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*A*ortic *V*alve Repl*A*cemen*T* versus Conservative Treatment in *A*symptomatic Seve*R*e Aortic Stenosis: The AVATAR Trial

Running Title: *Banovic et al.; Intervention in asymptomatic aortic stenosis*

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Abstract

Background: Surgical aortic valve replacement (SAVR) represents a class I indication in symptomatic patients with severe aortic stenosis (AS). However, indications for early SAVR in asymptomatic patients with severe AS and normal left ventricular function remain debated.

Method: The Aortic Valve replAcemenT versus conservative treatment in Asymptomatic seveRe aortic stenosis (AVATAR) trial is an investigator-initiated international prospective randomized controlled trial that evaluated the safety and efficacy of early SAVR in the treatment of asymptomatic patients with severe AS, according to common criteria (valve area ≤1 cm2 with aortic jet velocity >4 m/s or a mean trans-aortic gradient ≥40 mm Hg), and with normal LV function. Negative exercise testing was mandatory for inclusion. The primary hypothesis was that early SAVR would reduce the primary composite endpoint of all-cause death, acute myocardial infarction, stroke or unplanned hospitalization for heart failure, as compared to a conservative strategy according to guidelines. The trial was designed as event-driven to reach a minimum of 35 prespecified events. The study was performed in 9 centers in 7 European countries.

Results: Between June 2015 and September 2020, 157 patients (mean age 67 years, 57% men) were randomly allocated to early surgery (n=78) or conservative treatment (n=79). Follow-up was completed in May 2021. Overall median follow-up was 32 months: 28 months in the early surgery group and 35 months in the conservative treatment group. There was a total of 39 events, 13 in early surgery and 26 in conservative treatment group. In the early surgery group, 72 patients (92.3%) underwent SAVR with operative mortality of 1.4%. In an intention-to-treat analysis, patients randomized to early surgery had a significantly lower incidence of primary composite endpoint than those in the conservative arm (HR 0.46, 95% CI 0.23-0.90, p=0.02). There was no statistical difference in secondary endpoints, including all-cause mortality, first heart failure hospitalizations, major bleeding or thromboembolic complications, but trends were consistent with the primary outcome.

Conclusion: In asymptomatic patients with severe AS, early surgery reduced a primary composite of all-cause death, acute myocardial infarction, stroke or unplanned hospitalization for heart failure compared with conservative treatment. This randomized trial provides preliminary support for early SAVR once AS becomes severe, regardless of symptoms.

Clinical Trial Registration: NCT02436655 (URL: www. clinical trials.gov)

Key Words: aortic stenosis, asymptomatic, intervention, randomized controlled trial

Non-standard Abbreviations and Acronyms:
AVATAR: *A*ortic *V*alve Repl*A*cemen*T* versus Conservative Treatment in *A*symptomatic Seve*R*e Aortic Stenosis
AS: Aortic stenosis
SAVR: Surgical aortic valve replacement
TAVR: transcatheter aortic valve replacement
LVEF: Left ventricular ejection fraction
DSMB: data and safety monitoring board
TTE: transthoracic echocardiography
MACE: Major adverse cardiovascular events
SAE: Serious adverse events

Clinical Perspective

What is new?

- It is unclear whether early/elective surgical aortic valve replacement is beneficial in asymptomatic patients with severe aortic stenosis and normal left ventricular systolic function

What are the clinical implications?

- In this randomized clinical trial that included 157 patients, when compared to subjects randomized to the conservative surgery, subjects randomized to early surgical aortic valve replacement had a lower incidence of primary composite endpoint including all-cause death, acute myocardial infarction, stroke or unplanned hospitalization for heart failure (15.22% (13 events) vs 34.70% (26 events) in the early surgery and the conservative groups, respectively).
- These results provide preliminary support for early aortic valve replacement in severe AS regardless of symptoms.

Introduction

Surgical aortic valve replacement (SAVR) and, more recently, transcatheter aortic valve replacement (TAVR) procedures, are strongly recommended (class I recommendation) in symptomatic patients with severe aortic stenosis (AS) to relieve symptoms and improve survival[1,2]. However, indications for valve replacement in asymptomatic patients with severe AS remain a matter of debate[3]. The problem is of importance since almost a quarter of patients with severe AS referred to hospital for the evaluation of severe AS were asymptomatic in a recent survey, and the proportion is likely to be higher in the general population[4]. Current international cardiology guidelines recommend watchful waiting and delaying AVR until onset of AS-related symptoms or left ventricular (LV) systolic dysfunction[1-2]. The decision to operate on an asymptomatic patient with severe AS remains subjective and supported mainly by observational studies with a low level of evidence. Only one randomized trial, performed at four medical centers within one country, appears to support early surgery in asymptomatic patients with very severe, critical AS[5]. However, true absence of symptoms was not well documented as no regular exercise testing was performed[6-7].

The Aortic Valve replAcemenT versus conservative treatment in Asymptomatic seveRe aortic stenosis (AVATAR trial, NCT02436655) is an investigator-initiated, prospective, multinational, randomized, controlled, parallel group, event-driven trial that evaluated the safety and efficacy of early surgery in the treatment of asymptomatic patients with severe AS and normal LV ejection fraction (LVEF) who were asymptomatic and had a negative exercise test. The primary hypothesis is that early surgery will reduce a primary composite outcome comprised of all cause death, acute myocardial infarction, stroke or unplanned hospitalization for heart failure, as compared with patients managed conservatively according to guidelines, i.e watchful waiting with optimal treatment of co-

morbidities and SAVR after symptoms onset or a drop in left ventricular ejection fraction (LVEF).

Methods

The authors declare that they will make the data, methods used in the analysis, and materials used to conduct the research available to any researcher to reproduce the results or replicate the procedures.

