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Early Surgery or Conservative Care for Asymptomatic Aortic Stenosis

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ABSTRACT

BACKGROUND

The timing and indications for surgical intervention in asymptomatic patients with severe aortic stenosis remain controversial.

METHODS

In a multicenter trial, we randomly assigned 145 asymptomatic patients with very severe aortic stenosis (defined as an aortic-valve area of ≤0.75 cm^2 with either an aortic jet velocity of ≥4.5 m per second or a mean transaortic gradient of ≥50 mm Hg) to early surgery or to conservative care according to the recommendations of current guidelines. The primary end point was a composite of death during or within 30 days after surgery (often called operative mortality) or death from cardiovascular causes during the entire follow-up period. The major secondary end point was death from any cause during follow-up.

RESULTS

In the early-surgery group, 69 of 73 patients (95%) underwent surgery within 2 months after randomization, and there was no operative mortality. In an intention-to-treat analysis, a primary end-point event occurred in 1 patient in the early-surgery group (1%) and in 11 of 72 patients in the conservative-care group (15%) (hazard ratio, 0.09; 95% confidence interval [CI], 0.01 to 0.67; P=0.003). Death from any cause occurred in 5 patients in the early-surgery group (7%) and in 15 patients in the conservative-care group (21%) (hazard ratio, 0.33; 95% CI, 0.12 to 0.90). In the conservative-care group, the cumulative incidence of sudden death was 4% at 4 years and 14% at 8 years.

CONCLUSIONS

Among asymptomatic patients with very severe aortic stenosis, the incidence of the composite of operative mortality or death from cardiovascular causes during the follow-up period was significantly lower among those who underwent early aortic-valve replacement surgery than among those who received conservative care. (Funded by the Korean Institute of Medicine; RECOVERY ClinicalTrials.gov number, NCT01161732.)

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Aortic stenosis is the most common valvular disease for which surgery is indicated in developed countries, and the prevalence of this condition is increasing because of the aging population.[1] Aortic-valve replacement is the only effective therapy for severe symptomatic aortic stenosis, and despite limited data from randomized clinical trials, current guidelines recommend aortic-valve replacement because of the dismal natural history of this disorder.[1,2] Although one third to one half of patients with severe aortic stenosis are asymptomatic at the time of diagnosis,[3,4] appropriate timing of intervention for these patients remains controversial.[5,6] On the basis of a consensus opinion that the potential benefit of aortic-valve replacement to prevent sudden death in asymptomatic patients (which has an incidence of approximately 1% per year) may not be greater than the risk of death during or within 30 days after surgery (often called operative mortality) and death related to the aortic-valve prosthesis, observation is recommended for the majority of asymptomatic patients with severe aortic stenosis, and aortic-valve replacement is recommended once symptoms develop.[1,2,4] However, advances in surgical techniques and aortic-valve prostheses may change the risk-to-benefit ratio of aortic-valve replacement, especially among patients at low surgical risk.[7-9]

The Randomized Comparison of Early Surgery versus Conventional Treatment in Very Severe Aortic Stenosis (RECOVERY) trial was designed to compare long-term clinical outcomes of early surgical aortic-valve replacement with those of a conservative care strategy based on current guidelines in asymptomatic patients with very severe aortic stenosis (transvalvular velocity ≥4.5 m per second). The major hypothesis of this trial was that the incidence of death from cardiovascular causes would be lower among patients who underwent early surgery than among those who received conservative care.

Methods

Trial Design and Oversight

We conducted this multicenter, randomized, parallel-group, open-label trial involving asymptomatic patients with very severe aortic stenosis who were candidates for either early surgery or conservative care at four medical centers in Korea. The trial protocol (available with the full text of this article at NEJM.org) was designed by the principal investigator and approved by the institutional review board at each participating center. The Korean Institute of Medicine, which supported the trial coordinators during the first 2 years of the trial, had no role in the collection, analysis, or interpretation of the data, writing of the manuscript, or any other aspect of the trial. The trial received no other external sources of funding.

