Aortic valve replacement vs. conservative treatment in asymptomatic severe aortic stenosis: long-term follow-up of the AVATAR trial

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Abstract

Background and Aims
The question of when and how to treat truly asymptomatic patients with severe aortic stenosis (AS) and normal left ventricular (LV) systolic function is still subject to debate and ongoing research. Here, the results of extended follow-up of the AVATAR trial are reported (NCT02436655, ClinicalTrials.gov).

Methods
The AVATAR trial randomly assigned patients with severe, asymptomatic AS and LV ejection fraction ≥ 50% to undergo either early surgical aortic valve replacement (AVR) or conservative treatment with watchful waiting strategy. All patients had negative exercise stress testing. The primary hypothesis was that early AVR will reduce a primary composite endpoint comprising all-cause death, acute myocardial infarction, stroke, or unplanned hospitalization for heart failure (HF), as compared with conservative treatment strategy.

Results
A total of 157 low-risk patients (mean age 67 years, 57% men, mean Society of Thoracic Surgeons score 1.7%) were randomly allocated to either the early AVR group (*n* = 78) or the conservative treatment group (*n* = 79). In an intention-to-treat analysis, after a median follow-up of 63 months, the primary composite endpoint outcome event occurred in 18/78 patients (23.1%) in the early surgery group and in 37/79 patients (46.8%) in the conservative treatment group [hazard ratio (HR) early surgery vs. conservative treatment 0.42; 95% confidence interval (CI) 0.24–0.73, *P* = .002]. The Kaplan–Meier estimates for individual endpoints of all-cause death and HF hospitalization were significantly lower in the early surgery compared with the conservative group (HR 0.44; 95% CI 0.23–0.85, *P* = .012, for all-cause death and HR 0.21; 95% CI 0.06–0.73, *P* = .007, for HF hospitalizations).

Conclusions
The extended follow-up of the AVATAR trial demonstrates better clinical outcomes with early surgical AVR in truly asymptomatic patients with severe AS and normal LV ejection fraction compared with patients treated with conservative management on watchful waiting.

Keywords: Aortic stenosis, Asymptomatic, Treatment, Low-risk, Outcomes, Aortic valve surgery.

Topic: myocardial infarction, acute, aortic valve stenosis, cerebrovascular accident, ischemic stroke, heart failure, aortic valve replacement, exercise stress test, follow-up, surgical procedures, operative, watchful waiting, ejection fraction, surrogate endpoints, conservative treatment, composite outcomes, avatar.

Introduction

Aortic stenosis (AS) is the single most common valvular heart disease requiring intervention in developed countries and is projected to double by 2050 in both the USA and Europe.1 The approach to symptomatic patients with severe AS is straightforward. Surgical aortic valve replacement (AVR) and, more recently, transcatheter aortic valve implantation (TAVI) procedures are Class I recommendation to relieve symptoms and improve survival in symptomatic patients with severe AS.2,3

Conversely, the question of when and how to treat truly asymptomatic patients with severe AS and normal left ventricular (LV) systolic function is still subject to debate and ongoing research. To date, two randomized trials have demonstrated benefit of early AVR in comparison with conservative strategy in asymptomatic patients with severe and very severe AS patients.4,5 In addition, there are several ongoing randomized trials investigating the role of early TAVI and/or early surgical AVR in asymptomatic AS.

The Aortic Valve Replacement Versus Conservative Treatment in Asymptomatic Severe Aortic Stenosis (AVATAR) trial is an investigator-initiated, prospective, multinational, randomized, controlled, parallel-group, event-driven trial that compared the safety and efficacy of early surgery in the treatment of truly asymptomatic patients with severe AS and LV ejection fraction (LVEF) ≥ 50% vs. conservative treatment with watchful waiting strategy and AVR only after symptom onset, or other guidelines directed Class I or II indications for AVR.3,6 In the primary analysis of the AVATAR trial, asymptomatic AS patients randomized to early surgery had a lower incidence of the composite primary outcome comprising all-cause death, acute myocardial infarction, stroke, or unplanned hospitalization for heart failure (HF), compared with patients who were randomized to conservative treatment.5 We now report the results of the AVATAR trial after extended follow-up at 5 years.

Methods

Study design and oversight

The AVATAR trial (ClinicalTrials.gov identifier NCT02436655) protocol and protocol update were designed by the first co-authors and steering committee co-chairmen and was approved by the steering committee of the AVATAR trial.7,8 The clinical and outcomes data were collected by personnel at the participating sites and were sent directly to the data coordinating centre at the University Clinical Center of Serbia. 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 article, and its final contents. Independent statistician conducted the long-term data analyses.