Trial design and oversight

The trial protocol (NCT02436655) and its updated version were designed by the principal investigators and members of the Steering Committee. Patients were enrolled in 9 centers in 7 European countries (Belgium, Czech Republic, Italy, Croatia, Lithuania, Poland and Serbia). The study has been approved by Institutional Review and Ethics Committee at each participating center. No extramural funding was used to support this work. The authors, members of the Steering Committee and investigators are solely responsible for the design and conduct of this trial, all analyses, drafting and editing of the paper and its final contents.

The trial was conducted in accordance with the Declaration of Helsinki. An independent data and safety monitoring board (DSMB) adjudicated all serious adverse events and oversaw the safety of the trial. The first draft of the manuscript was prepared by the first author and was reviewed and edited by members of the Steering Committee and authors. All authors reviewed the manuscript, approved its submission for publication and vouched for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

Study Population

Consecutive patients > 18 years old presenting with severe AS according to standard echocardiographic criteria[1-2,8] were screened for enrollment. A total of 197 patients were screened of whom 157 were enrolled. The trial flowchart is shown in Figure 1. Patient enrollment per participating center is presented in the Supplementary Table 1. The trial design has been previously described[9-10]. In accordance with the 2012 European Society of Cardiology valvular guidelines on surgical indications for severe AS[11], used as the reference when the trial was designed, patients were excluded if they had exertional dyspnea, syncope or presyncope, angina, a LVEF < 50%, very severe AS (defined as maximal aortic jet velocity > 5.5m/s at rest), aortic regurgitation ≥3+, dilatation of the ascending aorta requiring replacement of aortic root or ascending aorta (> 5cm), significant mitral valve disease or if they had undergone previous cardiac surgery. We also excluded patients with any type of atrial fibrillation including present or documented history of atrial fibrillation, severe lung disease or limited life expectancy < 3 years (a full list of exclusion criteria in Supplementary appendix). Exercise testing was performed in all candidates to evaluate symptom status according to a standardized protocol (Supplemental appendix). In order to consider exercise testing negative, all candidates needed to reach a projected submaximal heart rate. Positive exercise test included onset of AS-related symptoms, fall in systolic blood pressure (≥ 20mmHg from the baseline values) or ECG or stress echocardiography signs of myocardial ischemia[12]. A total of 14 patients had a positive exercise test. Among them, 7 patients had chest pain/dyspnea with ECG changes, 2 had isolated pronounced dyspnea, 1 had dizziness and 4 did not increase their heart rate making test inconclusive. Among these 4 patients, 1 patient also experience a fall in blood pressure. To minimize inter-observer investigator variability, transthoracic echocardiography (TTE) and exercise testing were performed at each center

by the same operators throughout the trial duration using standardized procedures. All participants provided written informed consent.

Trial procedures

Each patient underwent a thorough evaluation of symptoms and medical records, and results of transthoracic echocardiography and exercise testing were reviewed within each center by the study team, including an experienced cardiologist and cardiac surgeon, and prior to confirming eligibility. Patients were randomly assigned to early surgery or conservative treatment using a Web-based interactive response system. The assignment to each treatment group was computer-generated and stratified according to the participating centers by means of a permuted-block sequence with variable block size. Details regarding trial procedures were published previously[9-10].

Patients assigned to the early-surgery group were expected to undergo early surgery within 8 weeks after randomization. Patients in conservative treatment group were referred for surgery in case of onset of AS-related symptoms, if the LVEF decreased to less than 50%, or if the peak aortic jet velocity increased each year by more than 0.3 m/s on follow-up echocardiography, according to ESC guidelines on valvular disease at the time the study was designed[11]. Conservative treatment included the treatment of risk factors and co-morbidities.

Trial endpoints

The primary endpoint was a composite of all-cause mortality or major adverse cardiovascular events (MACE) comprised of acute myocardial infarction (AMI), stroke and unplanned heart failure (HF) hospitalization needing intravenous treatment with diuretics or inotropes.

Prespecified secondary endpoints included:

- in-hospital and 30 days operative mortality in operated patients in both groups,
- repeat aortic valve surgery in operated patients in both groups,

- repeated major adverse cardiovascular events (MACE), including stroke, AMI and/or unplanned HF hospitalisation needing intravenous (iv) diuretic treatment,
- major bleeding defined as types 3, 4 and 5 according to consensus report from the Bleeding Academic Research Consortium[13],
- thromboembolic complications based on clinical symptoms, signs and imaging studies,
- time to death,
- time to first HF hospitalization

In addition, the incidence of overall serious adverse events (SAE) in both groups was analyzed. The detailed definition of SAE has been described within the Avatar trial protocol[9] and is given in the Supplementary appendix.

All patients were followed according to the protocol every 6 months with the in-person visits at the participating study center. For any event that was registered the medical records were asked for and reviewed. Adverse clinical events were adjudicated by the DSMB per protocol definitions[9,10]. DSMB members were not blinded to the treatment allocation during events review. They adjudicated the events by consensus.

Statistical analysis

The AVATAR study was designed as an "event driven" trial[14-15] with a target of 35 events and a projected total number of 312 subjects equally randomized to the 2 treatment groups. We assumed a 24-month enrolment duration and a 9% event rate at 12-months in the conservative treatment group. With this sample size, using a two-sided alpha of 5%, a Log-rank test was determined to have 80% power to detect a decrease in 12-month event rates by 5.5% i,e to 3.5% in the early surgery arm[9].

Baseline characteristics of study patients are presented as frequencies and percentages for categorical variables and median with 25^{th}-75^{th} percentiles for continuous variables.

