

Aortic Valve Replacement Versus Conservative Treatment in Asymptomatic Severe Aortic Stenosis: The AVATAR Trial

(AVATAR Trial Investigators) Banovic, Marko; Putnik, Svetozar; Penicka, Martin; Doros, Gheorghe; Deja, Marek A.; Kockova, Radka; Kotrc, Martin; Glaveckaite, Sigita; Gašparović, Hrvoje; Pavlović, Nikola; ...

Source / Izvornik: **Circulation, 2022, 145, 648 - 658**

Journal article, Published version

Rad u časopisu, Objavljena verzija rada (izdavačev PDF)

<https://doi.org/10.1161/CIRCULATIONAHA.121.057639>

Permanent link / Trajna poveznica: <https://um.nsk.hr/um:nbn:hr:105:007779>

Rights / Prava: [Attribution 4.0 International](#) / [Imenovanje 4.0 međunarodna](#)

Download date / Datum preuzimanja: **2024-11-29**



Repository / Repozitorij:

[Dr Med - University of Zagreb School of Medicine Digital Repository](#)





Aortic Valve Replacement Versus Conservative Treatment in Asymptomatic Severe Aortic Stenosis: The AVATAR Trial

Marko Banovic¹ MD, PhD; Svetozar Putnik, MD, PhD; Martin Penicka, MD, PhD; Gheorghe Doros, PhD; Marek A. Deja² MD, PhD; Radka Kockova³ MD, PhD; Martin Kotrc, MD; Sigita Glaveckaite, MD, PhD; Hrvoje Gasparovic, MD, PhD; Nikola Pavlovic, MD, PhD; Lazar Velicki, MD, PhD; Stefano Salizzoni⁴ MD, PhD; Wojtek Wojakowski⁵ MD, PhD; Guy Van Camp⁶ MD, PhD; Serge D. Nikolic, PhD; Bernard Lung⁷ MD; Jozef Bartunek⁸ MD, PhD; on behalf of the AVATAR Trial Investigators*

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.

METHODS: The AVATAR trial (Aortic Valve Replacement Versus Conservative Treatment in Asymptomatic Severe Aortic Stenosis) 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 transaortic gradient ≥ 40 mm Hg), and with normal left ventricular function. Negative exercise testing was mandatory for inclusion. The primary hypothesis was that early SAVR would reduce the primary composite end point of all-cause death, acute myocardial infarction, stroke, or unplanned hospitalization for heart failure compared with 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 the 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 end point than those in the conservative arm (hazard ratio, 0.46 [95% CI, 0.23–0.90]; $P=0.02$). There was no statistical difference in secondary end points, including all-cause mortality, first heart failure hospitalizations, major bleeding, or thromboembolic complications, but trends were consistent with the primary outcome.

CONCLUSIONS: 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.

REGISTRATION: URL: <https://www.clinicaltrials.gov>; Unique identifier: NCT02436655.

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

Correspondence to: Marko Banovic, MD, PhD, Cardiology Department, University Clinical Center of Serbia, Pasterova 2, Belgrade, Serbia; or Jozef Bartunek, MD, PhD, Cardiovascular Center, OLV Hospital, Moorselbaan 164, 9300 Aalst, Belgium. Email markobanovic71@gmail.com or jozef.bartunek@olvz-aalst.be

This work was presented at the American Heart Association Scientific Sessions 2021, November 13 to November 15, 2021.

*A complete list of the Avatar Committees and Investigators is available in the Supplemental Material.

Supplemental Material is available at <https://www.ahajournals.org/doi/suppl/10.1161/CIRCULATIONAHA.121.057639>.

For Sources of Funding and Disclosures, see page 657.

Continuing medical education (CME) credit is available for this article. Go to <http://cme.ahajournals.org> to take the quiz.

© 2021 American Heart Association, Inc.

Circulation is available at www.ahajournals.org/journal/circ

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 with subjects randomized to the conservative surgery, subjects randomized to early surgical aortic valve replacement had a lower incidence of primary composite end point including all-cause death, acute myocardial infarction, stroke, or unplanned hospitalization for heart failure (15.22% [13 events] versus 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 aortic stenosis regardless of symptoms.