The trial was conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent. An independent data and safety monitoring board (DSMB) adjudicated all serious adverse events and oversaw the safety of the trial. The article was prepared by the first author and steering committee co-chairmen and was reviewed and edited by members of the steering committee and authors. All authors reviewed the article, 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

The study inclusion and exclusion criteria are shown in *Table 1*; trial flowchart is shown in *Figure 1*. Briefly, a total of 157 patients with severe AS according to the guidelines were enrolled in the trial: 79 were randomized to conservative treatment and 78 were randomized to early surgery. To prove truly asymptomatic status, exercise testing was performed in all candidates to evaluate symptom status according to a standardized protocol using treadmill or semi-supine ergo-bicycle. To consider exercise testing negative, which was mandatory for inclusion, all candidates needed to reach a

projected submaximal heart rate. Positive exercise test included onset of AS-related symptoms, fall in systolic blood pressure (≥20 mmHg from the baseline values), or Electrocardiography (ECG) or stress echocardiography signs of myocardial ischaemia.9

Follow-up and trial endpoints

Patients were followed according to the protocol every 6 months for the first year and then yearly with the in-person visits at the participating study centre. As the trial was affected by the Covid-19 pandemic, contact with patients who could not come in person was made by phone. 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.7,8 Data and safety monitoring board members were not blinded to the treatment allocation during events review. They adjudicated the events by consensus.

The primary outcome was a composite of all-cause mortality or major adverse cardiovascular events (MACEs) composed of acute myocardial infarction, stroke, and unplanned HF hospitalization needing intravenous treatment with diuretics or inotropes. Secondary endpoints included in-hospital and 30-day post-operative mortality in operated patients in both groups; repeat aortic valve surgery in operated patients in both groups; repeated MACE; major bleeding defined as types 3, 4, and 5 according to the consensus report from the Bleeding Academic Research Consortium10; thromboembolic complications; time to death; and time to first HF hospitalization. We also analysed the incidence of cardiovascular death and sudden cardiac death, as well as the incidence of overall serious adverse events in both groups. Sudden cardiac death was defined as either witnessed instantaneous unexpected death, unwitnessed unexpected death, or if other cause of death was excluded with reasonable certainty. Serious adverse event was defined as any event that is dangerous to the health of patients and/or that implies hospitalization or prolongation of the existing hospitalization. Definitions of the trial endpoints have been reported previously.5

Statistical analysis

We conducted all analyses according to the intention-to-treat principle, where all patients were included in the analysis as they were randomized. For the analysis of the primary outcome, we built a Kaplan–Meier graph with a log rank *P*-value to test for a difference between early surgery and control intervention at a two-sided α value of 0.05 and used a Cox proportional hazards model to derive hazard ratios (HRs) with 95% confidence intervals (CIs) for treatment effect estimation. Time-to-event secondary outcomes were analysed using the same methods applied for the analysis of the primary outcome. For MACE, all-cause death, HF hospitalization, and cardiovascular death, we repeated the analysis as described above restricted to a 3-year follow-up, with complete 3-year follow-up information available for all patients. For binary outcomes, we used a generalized linear model assuming a binomial distribution with a log link function to report risk ratios and 95% CI. We conducted subgroup analyses accompanied by a *P* for interaction to assess the consistency of the treatment effect on the primary outcome according to the following pre-defined variables: age (<65 vs. ≥65), sex, baseline ejection fraction (<60% vs. ≥60%), and country of trial site. *P*-values and 95% CI for secondary outcomes and secondary analyses of the primary outcome were not adjusted for multiple testing and are considered exploratory. For the *post hoc* analyses of echocardiography readouts of valve severity and LVEF in patients in the conservative group, we calculated the mean change from baseline to 12-month follow-up for all patients in the conservative group with available data and the mean change from baseline to final follow-up for all patients in the conservative group that underwent surgery and had available data. We conducted paired *t*-tests to derive *P*-values and 95% CI for the mean changes from baseline.11 This analysis was repeated for patients in the conservative group that underwent AVR. Analyses were performed using Stata, version 18.0.

Results

Patients and follow-up

Main patient characteristics at baseline are summarized in *Table 2*. The average age of enrolled patients was 67 years, 57% were men, the majority of patients had a degenerative aetiology of AS (84.7%), and the median estimated operative mortality according to the Society of Thoracic Surgeons predicted risk of mortality score was 1.7%. No significant heterogeneity between both groups was noted. All patients were included in the analysis. Median follow-up for all patients was 63 months [interquartile range (IQR) 48–75). Median follow-up in survivors was 68 months (IQR 58–79). One patient, who was randomized to early surgery, has been lost to follow-up, and this patient was censored when the last follow-up information was available and included in the intention-to-treat analysis (*Figure 1*).

Aortic valve replacement procedures

In the early surgery group, AVR was performed in 72 of the 78 patients (92.3%). Among the six patients that did not undergo AVR per randomization, one patient, as above mentioned, was lost to follow-up, and one died prior to valve surgery. Four patients were available for the extended follow-up. Among them, one patient died unoperated after 2113 days; two became symptomatic and underwent intervention after 691 and 791 days, respectively; and one remained asymptomatic and AVR free throughout the entire follow-up (*Figure 1*). The median time from randomization to AVR in the early surgery group was 55 days (IQR 36–79).