Treatment differences on dichotomous variables were evaluated using Chi-Square tests. Continuous variables between treatments were compared by using two-sample t-tests. A Kaplan–Meier estimator was used to estimate the distribution of time to primary and time-to-event secondary endpoints (e.g. survival and time to first HF hospitalization) and a Log-rank test to compare them between the two treatment groups. A Cox proportional-hazards regression model that included treatment was used to estimate the Hazard Ratio comparing the early surgery and the conservative treatment groups. For dichotomous secondary endpoints (e.g. intraoperative or 30-day mortality), repeated MACE, thromboembolic complications, and major bleeding a logistic regression model was used to compare the two groups using odds ratios.

The primary analysis was performed as intention-to-treat (ITT) for all included patients who were randomized. In sensitivity analyses of the primary endpoint, patients randomized to the early surgery group in whom surgery was not performed were excluded. In post hoc heterogeneity analyses, we examined the consistency of the primary endpoint in six clinically relevant subgroups with formal interaction testing using Cox regression models. The factors included in the heterogeneity analyses were prospectively identified by the DSMB without access to the outcomes data.

A two-sided p-value <0.05 was considered to indicate statistical significance. The 95% confidence intervals for secondary endpoints have not been adjusted for multiple comparisons, and therefore inferences drawn from these intervals regarding secondary endpoints may not be reproducible. Statistical analyses were performed using R software, version 3.6.1 (R Project for Statistical Computing), and SAS software, version 9.4 (SAS Institute).

Results

Baseline characteristics

Between June 2015 and September 2020, 157 asymptomatic patients with severe AS were randomly allocated to either early surgery or conservative treatment. Six patients randomized into the early surgery group did not undergo surgery (Figure 1). The average age of enrolled patients was 67 years, 57% were males and median estimated operative mortality according to the Society for Thoracic Surgeons (STS) PROM score was 1.7%. The cause of AS was a degenerative valvular disease in 133 patients (84.7%), bicuspid aortic valve in 22 patients (14.0%), and rheumatic valvular disease in 2 patients (1.3%).

The early surgery and conservative treatment groups were generally well balanced with regard to their clinical characteristics, cardiovascular risk factors, baseline echocardiographic and laboratory parameters as well as medical therapy. Detailed description and comparison of baseline characteristics are summarized in Table 1.

Aortic valve replacement procedures

In the early surgery group, SAVR was performed in 72/78 patients (92.3%): 53% of patients in the early surgery group received a mechanical valve and 47% received a bioprosthetic valve. The median time from randomization to SAVR in the early surgery group was 55 days (interquartile range 36 -79).

Twenty-five patients in the conservative treatment group had surgery; 40% of patients received a mechanical valve. Median time from randomization to surgery in the conservative treatment group was 400 days (interquartile range 191-619). In 9 patients in the conservative treatment group the indication for surgery met the criteria of pre-specified trial endpoint (HF admission). In 15 patients the surgery was indicated by the onset of symptoms. Other reasons were progression of AS severity, decrease in LVEF or combination of these factors and these events were not counted in the comparative analyses (Table 2).

One patient died within one month after the surgery in the early surgery group (operative mortality 1.4%). One patient also died within 30-days after surgery in the conservative treatment group. Concomitant coronary artery bypass grafting (CABG) was performed in 3/72 patients (4.2%) in the early surgery group and 2/25 patients (8.0%) in the conservative treatment group who required surgery. All other patients underwent isolated SAVR. Post-operative hemodynamic parameters were similar between groups. Additional information about surgical procedures and post-operative complications are provided in Supplementary Tables 2 and 3 in the supplementary appendix.

Follow-up and endpoints

Although enrolment was lower than expected, the number of pre-specified events (35) was reached in October 2020 due to longer follow-up. Accordingly, the DSMB advised to stop enrolment on November the 1st, 2020. Data collection, including follow-up was completed in May 2021. The overall median follow-up of all patients was 32 months, 28 months in early surgery group and 35 months in the conservative treatment group. Contact with one patient in the early surgery group was lost prior to scheduled aortic valve replacement. This patient was analyzed in ITT analysis as being alive at latest follow-up.

There was a total of 39 events, 13 (16.6%) in early surgery and 26 (32.9%) in conservative treatment group. In a primary ITT analysis, patients randomized to early surgery had significantly lower incidence of primary composite endpoint comprising all-cause death, AMI, stroke or unplanned HF hospitalization as compared to the conservative group (15.2% vs 34.7%, , hazard ratio 0.46, 95% CI 0.23 - 0.90, p=0.02; Figure 2 and table 3A). Kaplan-Meier estimates of the individual endpoints of all-cause mortality and heart failure hospitalization tended to be higher in the conservative as compared to the early surgery group but did not reach statistical significance (Figure 3). Sudden death occurred in 6 patients of the conservative group as compared to 3 patients in the early surgery group, with one patient

dying suddenly while awaiting the surgery (Supplemental Table 4). There were no significant differences in other secondary endpoints between both groups (Table 3B and 3C). The incidence of composite endpoint-related MACE as well as overall MACE was significantly higher in the conservative treatment group as compared to early surgery group (16 (20.5%) in early surgery group vs 33 (41.8%) in conservative treatment group; p = 0.004; Table 4). The incidence of SAE was also numerically higher in the conservative treatment group without reaching statistical significance compared to the early surgery group (Supplementary Table 5 and Supplementary Figure 1 in supplementary appendix). Additional statistical analysis of the primary endpoint excluding patients who were not operated within the early surgery group was consistent with the ITT analysis (Supplementary Figure 2 in supplementary appendix). In a post-hoc heterogeneity analysis in study population dichotomized by median values, no significant interaction for heterogeneity was noted for any of analysed parameters (Supplementary Figure 3).