The trial was conducted in accordance with the principles of the Declaration of Helsinki. An independent clinical-events committee adjudicated all serious adverse events, and a data and safety monitoring board oversaw the safety of the trial. The first draft of the manuscript was prepared by the first author and was reviewed and edited by all the authors. All the authors made the decision to submit the manuscript for publication and vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

Patient Selection

We screened consecutive patients who were 20 to 80 years of age and who presented with very severe aortic stenosis, which was assessed by means of transthoracic echocardiography. In accordance with the 1998 American College of Cardiology–American Heart Association (ACC–AHA) guidelines and a traditional definition of severe aortic stenosis,[10,11] we defined very severe aortic stenosis as an aortic-valve area of 0.75 cm^2 or less with either a peak aortic jet velocity of 4.5 m per second or greater or a mean transaortic gradient of 50 mm Hg or greater.

In accordance with the 2006 ACC–AHA guidelines on surgical indications for severe aortic stenosis,[12] patients were excluded if they had exertional dyspnea, syncope, presyncope or angina, a left ventricular ejection fraction of less than 50%, or clinically significant aortic regurgitation or mitral valve disease or if they had undergone cardiac surgery. Exercise testing was selectively performed to evaluate patients with nonspecific symptoms, and patients with a positive exercise test were excluded. We also excluded patients who were not candidates for early surgery because of age (>80 years) or a medical condition such as cancer. All the participants provided written informed consent.

TRIAL PROCEDURES

Eligibility was determined after each patient underwent a thorough evaluation of symptoms and medical records and results of echocardiography and exercise testing were reviewed. Details regarding echocardiography and exercise testing are provided in the Supplementary Appendix, available at NEJM.org. Patients were randomly assigned in a 1:1 ratio to early surgery or conservative care with the use of a Web-based interactive response system. The assignment to each treatment group was computer-generated and stratified according to the participating center by means of a permuted-block sequence with variable block size.

The protocol specified that patients assigned to the early-surgery group should undergo aortic-valve replacement within 2 months after randomization. Patients assigned to the conservative-care group received treatment according to the ACC–AHA guidelines,[2,12] and they were referred for surgery if they became symptomatic during follow-up, if the left ventricular ejection fraction decreased to less than 50%, or if the peak aortic jet velocity increased each year by more than 0.5 m per second on follow-up echocardiography. Details regarding surgical procedures and patient follow-up are provided in the Supplementary Appendix.

TRIAL END POINTS

The primary end point was a composite of operative mortality or death from cardiovascular causes during the follow-up period (continuing until 4 years after the last patient was enrolled). Prespecified secondary end points included death from any cause, repeat aortic-valve surgery, clinical thromboembolic events, and hospitalization for heart failure during follow-up. Specific definitions of trial end points are provided in the Supplementary Appendix.

STATISTICAL ANALYSIS

On the basis of our previous observational study,[13] we estimated that a sample of 144 patients would provide the trial with 80% power, at a two-sided significance level of 0.05, to detect a significant difference with respect to the primary end point, assuming that the incidence of the primary end point would be 16% in the conservative-care group and 2% in the early-surgery group during a follow-up period that continued until 4 years after the last patient was enrolled. In calculating the sample size by a log-rank survival power analysis, we also assumed that an enrollment period of 2 years would be needed to complete enrollment and that the rate of loss to follow-up would be 10%.

Analyses were performed on an intention-to-treat basis. Differences between the treatment groups were evaluated with the use of Student's t-test for continuous variables and Fisher's exact test for categorical variables. Because randomization was stratified according to the participating center, we analyzed the end points with the use of stratified Cox proportional-hazards regression with Firth correction. Estimates of cumulative incidences were calculated by the Kaplan–Meier method and were compared with the use of the log-rank test. For the Kaplan–Meier analysis, we analyzed all clinical events according to the time to the first event. Hazard ratios with 95% confidence intervals were derived with the use of the stratified Cox proportional-hazards model with Firth correction. The 95% confidence intervals have not been adjusted for multiple comparisons, and therefore inferences drawn from these intervals may not be reproducible.