Thirty-five out of the 79 patients (44.3%) in the conservative treatment group had surgery during follow-up. Median time from randomization to surgery in the conservative treatment group was 476 days (IQR 226–1098). At the time of AVR, the mean age of patients in the control group was 67.9 years, while the mean age of patients in the early surgery group was 65.4 years (P = .19). Four patients in the conservative treatment group underwent TAVI procedure. Indications for surgery in the conservative treatment group are shown in *Table 3*. Median time to surgery upon establishing the indication was 123 days (IQR 90–297 days). There were no significant baseline differences between the patients in the conservative group who remained AVR-free during follow-up and those who later underwent AVR (see Supplementary data online, *Table S1*). Patients in the conservative group on the watchful waiting, including those undergoing valve surgery, experienced a progressive increase in the aortic valve severity associated with a significant decline in LVEF over time (see Supplementary data online, *Tables S2* and *S3*, respectively).

In total, 57/107 (53.3%) patients received a bioprosthetic valve and 50/107 received a mechanical valve (46.7%). In the early surgery group, 34/72 (47.2%) received a bioprosthetic valve, while 23/35 (65.7%) patients received a bioprosthetic valve in the conservative treatment group (P = .32). Three patients in early surgery group (3/78; 3.8%) and four patients in the conservative treatment group (4/35; 11.4%) have undergone concomitant coronary artery bypass grafting. No peri-procedural myocardial infarction has been noticed. The intraoperative mortality was low in both groups (1.3% in the early surgery vs. 2.5% in the conservative group; P = .54). There was no difference in length of hospitalization in the early surgery group vs. operated patients in the conservative treatment group (8.8 vs. 9.1 days; P = .87). Details of post-operative aortic valve function, procedural time, and mean hospitalization length between both groups are shown in Supplementary data online, *Table S4*. Three patients (3/78, 3.8%) in the early surgery group, and 1/35 (2.86%) patient in the conservative treatment group underwent redo AVR procedure (P = .79; Supplementary data online, *Table S5*.

Outcomes

There were a total of 55 primary outcome events comprising a composite of all-cause mortality or acute myocardial infarction, stroke, and unplanned HF hospitalization. A primary outcome event occurred in 18/78 patients (23.1%) in the early surgery group and in 37/79 patients (46.8%) in the

conservative treatment group (HR with early surgery vs. conservative treatment 0.42; 95% CI 0.24–0.73, *P* = .002; *Figure 2*). Forty patients died during follow-up: 13/78 (16.7%) in the early surgery group and 27/79 (34.17%) in the conservative treatment group. In the early surgery group, 11/72 patients died after valve surgery at median of 362 days (IQR 116–1211), of which 8 were cardiovascular deaths. In the conservative group, 8/35 patients died after surgery at shorter median of 131 days (IQR 47.8–603), of which 5 were cardiovascular deaths. Mortality causes for individual subjects are detailed in Supplementary data online, *Tables S6A* and *S6B*.

Kaplan–Meier estimates of the individual endpoints of all-cause death and HF hospitalization were significantly lower in the early surgery compared with the conservative group (HR 0.44; 95% CI 0.23–0.85, *P* = .012, for all-cause death and HR 0.21; 95% CI 0.06–0.73, *P* = .007, for HF hospitalizations) (*Figure 3* and *Table 4*). The risk of repeated MACE was significantly higher in the conservative treatment group (*Table 4*).

Sudden cardiac death occurred in 9/79 patients (11.4%) in the conservative group compared with 4/78 patients (5.1%) in the early surgery group (*P* = .17; *Table 4*). The annual rate of sudden cardiac death was twice higher in the conservatively treated group as compared with early surgery group (2.2% vs. 1%; *P* = .32). If not considering symptomatic patients in the watchful waiting group who died suddenly at home, the annual rate of sudden cardiac death in the conservative group reached 1.48%. One patient randomized to the early surgery group died suddenly while awaiting the surgery. There was a trend for higher rates of cardiovascular deaths in the conservative treatment group over time (19.3% vs. 11.6%; *P* = .1; *Figure 4*). The incidence of serious adverse events was also significantly higher in the conservative treatment group (49.4% vs. 26.4%; *P* = .013) (*Table 4*). No difference between groups was observed in the safety outcomes including major bleeding and thromboembolic complications (5.1% vs. 3.8%; *P* = .69; and 5.1% vs. 3.8%; *P* = .69; respectively; *Table 4*).

In a *post hoc* heterogeneity analysis in the study population, no significant interaction for heterogeneity was noted for any of the analysed parameters (see Supplementary data online, *Figure S1*) indicating that results are consistent across different patients' subgroups.

Discussion

The main findings from the extended follow-up of the AVATAR trial can be summarized as follows: (i) the primary composite outcome comprising of all-cause death, acute myocardial infarction, stroke, and HF hospitalizations was significantly and consistently lower with the early surgery approach compared with the conservative treatment approach; (ii) patients on conservative strategy appeared at almost 50% higher risk to experience all-cause death in comparison with patients undergoing early surgery; (iii) HF hospitalizations were significantly lower in patients with early surgery; and (iv) these beneficial outcomes were homogeneous across different subgroups without differences in safety outcomes (*Structured Graphical Abstract*).