Discussion

In the AVATAR trial, asymptomatic AS patients randomized to early surgery had a lower incidence of the composite primary outcome, comprising all cause death, AMI, stroke or unplanned hospitalization for HF, compared with patients who were randomized to conservative treatment.

The decision to operate on asymptomatic patients with severe AS and normal LV function remains a matter of debate. Traditionally, a watchful waiting strategy has been favoured as the risk of sudden death in such patients has been reported low and it appeared safe to delay surgery until symptoms develop[5-6,16]. Yet, although rates of sudden death in asymptomatic severe AS patients are low, they are higher than in the general population[17-18]. In addition, sustained pressure overload during the period of watchful waiting in severe AS is

associated with structural and functional impairment of LV[19] with potentially adverse clinical impact, including the development of heart failure with preserved or reduced LVEF[20]. Observational data also challenged a relatively benign course of asymptomatic AS with normal LVEF by reporting mortality rate reaching 10% at one year and increased MACE incidence on mid-term[21]. Several nonrandomized studies and a meta-analysis of observational studies suggested that early surgery was associated with improved outcomes in asymptomatic but significant AS[22-23]. The recent randomized RECOVERY trial provided the first direct support for early surgery in a highly selective subset of asymptomatic patients with very severe AS[5]. The AVATAR trial expands these findings by providing evidence of the benefit of early surgery in a setting representative of a dilemma in decision making, in truly asymptomatic patients with severe but not critical aortic stenosis and normal LV function. Inclusion criteria of the AVATAR trial correspond to conventional echocardiographic assessment of severe AS and with predominantly degenerative aetiology[1-2]. This is in contrast to patients in the RECOVERY trial that presented with more critical AS with a peak velocity > 4.5 m/s with mainly bicuspid aortic valve aetiology. Given that 20-30% of asymptomatic patients with AS may turn symptomatic in response to exercise[1-2,24], exercise testing was required in the AVATAR trial to include strictly asymptomatic patients, which was not systematically the case in the RECOVERY trial. The trial methodology was associated with low screening failure rate, reflecting its generalizability to real-world practice. The inclusion criteria were consistent with lower risk patient population as reflected by lower rates of cardiovascular death in the conservative arm of the AVATAR trial as compared to the same group in the RECOVERY trial. On the other hand, differences in cumulative mortality between both trials might be also related to longer clinical follow-up in the RECOVERY trial. In this regard, proportion of patients within the conservative treatment group who remained AVR-free during follow-up was substantially higher in the current trial (64%) as

compared with the conservative arm in the RECOVERY trial (26%). In addition, the AVATAR trial is multicentre, multinational reflecting a broader clinical setting than a single country clinical practice in the RECOVERY trial. This was also reflected by varying choices of the implanted valves by practitioners and patients and surgical aortic valve replacement techniques and likely explains differences in use of mechanical valves between early surgery and conservative groups. Intra-operative mortality in the early surgery group in our trial was in line with anticipated mortality for elective isolated SAVR[25]. Taken together, present findings highlight the relevance of the careful patient evaluation in asymptomatic AS with thorough consideration of exercise testing. In such carefully evaluated patients with significant AS and normal LV function, the primary outcome and overall experience from the AVATAR study have emerged as supportive for early surgery to improve their clinical outcome. According to post-hoc analysis the treatment effect was homogenous among the represented subgroups. All-cause mortality as well as heart failure hospitalizations were numerically but not significantly higher in the conservative treatment group. Of note, sudden death occurred in 6 patients in the conservative group and one patient randomized to early surgery died suddenly while waiting for the operation without preceding symptoms. Nevertheless, overall cardiovascular death did not significantly differ between randomized groups. It should be also noted that Covid 19 - related pneumonia was present in 3 deceased patients in the conservative treatment group, while no Covid 19 - related mortality was observed in the early surgery group.

There are limitations to consider. There are differences in patients` enrolment rates across the centers related to differences in patient volumes and different timing in the trial entry. It should be also acknowledged that 115 out of 157 patients were enrolled at one center. There were no core-lab analyses of echocardiography and stress-testing. The absence of central analyses was mitigated by selective reciprocal inter-center echocardiography

control including images reviews. Since the severity of AS in the absence of the significant regurgitation can be underestimated but not overestimated on the basis of peak jet velocity and mean gradient, it is unlikely that patients with non-severe AS might have been included. There were baseline differences between the study groups with regard to age, and borderline difference between the prevalence of diabetes; however, this is unlikely to result in a significant bias since the trial was randomized. The trial did not reach pre-specified sample size based on the initial assumption of event- and enrolment rates. Patient inclusion in this trial was challenging as it is difficult to obtain consent in an asymptomatic patient to potentially undergo open-heart surgery in absence of guidelines recommendations. The trial design and definition of the asymptomatic and severe AS has been based on the 2012 ESC guidelines. However, severity threshold remained unchanged and there have been only minor changes in recommendations for intervention in the most recent guidelines[2]. History of coronary artery disease and PCI, or concomitant bypass surgery were not formally excluded and might have impacted the clinical follow-up. Nevertheless, number of such patients was very low and comparable between both group. The trial enrolment and its course have been affected by the Covid-19 pandemics leading also to surgery delays in patients randomized to the early surgery. As the pre-specified number of events has been reached due to longer follow-up despite the smaller actual sample size and following the DSMB recommendation the trial inclusion has been stopped despite the smaller sample size. Consequently, the trial findings will require further confirmation in a larger study.

In conclusion, the AVATAR trial demonstrated that early SAVR improved a primary composite outcome comprised of all cause death, acute myocardial infarction, stroke or unplanned hospitalization for heart failure, as compared to patients treated with conservative management and SAVR only after symptom onset. These findings advocate that once AS

becomes significant early valve replacement improves patient outcomes regardless of the symptom status.