Nonstandard Abbreviations and Acronyms

AVATAR	Aortic Valve Replacement Versus Conservative Treatment in Asymptomatic Severe Aortic Stenosis
AS	aortic stenosis
DSMB	data and safety monitoring board
HF	heart failure
LV	left ventricular
LVEF	left ventricular ejection fraction
MACE	major adverse cardiovascular event
SAVR	surgical aortic valve replacement

Surgical aortic valve replacement (SAVR) and, more recently, transcatheter aortic valve replacement 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 because almost a quarter of patients with severe AS referred to the 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 aortic valve replacement 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 1

randomized trial, performed at 4 medical centers within 1 country, appears to support early surgery in asymptomatic patients with severe, critical AS.⁵ However, true absence of symptoms was not well documented because no regular exercise testing was performed.^{6,7}

The AVATAR trial (Aortic Valve Replacement Versus Conservative Treatment in Asymptomatic Severe Aortic Stenosis; URL: www.clinicaltrials.gov; Unique identifier: 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 composed of all-cause death, acute myocardial infarction, stroke, or unplanned hospitalization for heart failure (HF) compared with patients managed conservatively according to guidelines, ie, watchful waiting with optimal treatment of comorbidities and SAVR after symptoms onset or a drop in 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 (URL: www.clinicaltrials.gov; Unique identifier: 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 the 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 article, 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 article was prepared by the first author 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

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 Table S1. 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%, severe AS (defined as maximal aortic jet velocity >5.5 m/s at rest), aortic regurgitation ≥3+, dilatation of the ascending aorta requiring replacement of aortic root or ascending aorta (>5 cm), or 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 the Supplemental Methods). Exercise testing was performed in all candidates to evaluate symptom status according to a standardized protocol (Supplemental Methods). 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 (≥20 mmHg 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 the test inconclusive. Among these 4 patients, 1 patient also experienced a fall in blood pressure. To minimize interobserver investigator variability, transthoracic echocardiography 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 before 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 about 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.

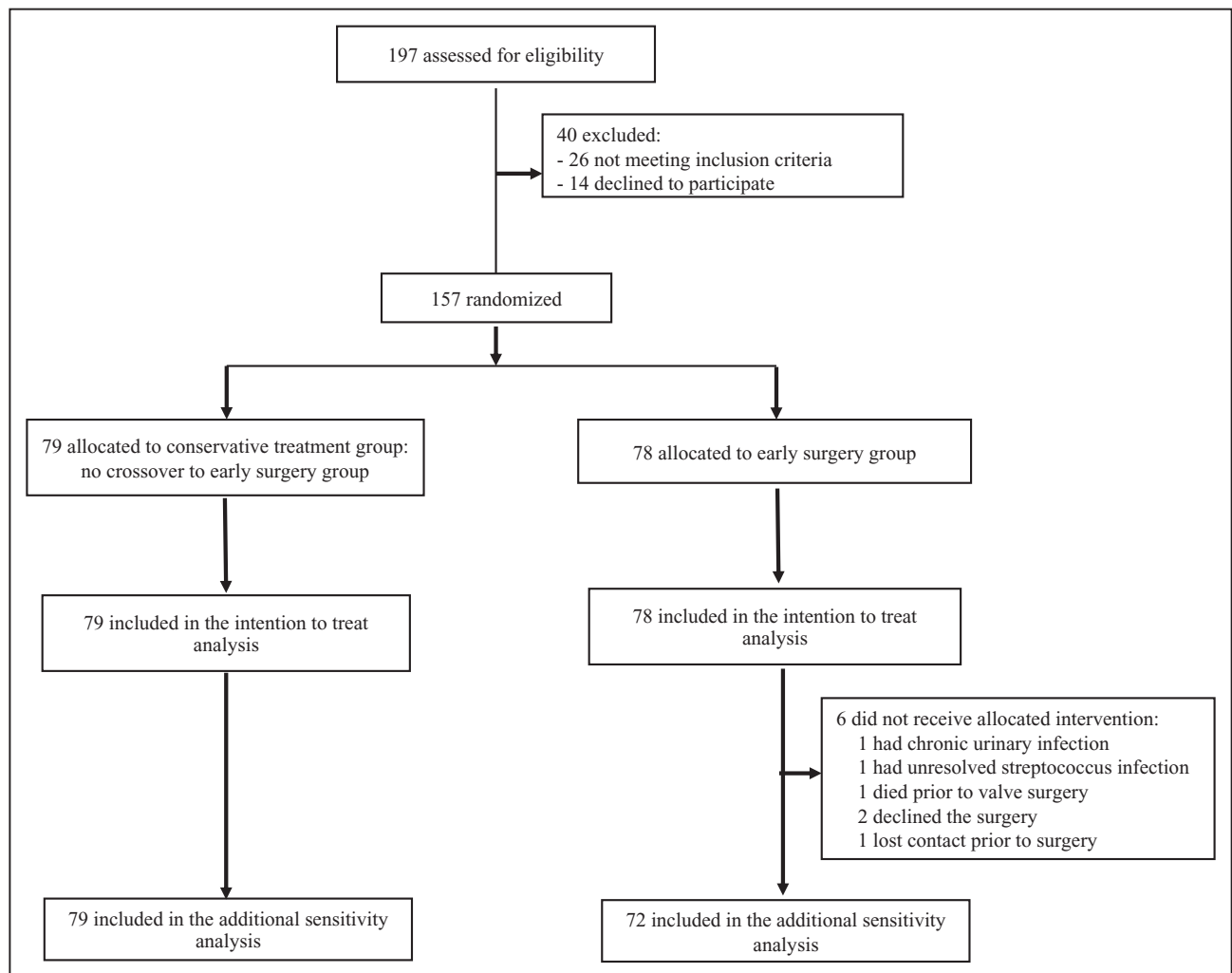


Figure 1. Flowchart of the trial and patient allocation.