The intraoperative mortality was low in both groups and in line with anticipated mortality for elective isolated AVR.12 The annual rate of sudden cardiac death was twice higher in the conservative than in the early surgery group. However, three patients in the conservative group were already symptomatic at the time of sudden cardiac death. It should be noted that several patients experienced sudden cardiac death during the Covid-19 pandemic, at times of suboptimal health care accessibility including delays in providing emergency services. Nevertheless, these findings highlight the risk of delays in reporting the symptom onset during the watchful waiting. In this regard, the rigorous watchful waiting with implementation of either regular stress testing or in-person visits with detailed phenotypic screening may mitigate the overall prognostic risk by prompting the timely intervention.

In the extended follow-up, a more frequent use of bioprosthetic valves has been observed. This may reflect a general trend of using surgical bioprosthetic valves in low-risk patients with severe AS and

awareness of future TAVI as a valid therapeutic option in failed surgical bioprosthetic aortic valves with valve-in-valve technique.

Although results of two randomized trials[4,5] provided corroborative evidence signals, the decision to operate on asymptomatic patients with severe AS and normal LV function remains a matter of debate.[13] Current findings of the extended AVATAR trial follow-up further strengthen the benefit of the early intervention in patients with severe AS and normal LV systolic function even in the absence of documented symptoms, including negative exercise testing. Extended follow-up outcomes warrant the early surgery without safety concerns. The benefit of early invasive strategy is underscored by divergent mortality curves over time between both groups, with a linear increase in mortality in the conservative group. The increased rates of MACE were associated with progressive increase in AS severity impacting negative LV systolic function with its significant decline throughout the follow-up. Earlier AVATAR sub-study of the baseline echocardiographic parameters suggested that in contrast to global ejection fraction, novel indices of LV systolic function, like myocardial work, may provide more refine evaluation of the LV function in the presence of asymptomatic severe AS[14] and thereby better inform further clinical decision-making. Cardiovascular events that occurred after the surgery were also more frequent in the conservative group patients undergoing the intervention only after symptom onset as compared with the early surgery group with intervention prior to symptom onset. This, together with the signal of the cardiovascular mortality benefit, further advocates for early surgery strategy. Such a strategy may blunt the overall risk in AS patients related either to sudden cardiac death as compared with age-matched healthy subjects[15,16] or rapid worsening in the prognosis immediately after symptom onset.[17]

To recommend any kind of surgery, the evidence bar needs to be raised high, and this is especially true when it comes to asymptomatic patients. Looking at the totality of the available evidence, including the RECOVERY and AVATAR randomized trials[4,5] in tandem with observational studies and meta-analyses,[18–20] the findings are consistent across the studies and uniformly point at the benefit of early aortic valve intervention. Additional several large, randomized trials are ongoing[21–23] to further elucidate the role of early surgical or transcatheter AVR in asymptomatic patients with severe AS. Our study demonstrated the beneficial effect of early surgical AVR in mostly middle-aged population. Given the expansive clinical use of transcatheter approaches, it will be important to elucidate the lifetime strategy and the most-optimal treatment option in these patients in case early transcatheter treatment would favourably impact the clinical outcomes in the trial setting.

The limitations of the AVATAR trial have been detailed previously.[5] It should be noted that patient inclusion in this type of trial was challenging as regards the consent in an asymptomatic patient to potentially undergo open-heart surgery in the absence of guideline recommendations. Because the pre-specified number of events has been reached due to the longer follow-up and following the DSMB recommendation, the trial inclusion has been stopped despite not reaching the projected sample size. We submit that the plausibility of current results with extended follow-up compensates for the lower number of enrolled patients as initially projected. The trial enrolment and its course have been affected by the Covid-19 pandemic impacting physical visits with echocardiographic follow-up and lengthening AVR delays. Pre-defined physical visits were substituted by phone follow-up. Such surveillance within the watchful waiting may hypothetically impact timely detection of symptoms consequently leading to increased clinical risk, including sudden death. Nevertheless, in the conservative group, none of the patients experienced MACE or died while awaiting the scheduled surgery. It is of note that in the small number of patients undergoing TAVR, delays appeared shorter as compared with the surgical intervention.

Several patients, who presented with coronary artery disease, underwent concomitant percutaneous coronary intervention, or bypass surgery, and were not formally excluded and might have affected the clinical follow-up. Nevertheless, the number of such patients was low and comparable between both groups.

In conclusion, the extended follow-up at 5 years of the AVATAR trial confirms the better clinical outcomes with early AVR in truly asymptomatic patients with severe AS and normal LVEF compared

with patients treated with conservative management on watchful waiting. These findings provide additional evidence advocating that once AS becomes severe, early valve replacement should be considered in low-risk patients regardless of the symptom status.