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Supplemental Materials

Avatar committees and investigators

Supplemental methods: inclusion criteria, exclusion criteria, exercise testing, aortic valve replacement procedure

Definition of endpoints

Supplemental Tables 1-5

Supplemental Figures 1-3

Reference 26-27

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Table 1. Baseline clinical characteristics

	Early surgery group (n=78)	Conservative treatment group (n=79)	P value
Parameters	Median Min – Max 25th – 75th Percentiles	Median Min – Max 25th – 75th Percentiles	
Age, years	68 23 - 84 63-73	69 50 – 87 64 – 74.5	0.02
Sex (female) No (%)	32 (41.0%)	35 (44.3%)	0.67
STS PROM score (%)	1.6 0.4 – 7.8 1.1 - 2.2	1.7 0.6 – 7.1 1.2 – 2.6	0.67
Days from randomization to surgery (median + IQR)	55 1 - 898 36 - 79	400 20 - 1110 191-619	<0.001
Body Mass Index, Kg/m	27.2 20 – 39 25.6 – 29.3	27.4 18.4 - 40.8 25.4 – 30.9	0.59
Body Surface Area, m	1.9 1.5 – 2.5 1.8 – 2.1	1.9 1.5 – 2.3 1.8 – 2.0	0.41
Diabetes mellitus No (%)	14 (17.9%)	23 (29.1%)	0.07
Hypertension No (%)	69 (88.4%)	70 (88.6%)	0.44
Smoking (ex or active) No (%)	16 (20.5%)	14 (17.7%)	0.67
Dyslipidemia No (%)	31 (39.7%)	28 (35.4%)	0.33
History of coronary artery disease No (%)	1 (1.3%)	3 (3.8%)	0.37
History of PCI	1 (1.3%)	2 (2.5%)	0.44
History of stroke No (%)	2 (2.5%)	2 (2.5%)	0.92
Peripheral arterial disease No (%)	/	1 (1.36%)	0.80
Heart rate, bp/min	70 56-106 64 – 78	72 55-102 65 - 80	0.31
Systolic pressure, mmHg	135 110 – 170 127 - 144	137 110-178 125 - 150	0.33
Diastolic pressure, mmHg	80 58 – 105 70 - 85	80 60-100 70 - 85	0.33
Laboratory parameters			
BNP, pg/ml**	83 8 – 398 53 - 127	89 8 – 441 58 - 149	0.61
NTproBNP, pg/ml**	381 35 – 3359 153 - 663	346 66 – 5202 190 - 712	0.45
Urea, mmol/L	6.10 3.1 – 17 4.5 – 8.3	6.20 2.9 – 13.6 4.8 – 7.9	0.80
Hemoglobin, g/L	141 116 – 165 131 - 150	134 109 – 167 128 - 141	0.01
Total cholesterol, mmol/L	4.9 3.1 – 7.9 4.1 – 5.9	5.0 2.7 – 10.1 4.1 – 5.7	0.91
Creatinine, µmol/L	80 47 – 169 66 - 94	76 36 – 123 67 - 92	0.27
Blood glucose, mmol/L	5.6 4.2 – 12.4 5.3 – 6.7	5.6 3.8 – 11.9 5.1 – 6.8	0.70
Hb A1c,(%	5.6 4.5 – 7.8 5.2 – 6.7	5.6 4.7 – 8.5 5.2 – 6.8	0.15
Medications at baseline* no./total no.(%)			

Beta-blockers	48/73 (66%)	50/77 (65%)	0.52
ACE inhibitors	43/73 (59%)	44/77 (57%)	0.47
Calcium channel blockers	30/73 (41%)	30/77 (39%)	0.86
Diuretics	27/73 (37%)	30/77 (39%)	0.48
Statins	40/73 (55%)	48/77 (62%)	0.22
ARB	5/73 (7%)	15/77 (19%)	0.02
Antiplatelet agents drugs	44/73 (60%)	45/77 (58%)	0.47
Echocardiography			
LVESV, ml	27.8 8.1 – 59.5 20.9 – 40.1	32.8 10.5 – 54.5 22.3 – 42.3	0.96
LVEDV, ml	113 25.5 – 96.5 89.8 – 140.7	113 45.7 – 155.2 96.4 – 125.8	0.54
Left ventricular ejection fraction (%)	70 53 – 80 65 - 76	69 51 – 82 63 - 75	0.61
LV mass index, g/m	152 91.5 – 248.3 133.1 – 173.5	160 44.8 – 228.7 139 – 180.8	0.67
Relative wall thickness	0.45 0.3 – 0.7 0.4 - 0.5	0.45 0.3 – 0.6 0.4 – 0.5	0.69
Right ventricle diameter, cm	2.3 1.7 – 2.7 2.1 – 2.4	2.3 1.6 – 3.7 2 – 2.4	0.45
Left atrium, cm	4.1 2.8 – 5.2 3.8 – 4.3	4.2 2.4 – 4.9 3.9 – 4.4	0.68
SVi, ml/m	39 17.1 – 98 32.7 – 47.6	42 21.6 – 64.8 34.5 – 50.8	0.58
AP systolic pressure, mmHg	30 20 – 41 26 - 36	30 25 – 49 27 - 36	0.82
V_{max}, m/s	4.5 4.1 – 5.5 4.3 – 4.8	4.5 4.0 – 5.5 4.2 – 4.7	0.13
P_{mean}, mmHg	82.3 67 – 128 74 - 89	79 67 – 121 71 - 90	0.16
P_{max}, mmHg	50.7 30 – 105 45 - 58	49.5 37 – 73 43 - 58	0.18
AVA, cm^2	0.73 0.3 – 1 0.5 – 0.8	0.74 0.4 – 1 0.6 – 0.9	0.29
AVAi, cm^2/m^2	0.37 0.2 – 0.5 0.3 – 0.4	0.37 0.2 – 0.6 0.3 – 0.4	0.08
Zva, mmHg.mL-1.m	4.8 1.9 – 9.2 3.9 – 5.9	4.4 2.7 – 8.6 3.7 – 5.5	0.29
E/e`	12.2 1.2 – 31 10 – 16	12.2 1 – 30 9 - 18	0.54