For the primary end-point analysis, we also performed a competing-risk analysis in which death due to a cause other than a cardiovascular cause was considered as a competing risk, and hazard ratios with 95% confidence intervals were calculated with the use of the method of Fine and Gray. The cumulative incidences of the primary end point were also compared between the treatment groups with the use of Gray's test. Subgroup analyses were performed to determine whether the result of the primary end point was consistent in two prespecified subgroups defined according to peak aortic velocity and cause of aortic stenosis. A per-protocol analysis of the primary end point was also performed. All reported P values were two-sided, and a P value of less than 0.05 was considered to indicate statistical significance. We used SAS software, version 9.4 (SAS Institute), for statistical analyses.

RESULTS

PATIENTS

From July 2010 through April 2015, a total of 273 asymptomatic patients with very severe aortic stenosis were screened for participation in the trial, and 145 were enrolled and were randomly

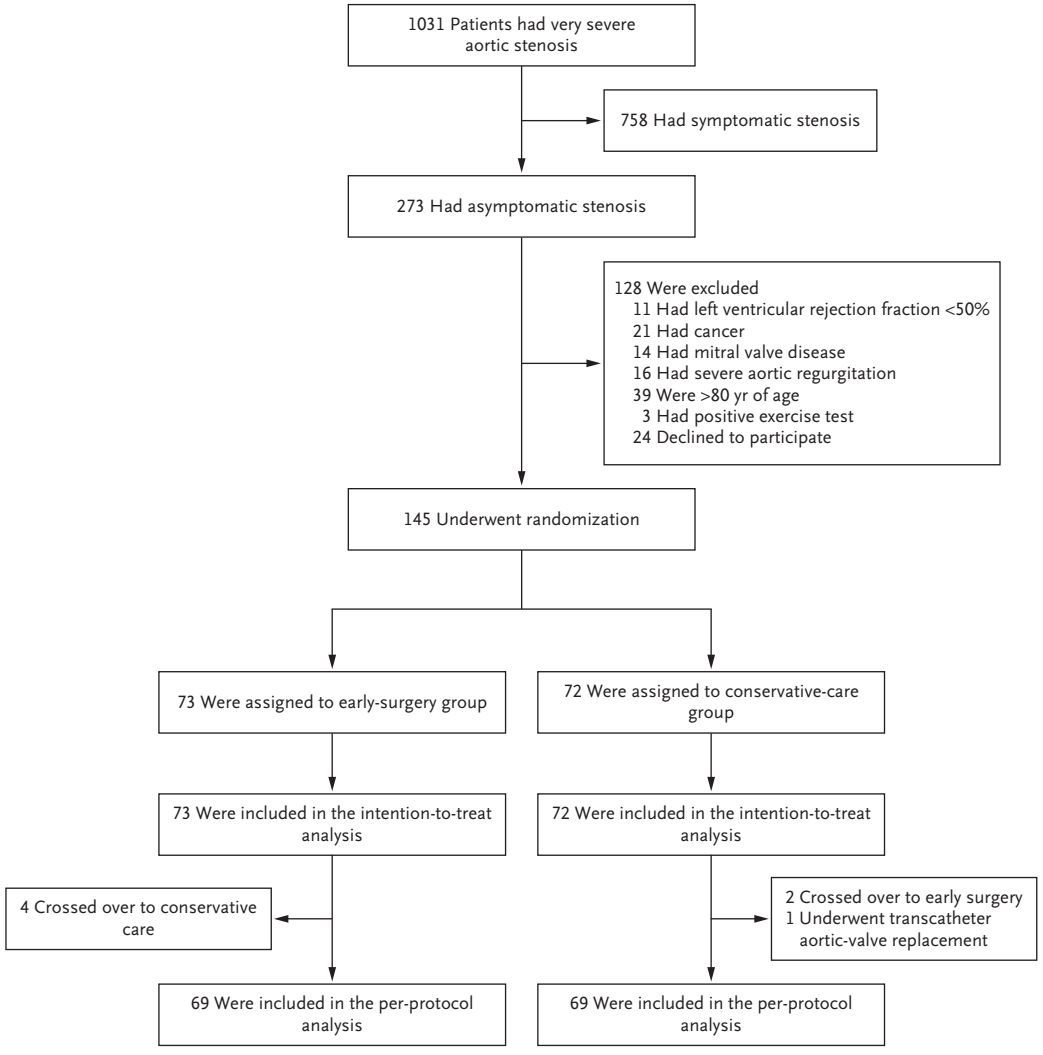

Figure 1. Enrollment, Randomization, and Follow-up.