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Table 1
Eligibility inclusion/exclusion criteria

Inclusion criteria
• Men and women of any ethnic origin aged ≥18 years • Written informed consent • V_{max} across the aortic valve > 4 m/s or *P* mean ≥ 40 mmHg and AVA ≤ 1 cm^2 or AVAi ≤ 0.6 cm^2/m^2 at rest • Without reported symptoms • Society of Thoracic Surgeons score < 8%
Exclusion criteria
Participation in another clinical trial within 30 days prior to randomization
• Pregnant or nursing women • Mental condition rendering the patient unable to understand the nature, scope, and possible consequences of the study or to follow the protocol • Positive stress-test defined as follows: a. Anginal chest pain during testing b. Syncope or dizziness during testing c. Decrease in systolic blood pressure during exercise ≥ 20 mmHg d. Malignant arrhythmia during exercise testing (VT or VF) • Left ventricular ejection fraction < 50% at rest • Very severe AS defined as V_{max} > 5.5 m/s at rest • Significant disease of other valves: mitral stenosis with P_{mean} > 5 mg, or any significant regurgitation ≥ 3+ • Recent previous myocardial infarction (<1 year) • Need for additional aortic root replacement (i.e. Bentall) or ascending aorta surgery in asymptomatic patients undergoing AVR • Previous coronary bypass surgery • Previous any heart valve surgery • Impaired renal function, i.e. creatinine > 200 µmol/L or glomerular filtration rate < 30 mL/min/1.73 m^2 • Significant pulmonary hypertension at rest (systolic pulmonary artery pressure > 50 mmHg) • Uncontrolled hypertension at rest (systolic blood pressure > 180 mmHg and diastolic blood pressure > 100 mmHg) • Significant comorbidity with reduced life expectancy (<3 years) • Uncontrolled diabetes mellitus (HbA1c > 9%) • Significant chronic obstructive pulmonary disease (FEV_1 < 70% of predicted value) • Permanent or documented paroxysmal atrial fibrillation

Table 2
Selected baseline characteristics of the study population

	Early surgery group (*n* = 78)	**Conservative treatment group (*n* = 79)**	***P*-value**
Demographics and comorbidities			
Age, years, median (IQR)	68 (63–73)	69 (64–75)	.02
Sex (female)	32 (41.0%)	35 (44.3%)	.67
STS score, median (IQR)	1.6 (1.1–2.2)	1.8 (1.2–2.7)	.67
Days from randomization to surgery, median (IQR)	55 (36–79)	476 (226–1098)	<.001
Diabetes mellitus	14 (17.9%)	23 (29.1%)	.07
Hypertension	69 (88.4%)	70 (88.6%)	.44
History of PCI	1 (1.3%)	2 (2.5%)	.44
History of stroke	2 (2.5%)	2 (2.5%)	.92
Peripheral arterial disease	0 (0%)	1 (1.36%)	.80
Laboratory parameters			
BNP, pg/mLa, median (IQR)	83 (53–127)	89 (58–149)	.61
NT-proBNP, pg/mLa, median (IQR)	381 (153–660)	347 (186–722)	.45
Haemoglobin, g/L, median (IQR)	141 (131–150)	134 (128–141)	.01
Creatinine, µmol/L, median (IQR)	80 (66–94)	76 (67–92)	.27
Blood glucose, mmol/L, median (IQR)	5.6 (5.3–6.7)	5.6 (5.1–6.8)	.70
Echocardiography			
LVESV, mL, median (IQR)	28 (20–41)	33 (22–42)	.96

	Early surgery group (*n* = 78)	Conservative treatment group (*n* = 79)	*P*-value
LVEDV, mL, median (IQR)	113 (89–142)	113 (96–126)	.54
LV mass index, g/m^2, median (IQR)	152 (133–175)	160 (139–183)	.67
Left atrium, cm	4.1 (3.8–4.4)	4.2 (3.9–4.4)	.68
SVi, mL/m^2, median (IQR)	39 (33–48)	42 (34–51)	.58
PA systolic pressure, mmHg, median (IQR)	30 (26–36)	30 (27–37)	.82
V_{max}, m/s, median (IQR)	4.5 (4.3–4.8)	4.5 (4.2–4.7)	.13
P_{mean}, mmHg, median (IQR)	51 (44–58)	50 (43–59)	.16
P_{max}, mmHg, median (IQR)	82 (74–90)	79 (70–90)	.18
AVA, cm^2, median (IQR)	0.73 (0.55–0.84)	0.74 (0.59–0.89)	.29
AVAi, cm^2/m^2, median (IQR)	0.37 (0.3–0.42)	0.37 (0.31–0.46)	.08
E/*e*', median (IQR)	12.2 (9.6–16.3)	12.2 (8.8–18.1)	.54

AVA, aortic valve area; AVAi, indexed aortic valve area; [a]BNP, B-type natriuretic peptide; EDV, end-diastolic volume; ESV, end-systolic volume; IQR, interquartile range; LV, left ventricle; [a]NT-proBNP, N-terminal pro-B-type natriuretic peptide; PA, pulmonary artery; PCI, percutaneous coronary intervention; P_{max}, maximal gradient across the aortic valve; P_{mean}, mean transaortic valvular gradient; PROM, predicted risk of mortality; STS, Society of Thoracic Surgeons; SVi, indexed stroke volume; V_{max}, maximal velocity across the aortic valve.

Table 3
Indications for aortic valve replacement in the conservative treatment group

Symptom onset (including increased fatigue)	18 (51.4%)
AS progression	6 (17.1%)
Decrease in LVEF	3 (8.6%)
Combination of factors	8 (22.9%)

AS, aortic stenosis; LVEF, left ventricular ejection fraction.