Data are presented as frequencies and percentages for categorical variables and median, range and Inter Quartile Range for continuous variables; IQR - Interquartile range; Zva - valvulo-arterial impedance; STS - Society for Thoracic Surgeons; PCI-percutaneous coronary intervention; LV - left ventricle; ESV - end-systolic volume; EDV - end-diastolic volume; SVi - indexed stroke volume; BNP - brain natriuretic peptide; AP – pulmonary artery; AVA - aortic valve area; V_{max} - maximal velocity across the aortic valve; P_{mean} - mean transaortic valvular gradient; P_{max} - maximal gradient across the aortic valve; ; ACE - Angiotensin converting enzyme inhibitors, ARB - Angiotensin receptors blockers; *Medications as given at the inclusion; **BNP was measured in 62 patients, NTproBNP was measured in 45 patients, 34 patients had both BNP and NPproBNP, and in 16 patients BNP or NTproBNP were missing.

Table 2. Indications for Aortic-Valve Replacement in the Conservative treatment group

Indication for SAVR	Number (%)
AS-related symptom onset	15 (60%)
AS progression	4 (16%)
Decrease in LVEF below 50%	1 (4%)
Combination of factors	5 (20%)

SAVR – surgical aortic valve replacement; AS – aortic stenosis; LVEF: lef ventricular ejection fraction

Table 3. Primary and secondary outcomes.

Primary outcome: Time to first MACE			
Outcome	Early surgery group 3-Year KM estimate (%)	Conservative treatment group 3-Year KM estimate (%)	Hazard Ratio [95% CI]
Primary endpoint	15.22%	34.70%	0.46 [0.23, 0.90]
Time-to-Event secondary outcomes			
HF hospitalization	9.54%	20.11%	0.32 [0.08, 1.19]
All cause death rate (median + IQR)	4.01%	12.94%	0.56 [0.24, 1.27]
SAE	17.31%	27.50%	0.57 [0.28, 1.12]
Cardiovascular death	9.54%	9.09%	1.02 [0.40, 2.58]
Binary secondary outcomes			
	Early surgery group N (%)	Conservative treatment group N (%)	Odds Ratio [95% CI]
Intraoperative or 30 day mortality	1 (1.4%)	1 (4%)	0.34 [0.02 – 5.61]
Repeated MACE	3 (3.8%)	7 (8.9%)	0.41 [0.10, 1.65]
Thromboembolic complication	2 (2.6%)	2 (2.3)	1.03 [0.14, 7.67]
Major bleeding complications	4 (5.1%)	1 (1.3%)	3.52 [0.37, 32.68]

HF – heart failure; SAE serious adverse event;CI – confidence interval

Table 4. Number of MACE

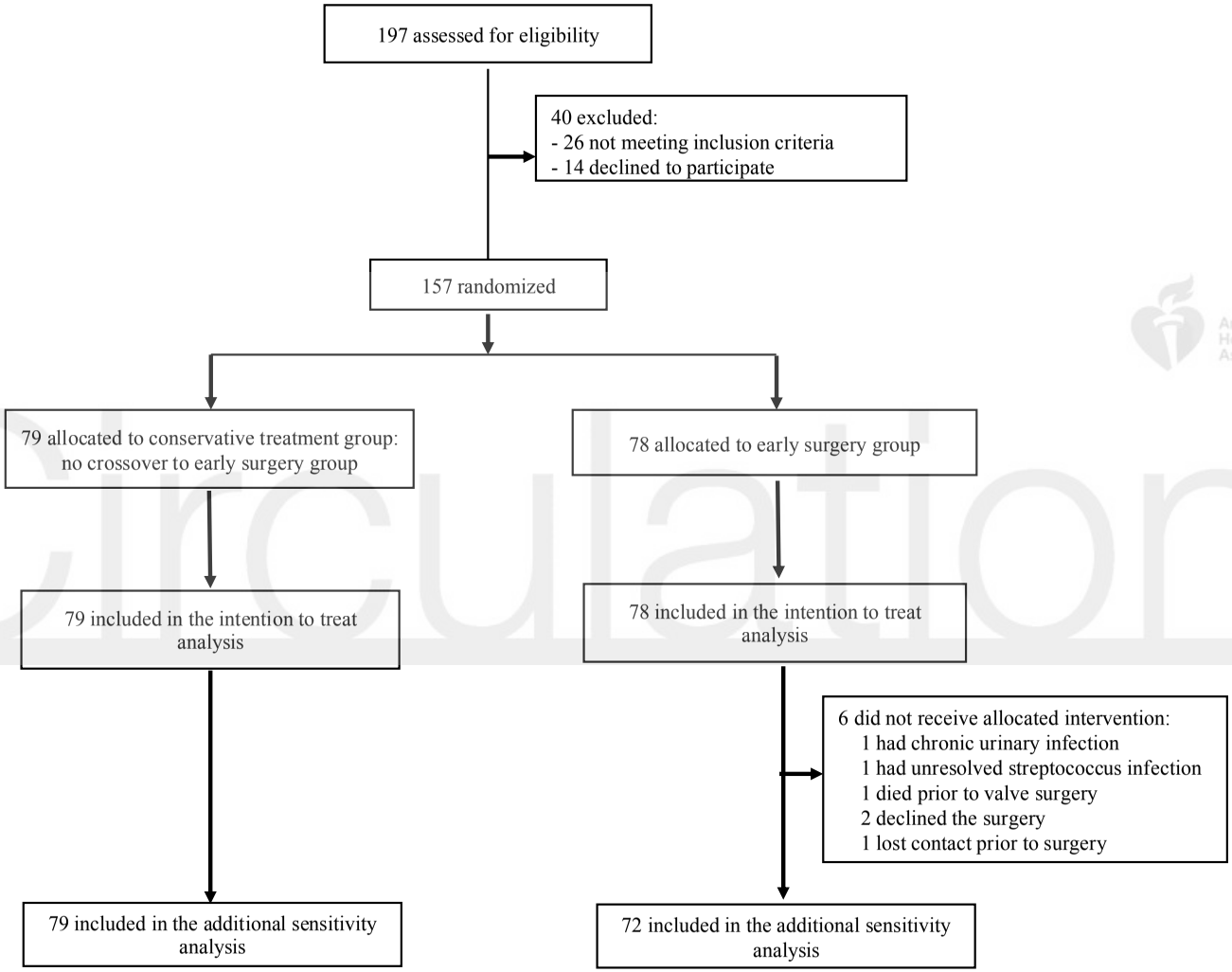
PRIMARY ENDPOINT (all cause death + MACE)	Group	
	Conservative	Early surgery
All cause death	16	9
Heart failure	7	1
AMI	2	1
Stroke	1	2
Total	26	13
TOTAL MACE (including repeated MACE)	Group	
	Conservative	Early surgery
All cause death	16	9
Heart Failure	10	3
AMI	4	1
Stroke	3	3
Total	33	16

