replacement.

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Variables	Overall patients (n=1057)	Full sternotomy (n=435)	Mini sternotomy (n=622)	P-value
Age, years (median, IQR)	75.0 (69.4-79.0)	75.0 (69.7-79.0)	75.0 (69.3-79.0)	0.545
Gender				
Males, n (%)	508 (48.1)	214 (49.2)	294 (47.3)	0.553
Females, n (%)	549 (51.9)	221 (50.8)	328 (52.7)	
BMI (median, IQR)	25.8 (23.4-29.4)	26.2 (23.5-29.2)	25.4 (23.2-29.6)	0.160

Table 1: Baseline characteristics

Table legend: BMI= body mass index; CAD=coronary artery disease; COPD= chronic obstructive pulmonary disease; IQR= interquartile range; LVEF= left ventricle ejection fraction; NYHA=New York Heart Association; STS-PROM= Society of Thoracic Surgeons-Predicted Risk of Operative Mortality

Diabetes mellitus, n (%)	247 (23.4)	87 (20.0)	160 (25.7)	0.062
Extracardiac arteriopathy, n (%)	143 (13.5)	66 (15.2)	77 (12.4)	0.191
COPD, n (%)	158 (14.9)	49 (11.3)	109 (17.5)	0.005
Serum creatinine, mg/dL (median, IQR)	0.90 (0.75-1.10)	0.89 (0.76-1.10)	0.90 (0.74-1.07)	0.297
History of CAD, n (%)	164 (15.5)	81 (18.6)	83 (13.3)	0.020
NYHA functional class				0.543
Class I, n (%)	92 (8.7)	38 (8.7)	54 (8.7)	
Class II, n (%)	436 (41.2)	168 (38.6)	268 (43.1)	
Class III, n (%)	503 (47.6)	217 (49.9)	286 (46.0)	
Class IV, n (%)	26 (2.5)	12 (2.8)	14 (2.2)	
LVEF, % (median, IQR)	60.0 (55.0-65.2)	60.0 (55.0-66.0)	60.0 (55.0-65.0)	0.916
Mitral valve regurgitation*				<0.001
Absent	443 (41.9)	141 (32.4)	302 (48.6)	
Mild	454 (43.0)	223 (51.3)	231 (37.1)	
Moderate	124 (11.7)	53 (12.2)	71 (11.4)	
Severe	15 (1.4)	9 (2.1)	6 (1.0)	
*21 missing				
STS-PROM, % (median, IQR)	1.80 (1.24-2.59)	1.81 (1.26-2.70)	1.79 (1.23-2.52)	0.254

Table 2: Intraoperative variables

Variables	Overall patients (n=1057)	Full sternotomy (n=435)	Mini sternotomy (n=622)	Estimate	95% CI of Estimate	P-value
CBP, minutes (median, IQR)	80.0 (64.0-99.0)	78.5 (64.0-96.0)	83.0 (64.0-100.0)	1.062	0.672-1.677	0.414
ACC, minutes (median, IQR)	55.0 (44.0-68.0)	55.0 (44.0-70.0)	54.0 (44.0-66.0)	1.034	0.707-1.511	0.443
Peripheral cannulation	96 (9.1)	13 (3.0)	83 (13.3)	-	-	-
Intraoperative complications, n (%)	40 (3.8)	13 (3.0)	27 (4.3)	2.116	0.174-25.702	0.310
VARC Device success, n (%)	1014 (95.9)	408 (93.8)	606 (97.4)	1.001	0.001-1458.7	0.499

Table legend: ACC=aortic cross-clamp; CI=confidence interval; CBP=cardiopulmonary bypass; IQR=interquartile range; VARC=Valve Academic Research Consortium