Very severe aortic stenosis was defined as an aortic-valve area of 0.75 cm^2 or less with a peak aortic jet velocity of at least 4.5 m per second or a mean transaortic gradient of at least 50 mm Hg. Of the four patients in the early-surgery group who crossed over to conservative care and were excluded from the per-protocol analysis, three underwent surgery later after the development of symptoms and one did not undergo surgery.

assigned (73 patients to early surgery and 72 patients to conservative care) (Fig. 1). Baseline characteristics of the excluded patients are listed in Table S1 in the Supplementary Appendix. After randomization, 2 patients assigned to conservative care crossed over to early surgery and 4 patients assigned to early surgery crossed over to conservative care; surgical aortic-valve replacement in these 4 patients was later performed after development of symptoms in 3 patients and was not attempted in 1.

The treatment groups were generally well balanced with regard to baseline clinical characteristics (Table 1). The mean (±SD) age of the patients was 64.2±9.4 years, and 49% were men. The cause of aortic stenosis was a bicuspid aortic valve in 88 patients (61%), degenerative valvular disease in 48 (33%), and rheumatic valvular disease in 9 (6%). The mean peak aortic jet velocity was 5.1±0.5 m per second, and the mean aortic-valve area was 0.63±0.09 cm^2. Medication use at baseline was also similar in the two groups.

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Conservative Care (N=72)	Early Surgery (N=73)
Age — yr	63.4±10.7	65.0±7.8
Male sex — no. (%)	34 (47)	37 (51)
Body-surface area — m^2	1.64±0.17	1.69±0.17
Body-mass index†	24.0±2.6	24.7±3.4
Diabetes — no. (%)	7 (10)	13 (18)
Hypertension — no. (%)	39 (54)	40 (55)
Smoking — no. (%)	21 (29)	19 (26)
Hypercholesterolemia — no. (%)	42 (58)	41 (56)
Coronary artery disease — no./total no. (%)‡	1/59 (2)	5/72 (7)
Previous PCI — no. (%)	1 (1)	3 (4)
Previous stroke — no. (%)	3 (4)	3 (4)
Peripheral vascular disease — no. (%)	2 (3)	1 (1)
Atrial fibrillation — no. (%)	6 (8)	3 (4)
Serum creatinine level — mg/dl	0.83±0.16	0.84±0.23
EuroSCORE II score — %§	0.9±0.4	0.9±0.3
Medication — no. (%)		
Angiotensin-converting–enzyme inhibitor	0	4 (5)
Angiotensin-receptor blocker	28 (39)	24 (33)
Calcium antagonist	20 (28)	19 (26)
Beta-blocker	8 (11)	13 (18)
Diuretic	17 (24)	13 (18)
Statin	32 (44)	34 (47)
Echocardiographic findings		
Cause of aortic stenosis — no. (%)		
Bicuspid aortic valve	39 (54)	49 (67)
Degenerative valvular disease	26 (36)	22 (30)
Rheumatic valvular disease	7 (10)	2 (3)
Peak aortic jet velocity — m/sec	5.04±0.44	5.14±0.52
Transaortic pressure gradient — mm Hg		
Peak	102.5±18.4	106.9±21.9
Mean	62.7±12.4	64.3±14.4
Aortic valve		
Area — cm^2	0.64±0.09	0.63±0.09
Area index — cm^2/m^2	0.39±0.07	0.38±0.06
Left ventricular mass index — g/m^2	133.7±31.1	135.6±38.2
Left ventricular ejection fraction — %	64.8±4.1	64.8±5.2