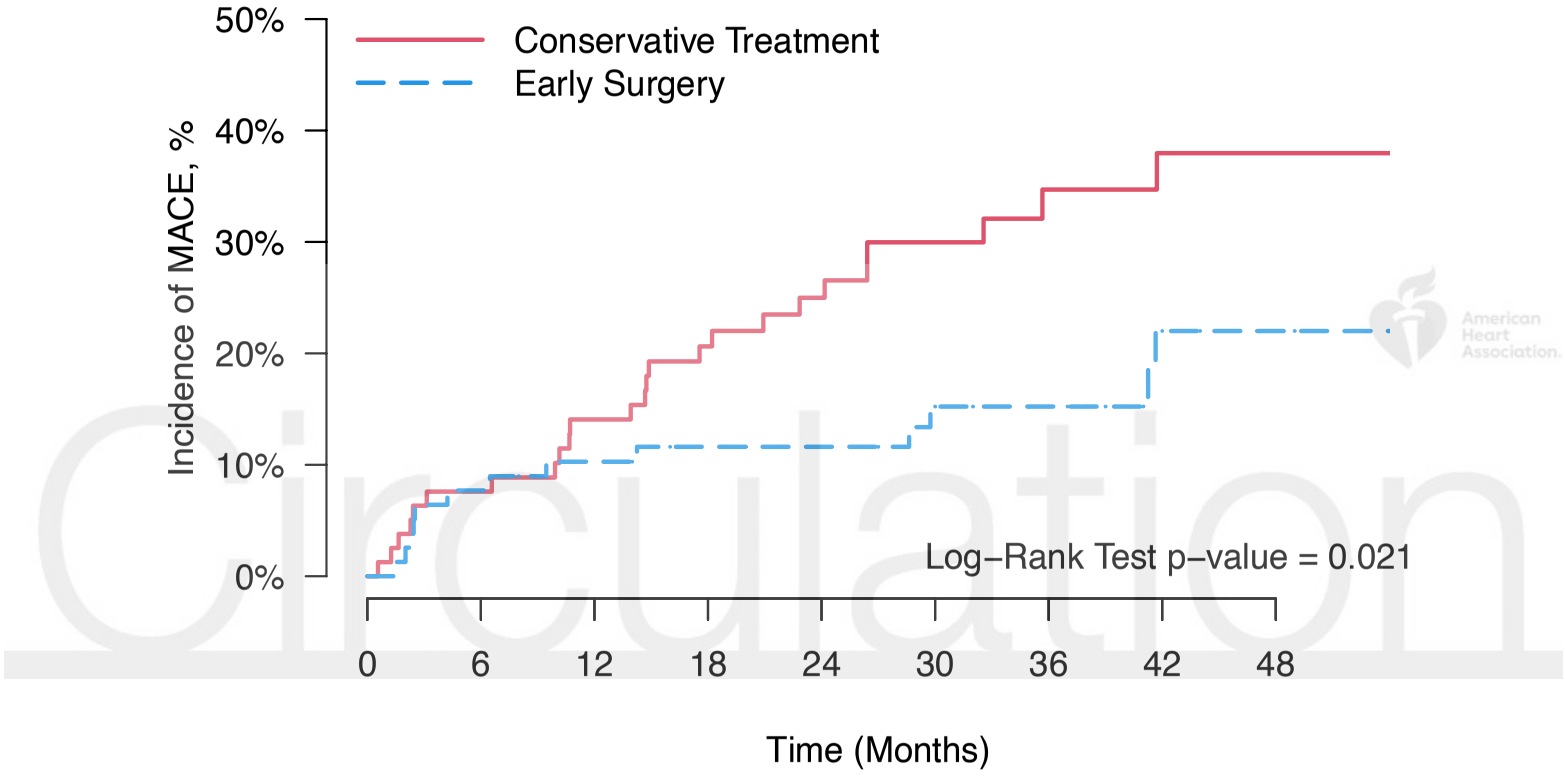
Figure Legends

Figure 1: Flowchart of the trial and patient allocation

Figure 2: Kaplan-Meier cumulative incidence rates estimates of the primary composite end-point as analyzed by intention-to-treat analysis.