Table 4
Primary composite outcome and secondary endpoint analyses

	Early surgery no. (5-year KM estimate, %)	Conservative treatment no. (5-year KM estimate, %)	Hazard ratio (95% CI)	*P*-value
Primary composite outcome	18 (18.0)	37 (45.6)	0.42 (0.24–0.73)	.002
Time-to-event secondary outcomes				
All-cause death	13 (12.9)	27 (31.1)	0.44 (0.23–0.85)	.012
HF hospitalization	3 (4.0)	13 (17.0)	0.21 (0.06–0.73)	.007
All-cause death or HF hospitalization	14 (17.9)	35 (44.3)	0.34 (0.18–0.63)	<.001
Acute myocardial infarction	1 (1.4)	6 (9.3)	0.15 (0.02–1.29)	.047
Stroke	4 (4.1)	4 (6.4)	0.91 (0.23–3.65)	.89
Cardiovascular death	10 (11.6)	17 (19.5)	0.54 (0.25–1.18)	.11
Serious adverse events	20 (26.4)	35 (49.4)	0.50 (0.29–0.88)	.013
	No. (Event Risk %)	**No. (Event Risk %)**	**Risk ratio (95% CI)**	***P*-value**
Binary secondary outcomes				

	Early surgery no. (5-year KM estimate, %)	Conservative treatment no. (5-year KM estimate, %)	Hazard ratio (95% CI)	*P*-value
Intraoperative/30-day mortality	1 (1.3)	2 (2.5)	0.51 (0.05–5.47)	.58
Sudden cardiac death	4 (5.1)	9 (11.4)	0.45 (0.14–1.40)	.17
Repeated MACE	3 (3.8)	14 (17.7)	0.22 (0.06–0.73)	.013
Thromboembolic complications	4 (5.1)	3 (3.8)	1.35 (0.31–5.84)	.69
Major bleeding	4 (5.1)	3 (3.8)	1.35 (0.31–5.84)	.69

Structured Graphical Abstract

The design and main result of the AVATAR randomized trial (intention-to-treat population). AMI, acute myocardial infarction; CI, confidence interval; HF, heart failure; HR, hazard ratio; LV, left ventricular.