Patients in the conservative treatment group were referred for surgery in case of onset of AS-related symptoms, if the LVEF decreased to <50%, or if the peak aortic jet velocity increased each year by >0.3 m/s on follow-up echocardiography, according to European Society of Cardiology guidelines on valvular disease at the time the study was designed.¹¹ Conservative treatment included the treatment of risk factors and comorbidities.

Trial End Points

The primary end point 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. Prespecified secondary end points included the following:

- In-hospital and 30-day postoperative mortality in operated patients in both groups
- Repeat aortic valve surgery in operated patients in both groups
- Repeated MACEs, including stroke, acute myocardial infarction, or unplanned HF hospitalization needing IV diuretic treatment
- Major bleeding defined as types 3, 4, and 5 according to the consensus report from the Bleeding Academic Research Consortium¹³
- Thromboembolic complications on the basis of clinical symptoms, signs, and imaging studies
- Time to death
- Time to first HF hospitalization

In addition, the incidence of overall serious adverse events in both groups was analyzed. The detailed definition of a serious adverse event has been described within the AVATAR trial protocol⁹ and is given in the [Supplemental Methods](#).

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 enrollment duration and a 9% event rate at 12 months in the conservative treatment group. With this sample size, using a 2-sided α of 5%, a log-rank test was determined to have 80% power to detect a decrease in 12-month event rates by 5.5%, ie, 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 25th to 75th percentiles for continuous variables. Treatment differences on dichotomous variables were evaluated using χ^2 tests. Continuous variables between treatments were compared by using 2-sample *t* tests. A Kaplan-Meier estimator was used to estimate the distribution of time to primary and time-to-event secondary end points (eg, survival and time to first HF hospitalization) and a log-rank test to compare

them between the 2 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 end points (eg, intraoperative or 30-day mortality), repeated MACEs, thromboembolic complications, and major bleeding, a logistic regression model was used to compare the 2 groups using odds ratios.

The primary analysis was performed as intention-to-treat for all included patients who were randomized. In sensitivity analyses of the primary end point, 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 end point in 6 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 2-sided *P* value <0.05 was considered to indicate statistical significance. The 95% CIs for secondary end points have not been adjusted for multiple comparisons, and therefore, inferences drawn from these intervals about secondary end points 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 men, and the median estimated operative mortality according to the Society for Thoracic Surgeons predicted risk of mortality 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, and 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 of 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

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, y	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 ²	27.2 20–39 25.6–29.3	27.4 18.4–40.8 25.4–30.9	0.59
Body surface area, m ²	1.9 1.5–2.5 1.8–2.1	1.9 1.5–2.3 1.8–2.0	0.41
Diabetes, No. (%)	14 (17.9%)	23 (29.1%)	0.07
Hypertension, No. (%)	69 (88.4%)	70 (88.6%)	0.44
Smoking (previous 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, No. (%)	1 (1.3%)	2 (2.5%)	0.44
History of stroke, No. (%)	2 (2.5%)	2 (2.5%)	0.92
Peripheral arterial disease, No. (%)	0	1 (1.36%)	0.80
Heart rate, bp/min	70 56–106 64–78	72 55–102 65–80	0.31
Systolic pressure, mm Hg	135 110–170 127–144	137 110–178 125–150	0.33
Diastolic pressure, mm Hg	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
NT-proBNP, 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

(Continued)

Table 1. Continued

	Early surgery group (n=78)	Conservative treatment group (n=79)	P value
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
HbA1c, %	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. (%)			
β-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 (without 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
LV ejection fraction, %	70 53–80 65–76	69 51–82 63–75	0.61
LV mass index, g/m ²	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 ²	39 17.1–98 32.7–47.6	42 21.6–64.8 34.5–50.8	0.58
AP systolic pressure, mm Hg	30 20–41 26–36	30 25–49 27–36	0.82

(Continued)

Table 1. Continued

	Early surgery group (n=78)	Conservative treatment group (n=79)	P value
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_{max} , mmHg	82.3 67–128 74–89	79 67–121 71–90	0.16
P_{mean} , 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 ²	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 as median, range, and IQR for continuous variables. ACE indicates angiotensin-converting enzyme inhibitor; AP, pulmonary artery; ARB, angiotensin receptor blocker; AVA, aortic valve area; AVAi, indexed aortic valve area; BNP, brain natriuretic peptide; EDV, end-diastolic volume; ESV, end-systolic volume; HbA1C, Hemoglobin A1 C; IQR, interquartile range; LV, left ventricle; Max, maximum; Min, minimum; NT-proBNP, N-terminal pro-B-type natriuretic peptide; 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 for Thoracic Surgeons; SVI, indexed stroke volume; V_{max} , maximal velocity across the aortic valve; and Zva, valvulo-arterial impedance.