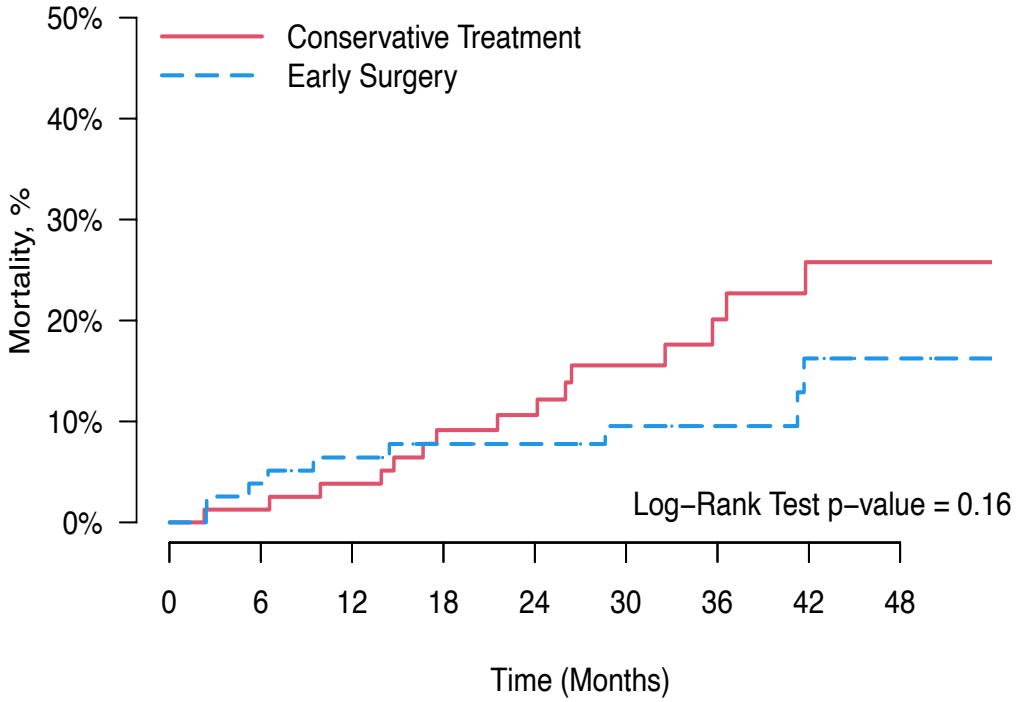
Figure 3. Kaplan-Meier cumulative incidence rates estimates of all-cause death (upper panel) and heart failure hospitalization (lower panel) analyzed by intention-to-treat analysis.





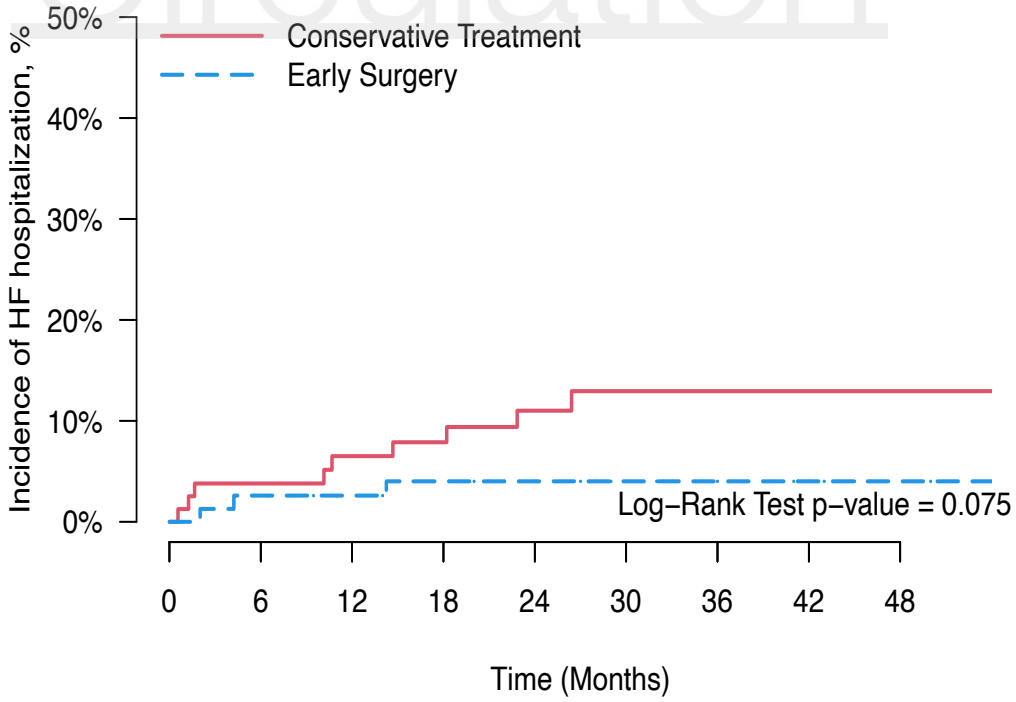
Patients, n

Conservative Treat.	79	73	66	59	49	36	25	19	12
Early Surgery	78	72	68	63	56	46	38	23	13



Patients, n

Conservative Treat.	79	78	74	67	59	45	32	24	16
Early Surgery	78	75	71	66	59	49	41	25	14



Patients, n

Conservative Treat.	79	75	69	63	54	39	27	20	13
Early Surgery	78	74	70	65	58	48	40	24	14

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