* Plus–minus values are means ±SD. To convert values for serum creatinine to micromoles per liter, multiply by 88.4. There were no significant between-group differences. PCI denotes percutaneous coronary intervention.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ Coronary computed tomography or coronary angiography was performed before aortic-valve replacement in 59 patients in the conservative-care group and in 72 patients in the early-surgery group.
§ Scores on the European System for Cardiac Operative Risk Evaluation II (EuroSCORE II), which measures patient risk at the time of cardiovascular surgery, are calculated by means of a logistic-regression equation and range from 0 to 100%, with higher scores indicating greater risk.

Table 2. Primary and Secondary End Points.

Outcome	Conservative Care (N=72)	Early Surgery (N=73)	Hazard Ratio (95% CI)*
	number (percent)		
Primary end point: operative mortality or death from cardiovascular causes during follow-up†	11 (15)	1 (1)	0.09 (0.01–0.67)‡
Secondary end points			
Death from any cause	15 (21)	5 (7)	0.33 (0.12–0.90)§
Clinical thromboembolic event	4 (6)	1 (1)	0.30 (0.04–2.31)§
Stroke	3	1	
Myocardial infarction	1	0	
Repeat aortic-valve surgery	2 (3)	0	0.19 (0.10–8.00)§
Hospitalization for heart failure	8 (11)	0	0.05 (0.00–1.05)§

* The 95% confidence intervals have not been adjusted for multiple comparisons, and therefore inferences drawn from these intervals may not be reproducible.
† Operative mortality was defined as death during or within 30 days after surgery.
‡ This hazard ratio was calculated with the use of a Fine and Gray competing-risks analysis.
§ This hazard ratio was calculated with the use of stratified Cox proportional-hazards models with Firth correction.

AORTIC-VALVE REPLACEMENT PROCEDURES

In the early-surgery group, surgical aortic-valve replacement was successfully performed in all 72 patients in whom the procedure was attempted; 36 patients (50%) received a mechanical valve and 36 (50%) received a biologic prosthesis. All the patients except those who crossed over underwent surgery within 2 months after randomization; the median time between randomization and surgery was 23 days (interquartile range, 10 to 36). There was no operative mortality in the early-surgery group.

Of the 72 patients assigned to conservative care, 53 patients (74%) underwent surgical aortic-valve replacement (52 patients) or transcatheter aortic-valve replacement (TAVR) (1 patient) during follow-up, mainly because of the development of symptoms (in 43 patients). Indications for aortic-valve replacement are listed in Table S2. Among these 53 patients, urgent surgery was performed in 9 patients (17%) who were admitted from the emergency department. There was no operative mortality among the patients who later underwent aortic-valve replacement; the median time from randomization to aortic-valve replacement was 700 days (interquartile range, 277 to 1469). Additional information on surgical procedures and results are provided in Table S3 and the Supplemental Surgical Results section in the Supplementary Appendix.

FOLLOW-UP AND END POINTS

Data collection ended in April 2019, when the last enrolled patient had completed 4 years of follow-up. The median follow-up was 6.2 years (interquartile range, 5.0 to 7.4) in the early-surgery group and 6.1 years (interquartile range, 4.5 to 7.3) in the conservative-care group. No patients were lost to follow-up.

In an intention-to-treat analysis including all the trial patients, 1 of 73 patients assigned to early surgery (1%) and 11 of 72 patients assigned to conservative care (15%) died from cardiovascular causes (hazard ratio, 0.09; 95% confidence interval [CI], 0.01 to 0.67) (Table 2). The number needed to treat to prevent one death from cardiovascular causes within 4 years was 20 patients. The cumulative incidence of the primary end point (operative mortality or death from cardiovascular causes during the follow-up period), as calculated with the use of a Kaplan–Meier analysis, was 1% at both 4 and 8 years in the early-surgery group, as compared with 6% at 4 years and 26% at 8 years in the conservative-care group (P=0.003) (Fig. 2A).