Table 3: Postoperative variables

Variables	Overall patients (n=1057)	Full sternotomy (n=435)	Mini sternotomy (n=622)	Estimate	95% CI of Estimate	P-value
ICU stay, hours (median, IQR)	45 (24-48)	45 (24-49)	46 (23-48)	1.062	0.298-3.789	0.468
Hospital stay, days (median, IQR)	7 (6-10)	8 (7-11)	7 (6-9)	1.058	0.410-2.729	0.461
VARC mortality, n (%)	11 (1.0)	7 (1.6)	4 (0.6)	0.312	0.074-1.000	0.074
VARC acute myocardial injury, n (%)	7 (0.7)	2 (0)	5 (0.8)	1.936	0.397-14.559	0.444
VARC stroke, n (%)	26 (2.5)	11 (3)	15 (2.4)	0.662	0.017-25.436	0.573
VARC bleeding, n (%)	54 (5.1)	22 (5)	32 (5.1)	1.301	0.144-11.778	0.422
VARC vascular complications, n (%)	20 (1.9)	9 (2)	11 (1.8)	1.151	0.097-13.681	0.462
Pace-maker implantation, n (%)	69 (6.5)	29 (7)	40 (6.4)	1.036	0.382-2.809	0.476
Patient-prosthesis mismatch						
Absent, n (%)	988 (93.5)	406 (93)	582 (93.6)	0.596	0.063-5.679	0.647
Present, n (%)	69 (6.5)	29 (7)	40 (6.4)			
Absent + Mild, n (%)	1053 (99.6)	432 (99)	621 (99.8)	0.458	0.010-21.024	0.631
Moderate, n (%)	4 (0.4)	3 (1)	1 (0.2)			
Paravalvular leak*						
Absent, n (%)	927 (88.7)	385 (88.5)	503 (80.9)	1.231	0.765-1.980	0.392
Mild, n (%)	57 (5.4)	20 (4.6)	37 (5.9)			
Moderate, n (%)	4 (0.4)	1 (0.2)	3 (0.5)			

*69 missing

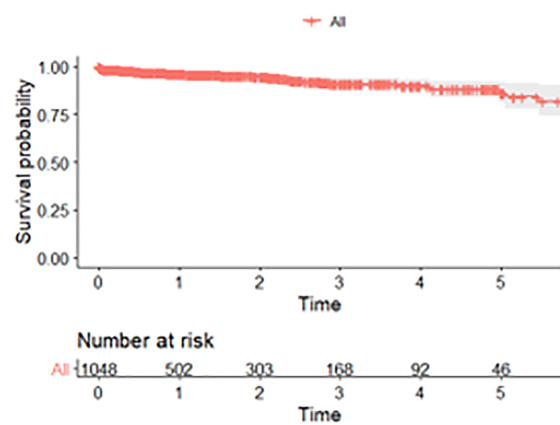
Table legend: CI= confidence interval; ICU= intensive care unit; IQR= interquartile range; VARC= Valve Academic Research Consortium

Figure Legends

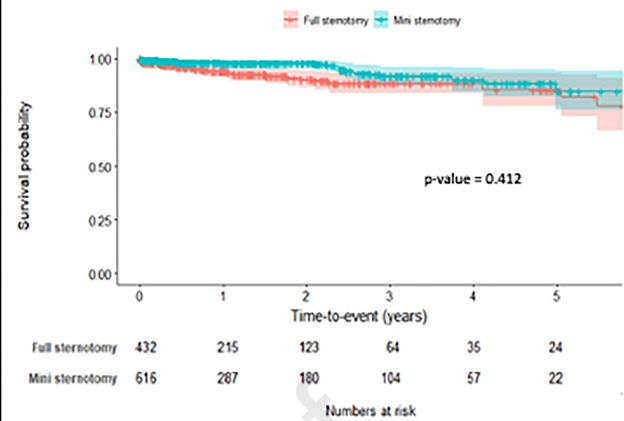
Figure 1: Kaplan-Meier analysis for survival in the overall population (1A) and in the two study groups (FS: full sternotomy; MS: mini sternotomy) (1B).

Figure 2: Valve size distribution in the two study groups (FS: full sternotomy; MS: mini sternotomy).

Figure 3: Changes of mean trans-aortic gradients over time, divided into small (19-21-23 mm), and large (25-27 mm) device size.



1A



1B