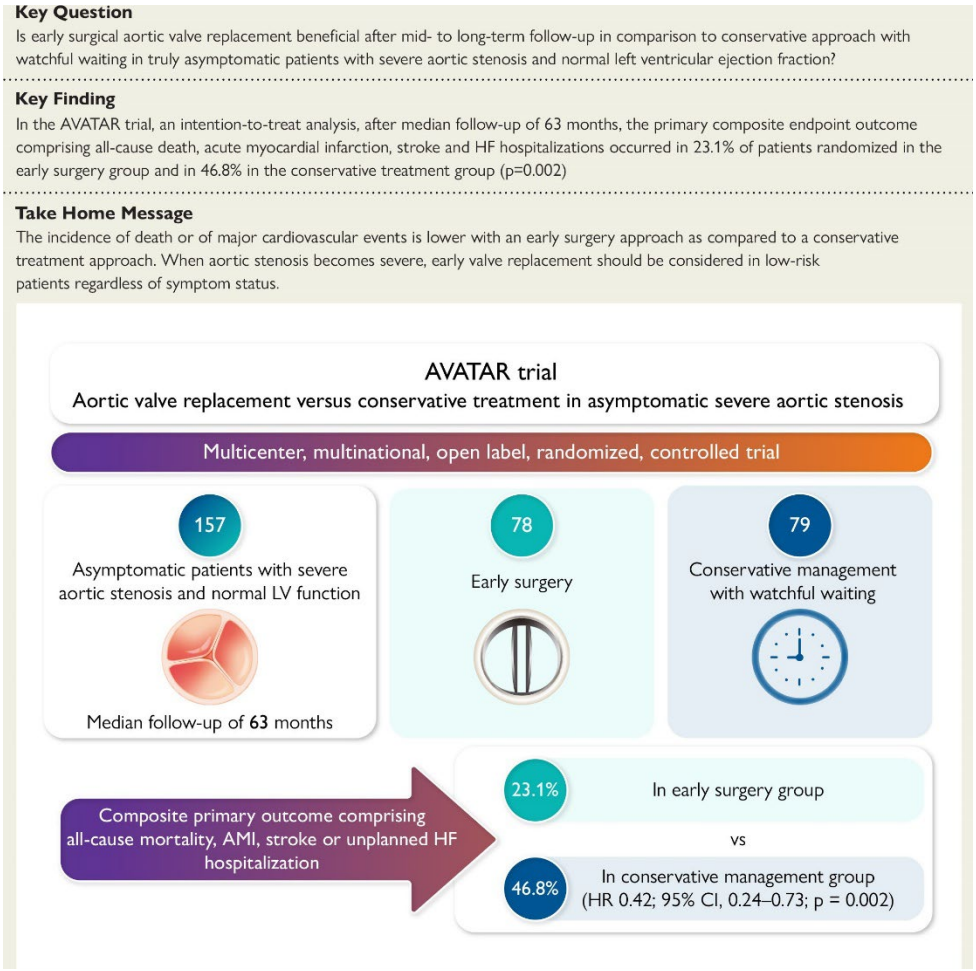

Figure 1
Trial flowchart including the extended follow-up

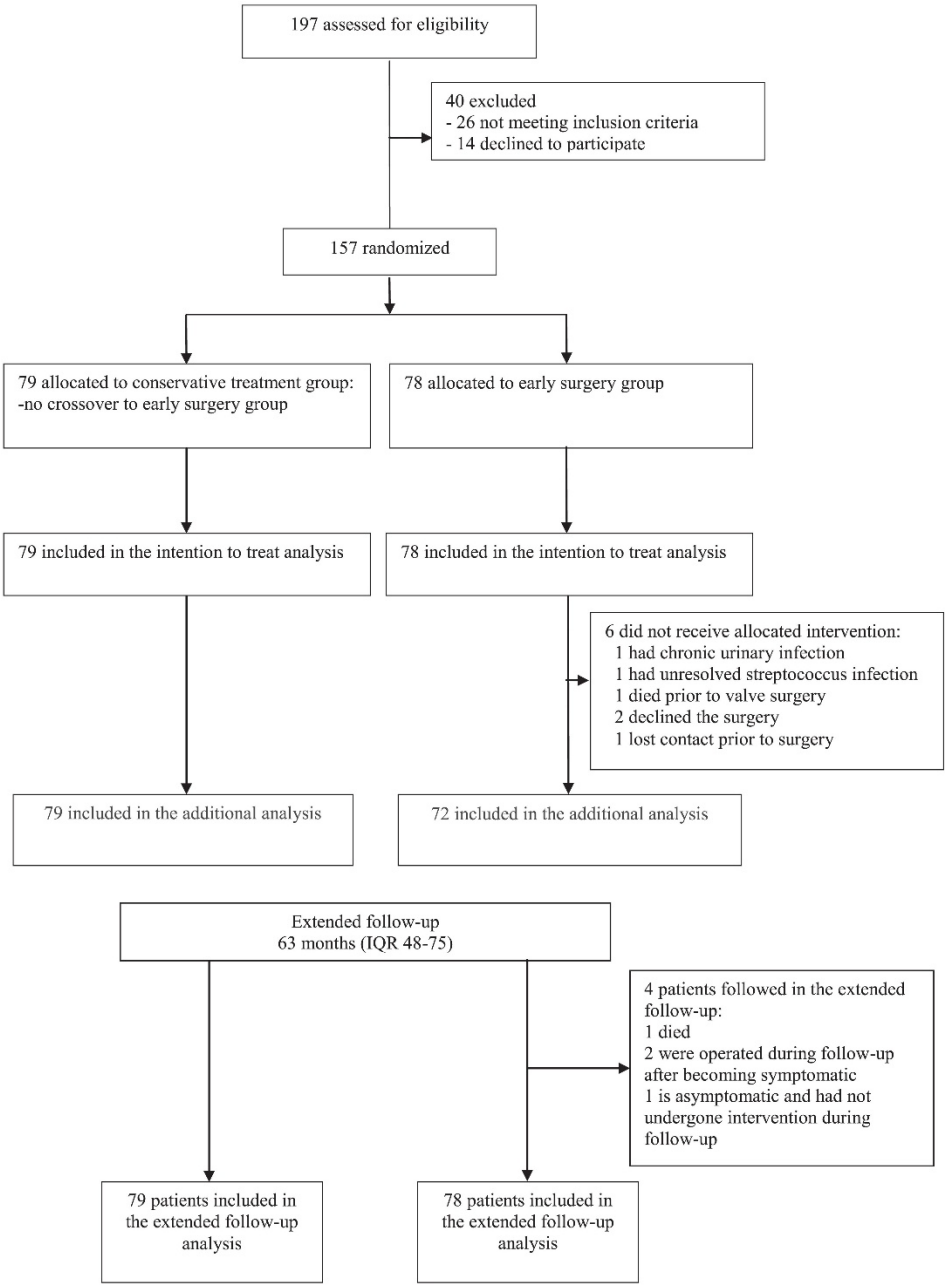

Figure 2
Cumulative incidence of primary composite outcome (intention-to-treat population)