A total of 5 deaths from any cause (7% of the patients) occurred in the early-surgery group and 15 deaths from any cause (21%) occurred in the conservative-care group (hazard ratio, 0.33; 95% CI, 0.12 to 0.90). The cumulative incidence of death from any cause was lower in the early-

surgery group than in the conservative-care group (4% vs. 10% at 4 years and 10% vs. 32% at 8 years) (Fig. 2B). Details regarding patients who died are summarized in Table S4. In the conservative-care group, the cumulative incidence of sudden death was 4% at 4 years and 14% at 8 years.

The incidences of other prespecified secondary end points are listed in Table 2. The incidence of hospitalization for heart failure was lower in the early-surgery group than in the conservative-care group (no cases vs. 11%). The cumulative incidence of the composite of any secondary end point or aortic-valve replacement in the conservative-care group was 62% at 4 years and 92% at 8 years (Fig. S1).

The results of the analyses involving the per-protocol population were consistent with those involving the intention-to-treat population (Table S5 and Fig. S2). Subgroup analyses were performed to assess the consistency of the results with regard to the primary end point and death from any cause in two prespecified subgroups (Table S6).

DISCUSSION

The RECOVERY trial compared early surgery with conservative care in asymptomatic patients with very severe aortic stenosis. The trial showed a lower incidence of the primary end point of operative mortality or death from cardiovascular causes during the follow-up period among patients who underwent early surgery than among those who received conservative care. Moreover, early surgery was associated with a lower incidence of death from any cause among such patients.

The decision to perform surgery in an asymptomatic patient requires careful weighing of the risks of early aortic-valve replacement against those of observation. In patients with asymptomatic severe aortic stenosis, it has generally appeared to be relatively safe to follow a watchful waiting strategy and delay surgery until symptoms develop.[14] However, this conservative care strategy is also associated with a risk of sudden death, denial or late reporting of symptoms by patients, irreversible myocardial damage, and an increase in surgical risk while waiting for symptoms to develop.[4-6] In previous observational studies, baseline differences between the treatment groups, treatment-selection bias, and unmeasured confounders might have influenced the results.[13,15]