*BNP was measured in 62 patients, NTproBNP was measured in 45 patients, 34 patients had both BNP and NT-proBNP, and in 16 patients, BNP or NT-proBNP was missing.

†Medications as given at the inclusion.

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 prespecified trial end point (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 1 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 was performed in 3 of 72 patients (4.2%) in the early surgery group and 2 of 25 patients (8.0%) in the conservative treatment group who required surgery. All other patients underwent isolated SAVR. Postoperative hemodynamic parameters were similar between groups. Additional information

Table 2. Indications for Aortic Valve Replacement in the Conservative Treatment Group

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

AS indicates aortic stenosis; LVEF, left ventricular ejection fraction; and SAVR, surgical aortic valve replacement.

about surgical procedures and postoperative complications is provided in Tables S2 and S3.

Follow-Up and End Points

Although enrollment was lower than expected, the number of prespecified events (35) was reached in October 2020 because of longer follow-up. Accordingly, the DSMB advised stopping enrollment on November 1, 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 the early surgery group and 35 months in the conservative treatment group. Contact with 1 patient in the early surgery group was lost before scheduled aortic valve replacement. This patient was analyzed in the intention-to-treat analysis as being alive at the latest follow-up.

There was a total of 39 events, 13 (16.6%) in the early surgery and 26 (32.9%) in the conservative treatment group. In a primary intention-to-treat analysis, patients randomized to early surgery had significantly lower incidence of primary composite end point comprising all-cause death, acute myocardial infarction, stroke, or unplanned HF hospitalization compared with the conservative group (15.2% versus 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 end points of all-cause mortality and HF hospitalization tended to be higher in the conservative compared with the early surgery group but did not reach statistical significance (Figure 3). Sudden death occurred in 6 patients in the conservative group compared with 3 patients in the early surgery group, with 1 patient dying suddenly while awaiting the surgery (Table S4). There were no significant differences in other secondary end points between both groups (Table 3B and 3C). The incidence of composite end point–related MACEs as well as overall MACEs was significantly higher in the conservative treatment group compared with the early surgery group (16 [20.5%] in early surgery group versus 33 [41.8%] in conservative treatment group; $P=0.004$; Table 4). The incidence of serious adverse events was also numerically higher in the conservative treatment group without reaching statistical significance compared with the early surgery group (Table S5 and Figure S1). Additional statistical analysis

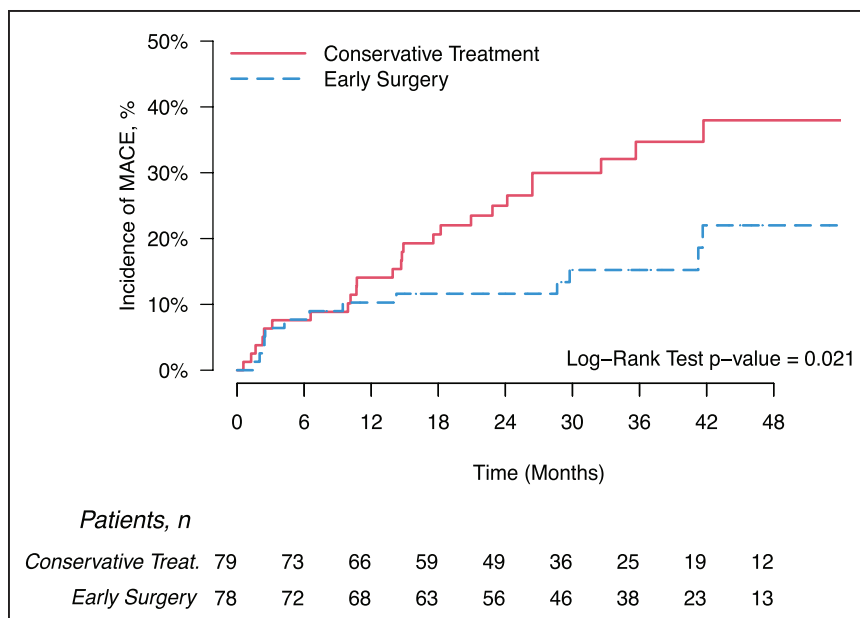


Figure 2. Kaplan-Meier cumulative incidence rates estimates of the primary composite end point as analyzed by intention-to-treat analysis.

MACE indicates major adverse cardiovascular event; and Treat., treatment.

of the primary end point excluding patients who were not operated on within the early surgery group was consistent with the intention-to-treat analysis (Figure S2). In a post hoc heterogeneity analysis in the study population dichotomized by median values, no significant interaction for heterogeneity was noted for any of the analyzed parameters (Figure S3).