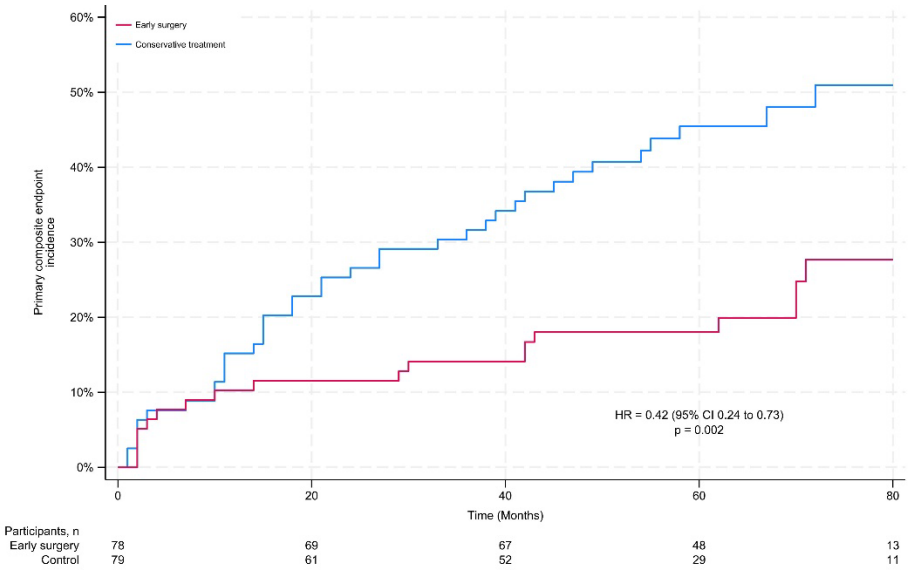

Figure 3
Cumulative incidence of all-cause death (upper panel) and heart failure hospitalization (lower panel) (intention-to-treat population)

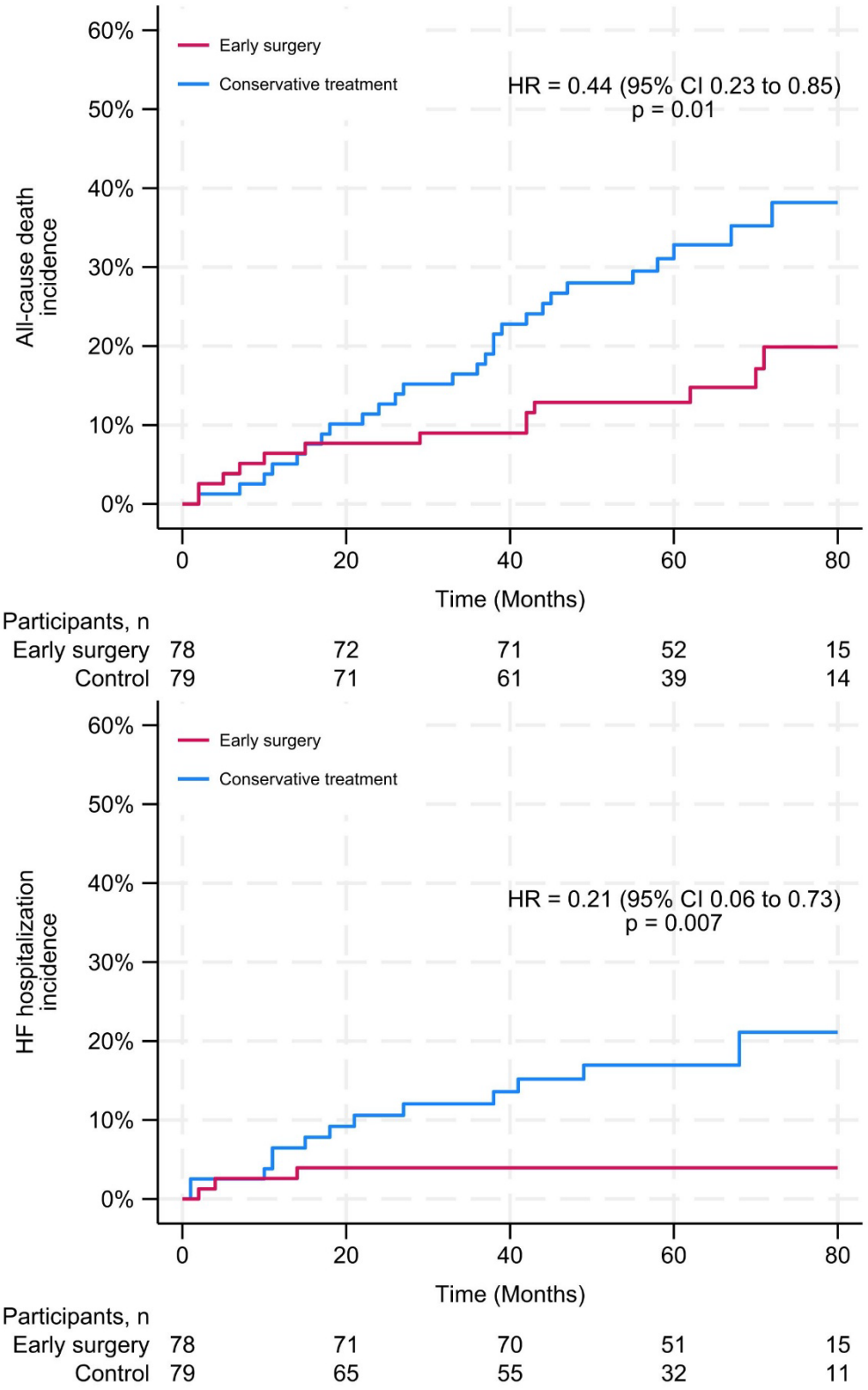

Figure 4
Cumulative incidence of cardiovascular death (intention-to-treat population)