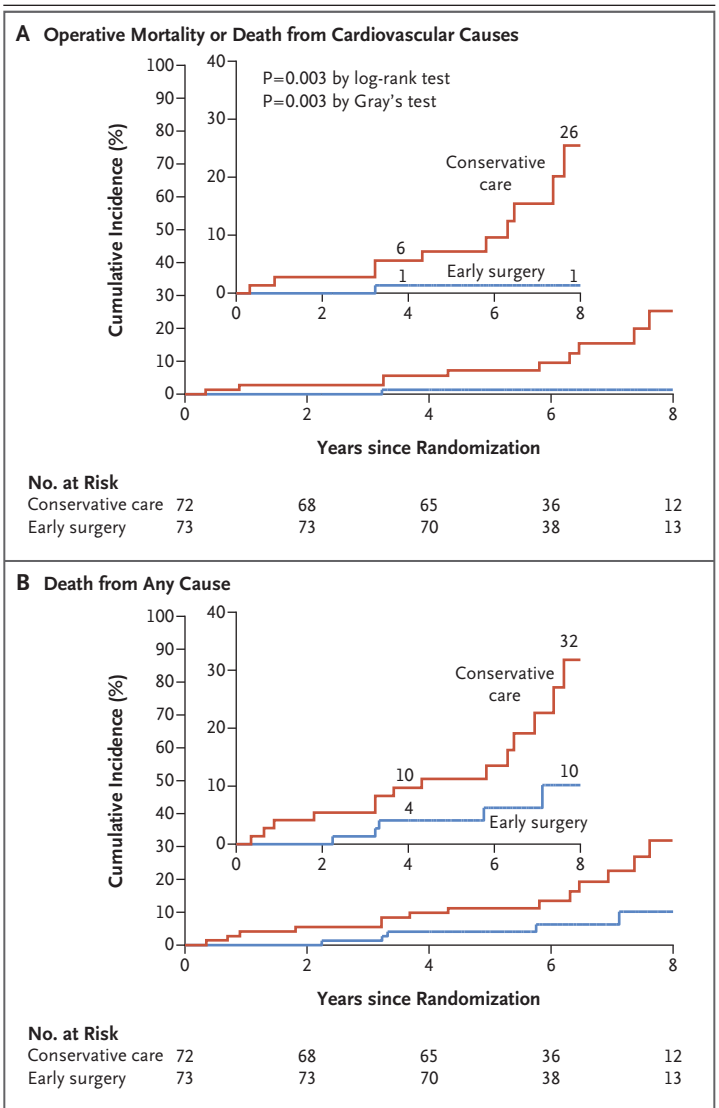

Figure 2. Time-to-Event Curves for the Primary Composite End Point and Death from Any Cause.

Shown are Kaplan–Meier estimates of the cumulative incidence of the primary end point of death during or within 30 days after surgery (often called operative mortality) or death from cardiovascular causes during the follow-up period (Panel A) and of the major secondary end point of death from any cause during follow-up (Panel B) among patients who were randomly assigned to undergo early surgery or to receive conservative care. The insets show the same data on an enlarged y axis.

By reducing these limitations inherent to observational studies,[4,16] this randomized trial provides evidence to support early aortic-valve replacement in asymptomatic patients with very severe aortic stenosis.

There may be several explanations for the significant difference in long-term survival between

the two groups. First, surgical risk was substantially lower in this trial and in recent trials comparing surgical aortic-valve replacement with TAVR in low-risk patients[8,9] than in previous studies; in our trial, the incidence of operative mortality was less than 1%. Close monitoring was performed after surgery, and improvements in postoperative care contributed to a substantial decrease in the long-term risk associated with early aortic-valve replacement. Second, early surgery appeared to prevent sudden death, because no cases of sudden death occurred in the early-surgery group. In contrast, in the conservative-care group, the annual risk of sudden death tended to increase during the progression of aortic stenosis before the development of symptoms. Third, eventual aortic-valve replacement was almost unavoidable in the conservative-care group, and the overall risk of aortic-valve replacement appeared to increase while surgery was deferred until symptoms developed. Cardiovascular events that occurred after surgery were more frequently observed in the conservative-care group, suggesting a higher long-term risk associated with later aortic-valve replacement.

Our trial has several limitations. First, the risk–benefit ratio may be shifted toward a benefit of early surgery in this trial involving patients with very severe aortic stenosis because the risk of waiting increases according to the severity of aortic stenosis.[5] The benefit of early surgery may be relatively smaller in asymptomatic patients with less severe aortic stenosis. Second, crossover occurred in 5% of the patients in the early-surgery group and in 3% of the patients in the conservative-care group. Nevertheless, the results of the per-protocol analysis were similar to those of the primary intention-to-treat analysis. Third, since this trial was not blinded, the nonfatal outcomes could have been influenced by the clinician's knowledge of the treatment the patient received. Fourth, exercise testing is reasonable to confirm the absence of symptoms in asymptomatic patients with severe aortic stenosis,[2] but it was performed only selectively in this trial. Fifth, the small numbers of trial patients and primary end-point events constitute an important limitation of this trial. However, it was the judgment of the investigators that a larger number of patients than the calculated sample size could not be enrolled for ethical and logistic reasons. Finally, this trial included relatively young patients (as compared with patients enrolled in recent TAVR trials involving low-risk patients[8,9]), among whom the incidence of bicuspid aortic-valve disease was high and who had normal left ventricular systolic function, few coexisting conditions, and low operative risk. Thus, our trial population is quite different from the populations enrolled in TAVR trials,[8,9,17-19] and the results of our trial cannot be directly applied to early TAVR for asymptomatic severe aortic stenosis. Because the incidence of operative mortality was very low in our trial, our results may not be applicable to low-volume medical centers or to patients at high operative risk.

In conclusion, in this randomized trial, early surgical aortic-valve replacement resulted in a significantly lower risk of operative mortality or death from cardiovascular causes during the follow-up period than conservative care among asymptomatic patients with very severe aortic stenosis.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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