DISCUSSION

In the AVATAR trial, asymptomatic patients with AS 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 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 favored because the risk of sudden death in such patients has been reported to be low, and it appeared safe to delay surgery until symptoms develop.^{5,6,16} Yet although rates of sudden death in asymptomatic severe patients with AS 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

Table 3. Primary and Secondary Outcomes

Primary outcome: Time to first MACE			
Outcome	Early surgery group 3-y KM estimate (%)	Conservative treatment group 3-y KM estimate (%)	Hazard ratio (95% CI)
Primary end point	15.22%	34.70%	0.46 (0.23–0.90)
Time-to-event secondary outcomes			
All cause death rate	9.54%	20.11%	0.56 (0.24–1.27)
HF hospitalization	4.01%	12.94%	0.32 (0.08–1.19)
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/N (%)	Conservative treatment group n/N (%)	Odds ratio (95% CI)
Intraoperative or 30-day mortality*	1/72 (1.4%)	1/25 (4%)	0.34 (0.02–5.61)
Repeated MACE	3/78 (3.8%)	7/79 (8.9%)	0.41 (0.10–1.65)
Thromboembolic complication	2/78 (2.6%)	2/79 (2.5%)	1.03 (0.14–7.67)
Major bleeding complications	4/78 (5.1%)	1/79 (1.3%)	3.52 (0.37–32.68)

HF indicates heart failure; IQR, interquartile range; MACE, major adverse cardiovascular event; and SAE, serious adverse event.

*Mortality counted in all patients undergoing with valve surgery in early surgery (n=72) and in the conservative group (n=25). For other binary secondary events, the denominator is 78 in the early surgery group and 79 in the conservative treatment group.

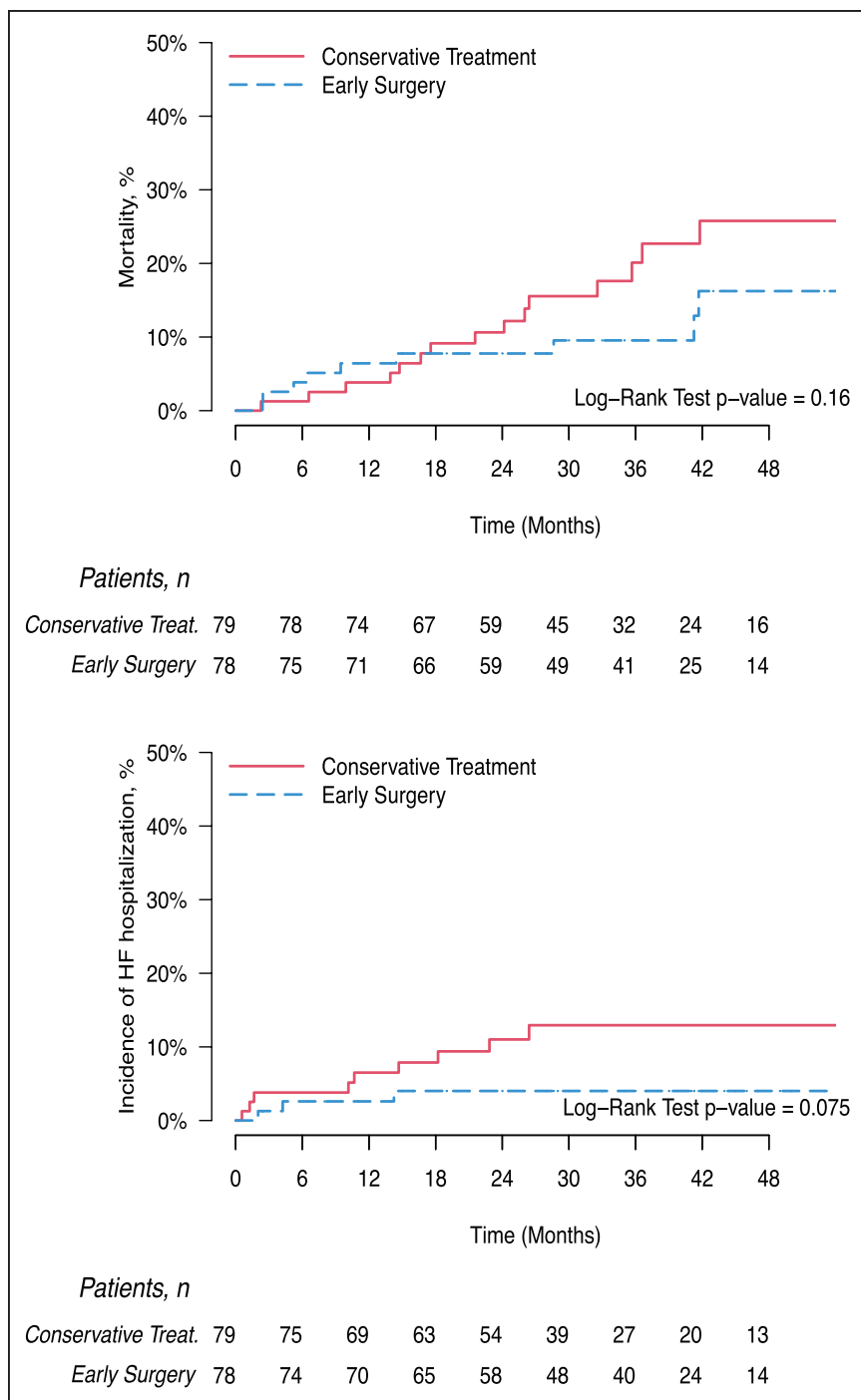


Figure 3. Kaplan-Meier cumulative incidence rates estimates of all-cause death (upper) and heart failure hospitalization (lower) analyzed by intention-to-treat analysis. HF indicates heart failure; and Treat., treatment.

is associated with structural and functional impairment of LV¹⁹ with potentially adverse clinical effects, including the development of HF with preserved or reduced LVEF.²⁰ Observational data also challenged a relatively benign course of asymptomatic AS with normal LVEF by reporting a mortality rate reaching 10% at 1e year and increased MACE incidence at midterm.²¹ Several non-randomized 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

(Early Surgery or Conservative Care for Asymptomatic Aortic Stenosis trial) provided the first direct support for early surgery in a highly selective subset of asymptomatic patients with 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 pathogenesis.^{1,2}

Table 4. Number of MACEs

	Group	
	Conservative	Early surgery
Primary end point (all-cause death + MACE)		
All-cause death	16	9
Heart failure	7	1
AMI	2	1
Stroke	1	2
Total	26	13
Total MACEs (including repeated MACEs)		
All-cause death	16	9
Heart Failure	10	3
AMI	4	1
Stroke	3	3
Total	33	16

AMI indicates acute myocardial infarction; and MACE, major adverse cardiovascular event.

This is in contrast with patients in the RECOVERY trial who presented with more critical AS with a peak velocity >4.5 m/s with mainly bicuspid aortic valve pathogenesis. Given that 20% to 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 a lower-risk patient population as reflected by lower rates of cardiovascular death in the conservative arm of the AVATAR trial compared with the same group in the RECOVERY trial. On the other hand, differences in cumulative mortality between both trials might also be related to longer clinical follow-up in the RECOVERY trial. In this regard, the proportion of patients within the conservative treatment group who remained aortic valve replacement-free during follow-up was substantially higher in the current trial (64%) compared with the conservative arm in the RECOVERY trial (26%). In addition, the AVATAR trial is multicenter and 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. Intraoperative mortality in the early surgery group in our trial was in line with anticipated mortality for elective isolated SAVR.²⁵ Taken together, the 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 HF 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 1 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 also be noted that COVID-19-related pneumonia was present in 3 deceased patients in the conservative treatment group, whereas no COVID-19-related mortality was observed in the early surgery group.

There are limitations to consider. There are differences in patients' enrollment 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 1 center. There were no core laboratory analyses of echocardiography and stress testing. The absence of central analyses was mitigated by selective reciprocal intercenter echocardiography control including image reviews. Because 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 nonsevere AS might have been included. There were baseline differences between the study groups with regard to age, and a borderline difference between the prevalence of diabetes; however, this is unlikely to result in a significant bias because the trial was randomized. The trial did not reach the prespecified sample size on the basis of the initial assumption of event and enrollment rates. Patient inclusion in this trial was challenging because it is difficult to obtain consent in an asymptomatic patient to potentially undergo open-heart surgery in the absence of guidelines recommendations. The trial design and definition of the asymptomatic and severe AS has been based on the 2012 European Society of Cardiology 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 percutaneous coronary intervention, or concomitant bypass surgery, 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. The trial enrollment and its course have been affected by the COVID-19 pandemic leading also to surgery delays in patients randomized to the early surgery. Because the prespecified number of events has been reached because of 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 composed of all-cause death, acute myocardial infarction, stroke, or unplanned hospitalization for HF compared with 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.

ARTICLE INFORMATION

Received September 22, 2021; accepted November 9, 2021.

Affiliations

Belgrade Medical School, University of Belgrade, Serbia (M.B., S.P.). Cardiology Department (M.B.), Cardiac-Surgery Department (S.P.), University Clinical Center of Serbia, Belgrade. Cardiovascular Center, OLV Hospital, Aalst, Belgium (M.P., G.V.C., J.B.). Boston University School of Public Health, Department of Biostatistics, MA (G.D.). Department of Cardiac Surgery, Medical University of Silesia, Katowice, Poland (M.A.D.). Department of Cardiology, Institute for Clinical and Experimental Medicine, Prague, Czech Republic (R.K., M.K.). Clinic of Cardiac and Vascular Diseases, Institute of Clinical Medicine, Faculty of Medicine, Vilnius University, Lithuania (S.G.). Department of Cardiac Surgery, University of Zagreb School of Medicine and University Hospital Center Zagreb, Croatia (H.G.). University Hospital Center Sestre Milosrdnice, Zagreb, Croatia (N.P.). Faculty of Medicine, University of Novi Sad, Serbia (L.V.). Institute of Cardiovascular Diseases Vojvodina, Sremska Kamenica, Serbia (L.V.). Division of Cardiosurgery, Cardiovascular and Thoracic Department, Città della Salute e della Scienza Hospital and University of Turin, Italy (S.S.). Division of Cardiology and Structural Heart Diseases, Medical University of Silesia, Katowice, Poland (W.W.). CorDynamix, Redwood City, CA (S.N.D.). Cardiology Department, Bichat Hospital AHPH and Université de Paris, France (B.I.).

Acknowledgments

The authors thank Susan Bryan for administrative assistance in the preparation of the article and Dr. Michael Pencina for helping design the trial.

Sources of Funding

None.

Disclosures

Dr Wojakowski serves on the Medtronic advisory board. The other authors report no conflicts.

Supplemental Material

Avatar Committees and Investigators
Supplemental Methods
Tables S1–S5
Figures S1–S3
References 26 and 27

REFERENCES

- Otto CM, Nishimura RA, Bonow RO, Carabello BA, Erwin JP III, Gentile F, Jneid H, Krieger EV, Mack M, McLeod C, et al. 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2021;143:e72–e227. doi: 10.1161/CIR.0000000000000923
- Vahanian A, Beyersdorf F, Praz F, Milojevic M, Baldus S, Bauersachs J, Capodanno D, Conradi L, De Bonis M, De Paulis R, et al. 2021 ESC/EACTS Guidelines for the management of valvular heart disease [published online August 28, 2021]. *Eur Heart J*. doi: 10.1093/eurheartj/ehab395
- Carabello BA. Should severe aortic stenosis be operated on before symptom onset? Aortic valve replacement should be operated on before symptom onset. *Circulation*. 2012;126:112–117. doi: 10.1161/CIRCULATIONAHA.111.079350
- lung B, Delgado V, Rosenhek R, Price S, Prendergast B, Wendler O, De Bonis M, Tribouilloy C, Evangelista A, Bogachev-Prokophiev A, et al; EORP VHD II Investigators. Contemporary presentation and management of valvular heart disease: the EURObservational Research Programme Valvular Heart Disease II Survey. *Circulation*. 2019;140:1156–1169. doi: 10.1161/CIRCULATIONAHA.119.041080
- Kang DH, Park SJ, Lee SA, Lee S, Kim DH, Kim HK, Yun SC, Hong GR, Song JM, Chung CH, et al. Early surgery or conservative care for asymptomatic aortic stenosis. *N Engl J Med*. 2020;382:111–119. doi: 10.1056/NEJMoa1912846
- San Román JA, Vilacosta I, Antunes MJ, lung B, Lopez J, Schäfers HJ. The 'wait for symptoms' strategy in asymptomatic severe aortic stenosis. *Heart*. 2020;106:1792–1797. doi: 10.1136/heartjnl-2020-317323
- Baumgartner H, lung B, Otto CM. Timing of intervention in asymptomatic patients with valvular heart disease. *Eur Heart J*. 2020;41:4349–4356. doi: 10.1093/eurheartj/ehaa485
- Baumgartner H, Hung J, Bermejo J, Chambers JB, Edvardsen T, Goldstein S, Lancellotti P, LeFevre M, Miller F Jr, Otto CM. Recommendations on the echocardiographic assessment of aortic valve stenosis: a focused update from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. *J Am Soc Echocardiogr*. 2017;30:372–392. doi: 10.1016/j.echo.2017.02.009
- Banovic M, lung B, Bartunek J, Asanin M, Beleslin B, Biocina B, Casselman F, da Costa M, Deja M, Gasparovic H, et al. Rationale and design of the Aortic Valve replacement versus conservative treatment in Asymptomatic severe aortic stenosis (AVATAR trial): A randomized multicenter controlled event-driven trial. *Am Heart J*. 2016;174:147–153. doi: 10.1016/j.ahj.2016.02.001
- Banovic M, lung B, Bartunek J, Penicka M, Vanderheyden M, Casselman F, van Camp G, Nikolic S, Putnik S. The Aortic Valve replacement versus conservative treatment in Asymptomatic severe aortic stenosis (AVATAR trial): a protocol update. *Am Heart J*. 2018;195:153–154. doi: 10.1016/j.ahj.2017.10.005
- Vahanian A, Alfieri O, Andreotti F, Antunes MJ, Barón-Esquivias G, Baumgartner H, Borger MA, Carrel TP, De Bonis M, Evangelista A, et al. Guidelines on the management of valvular heart disease (version 2012). The Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2012;33:2451–2496. doi: 10.1093/eurheartj/ehs109
- Pellikka PA, Nagueh SF, Elhendy AA, Kuehl CA, Sawada SG; American Society of Echocardiography. American Society of Echocardiography recommendations for performance, interpretation, and application of stress echocardiography. *J Am Soc Echocardiogr*. 2007;20:1021–1041. doi: 10.1016/j.echo.2007.07.003
- Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, Kaul S, Wiviott SD, Menon V, Nikolsky E, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. *Circulation*. 2011;123:2736–2747. doi: 10.1161/CIRCULATIONAHA.110.009449
- Lakatos E. Sample sizes based on the log-rank statistic in complex clinical trials. *Biometrics*. 1988;44:229–241.
- Lakatos E. Designing complex group sequential survival trials. *Stat Med*. 2002;21:1969–1989. doi: 10.1002/sim.1193
- Rosenhek R, Binder T, Porenta G, Lang I, Christ G, Schemper M, Maurer G, Baumgartner H. Predictors of outcome in severe, asymptomatic aortic stenosis. *N Engl J Med*. 2000;343:611–617. doi: 10.1056/NEJM200008313430903
- Pellikka PA, Sarano ME, Nishimura RA, Malouf JF, Bailey KR, Scott CG, Barnes ME, Tajik AJ. Outcome of 622 adults with asymptomatic, hemodynamically significant aortic stenosis during prolonged follow-up. *Circulation*. 2005;111:3290–3295. doi: 10.1161/CIRCULATIONAHA.104.495903
- Rosenhek R, Klaar U, Schemper M, Scholten C, Heger M, Gabriel H, Binder T, Maurer G, Baumgartner H. Mild and moderate aortic stenosis: natural history and risk stratification by echocardiography. *Eur Heart J*. 2004;25:199–205. doi: 10.1016/j.ehj.2003.12.002
- Maganti K, Rigolin VH, Sarano ME, Bonow RO. Valvular heart disease: diagnosis and management. *Mayo Clin Proc*. 2010;85:483–500. doi: 10.4065/mcp.2009.0706
- Everett RJ, Tastet L, Clavel MA, Chin CWL, Capoulade R, Vassiliou VS, Kwicinski J, Gomez M, van Beek EJR, White AC, et al. Progression of hypertrophy and myocardial fibrosis in aortic stenosis: a multicenter cardiac magnetic resonance study. *Circ Cardiovasc Imaging*. 2018;11:e007451. doi: 10.1161/CIRCIMAGING.117.007451
- Kvaslerud AB, Santic K, Hussain AI, Auensen A, Fiene A, Skulstad H, Aaberge L, Gullestad L, Broch K. Outcomes in asymptomatic, severe aortic stenosis. *PLoS One*. 2021;16:e0249610. doi: 10.1371/journal.pone.0249610

22. Taniguchi T, Morimoto T, Shiomi H, Ando K, Kanamori N, Murata K, Kitai T, Kawase Y, Izumi C, Miyake M, et al; CURRENT AS Registry Investigators. Initial surgical versus conservative strategies in patients with asymptomatic severe aortic stenosis. *J Am Coll Cardiol*. 2015;66:2827–2838. doi: 10.1016/j.jacc.2015.10.001
23. Lim WY, Ramasamy A, Lloyd G, Bhattacharyya S. Meta-analysis of the impact of intervention versus symptom-driven management in asymptomatic severe aortic stenosis. *Heart*. 2017;103:268–272. doi: 10.1136/heartjnl-2016-309830
24. Das P, Rimington H, Chambers J. Exercise testing to stratify risk in aortic stenosis. *Eur Heart J*. 2005;26:1309–1313. doi: 10.1093/eurheartj/ehi250
25. Bekerredjian R, Szabo G, Balaban Ü, Bleiziffer S, Bauer T, Ensminger S, Frerker C, Herrmann E, Beyersdorf F, Hamm C, et al. Patients at low surgical risk as defined by the Society of Thoracic Surgeons Score undergoing isolated interventional or surgical aortic valve implantation: in-hospital data and 1-year results from the German Aortic Valve Registry (GARY). *Eur Heart J*. 2019;40:1323–1330. doi: 10.1093/eurheartj/ehy699
26. Blackstone EH. The choice of a prosthetic heart valve: how shall patient-specific recommendations be made? *J Heart Valve Dis*. 1998;7:1–3.
27. Emery RW, Arom KV, Kshetry VR, Kroshus TJ, Von R, Kersten TE, Lillehei TJ, Nicoloff DM, Erickson CA. Decision-making in the choice of heart valve for replacement in patients aged 60-70 years: twenty-year follow up of the St. Jude Medical aortic valve prosthesis. *J Heart Valve Dis*. 2002;11(suppl 1):S37–S44.