ORIGINAL ARTICLE

Early Surgery or Conservative Care for Asymptomatic Aortic Stenosis at 10 Years

Duk-Hyun Kang, M.D., Ph.D.,[1] Sung-Ji Park, M.D., Ph.D.,[2] Ga Yun Kim, M.D.,[1] Sahmin Lee, M.D., Ph.D.,[1] Byung Joo Sun, M.D., Ph.D.,[1] Joon Bum Kim, M.D., Ph.D.,[3] Sung-Ho Jung, M.D., Ph.D.,[3] Hyung-Kwan Kim, M.D., Ph.D.,[4] Sung-Cheol Yun, Ph.D.,[5] Geu-Ru Hong, M.D., Ph.D.,[6] Jong-Min Song, M.D., Ph.D.,[1] and Cheol-Hyun Chung, M.D., Ph.D.[3]

ABSTRACT

BACKGROUND

Among asymptomatic patients with severe aortic stenosis, a previous analysis showed that the risk of a composite of death during surgery or within 30 days after surgery (called operative mortality) or death from cardiovascular causes was significantly lower with early surgery than with conservative care. However, the long-term survival benefit of early surgery, as compared with conservative care, remains unclear.

METHODS

We randomly assigned asymptomatic patients with very severe aortic stenosis (defined as an aortic-valve area of ≤0.75 cm^2 with a peak aortic jet velocity of ≥4.5 m per second) in a 1:1 ratio to undergo early surgery or receive conservative care. The primary end point was a composite of operative mortality or death from cardiovascular causes during the 10-year follow-up period.

RESULTS

A total of 145 patients underwent randomization. In an intention-to-treat analysis, a primary end-point event occurred in 2 of 73 patients (3%) in the early-surgery group and in 17 of 72 (24%) in the conservative-care group (hazard ratio, 0.10; 95% confidence interval [CI], 0.02 to 0.43; P=0.002). At 10 years, the cumulative incidence of operative mortality or death from cardiovascular causes was 1% in the early-surgery group and 19% in the conservative-care group. Death from any cause occurred in 11 patients (15%) in the early-surgery group and in 23 (32%) in the conservative-care group (hazard ratio, 0.42; 95% CI, 0.21 to 0.86).

CONCLUSIONS

Among asymptomatic patients with very severe aortic stenosis, early surgery led to a lower risk of a composite of operative mortality or death from cardiovascular causes than conservative care at 10 years. (Funded by the Korean Institute of Medicine; RECOVERY ClinicalTrials.gov number, NCT01161732.)

Author affiliations are listed at the end of the article. Duk-Hyun Kang can be contacted at dhkang@amc.seoul.kr or at the Division of Cardiology, Asan Medical Center, College of Medicine, University of Ulsan, 388-1, Poongnap-dong, Songpa-ku, Seoul 138-736, South Korea.

Duk-Hyun Kang and Sung-Ji Park contributed equally to this article.

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CME

Current guidelines recommend aortic-valve replacement for symptomatic patients with severe aortic stenosis.[1,2] For asymptomatic severe aortic stenosis, watchful waiting has been recommended with prompt intervention at symptom onset, given that the rate of sudden death during the asymptomatic phase is low (<1% per year).[1-3] However, clinical trials have challenged the appropriateness of conservative management in such patients, showing a very low procedural risk of aortic-valve replacement with a periprocedural mortality of less than 0.5%[4,5] and a survival benefit with early preemptive aortic-valve replacement as compared with conservative management.[5,6] Long-term follow-up data are necessary to evaluate whether these benefits would be sustained, given that the long-term risks related to prosthetic valves, including bioprosthetic-valve degeneration, thromboembolic complications, and anticoagulation-related bleeding, may exceed the risk of irreversible myocardial damage associated with more-prolonged exposure to pressure overload imposed by severe aortic stenosis.[7,8]

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In the Randomized Comparison of Early Surgery versus Conventional Treatment in Very Severe Aortic Stenosis (RECOVERY) trial, which enrolled asymptomatic patients with very severe aortic stenosis, early surgical aortic-valve replacement led to a substantially lower incidence of death from cardiovascular causes and death from any cause at a minimum follow-up of 4 years.[5] To further elucidate the long-term outcomes of early surgical aortic-valve replacement as compared with conservative care, we report here the final results of the RECOVERY trial, with an extended follow-up of more than 10 years.

METHODS

TRIAL DESIGN AND OVERSIGHT

We conducted a multicenter, randomized, parallel-group, open-label trial to compare outcomes between early surgery and conservative care in asymptomatic patients with very severe aortic stenosis. The design and the intermediate-term results of the RECOVERY trial have been published previously.[5] Although this trial was initially planned to complete follow-up 4 years after the enrollment of the last patient, participating trial centers agreed to take part in the extended follow-up study with a minimum follow-up of 10 years. The trial protocol, which is available with the full text of this article at NEJM.org, was designed by the principal investigator (first author) 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, the 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 authors vouch for the fidelity of the trial to the protocol and for the accuracy and completeness of the data.

PATIENT SELECTION

Details of the enrollment criteria have been published previously.[5] In brief, eligible patients were asymptomatic and had very severe aortic stenosis, defined as an aortic-valve area of no more than 0.75 cm^2 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. 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 previously. Each patient was specifically questioned about the presence of any symptoms during ordinary physical activity to ensure the enrollment of entirely asymptomatic patients. 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 patients provided written informed consent.

TRIAL PROCEDURES

Eligibility was determined after each patient underwent a thorough evaluation of symptoms and medical records and the results of echocardiography and exercise testing were reviewed. Patients were randomly assigned in a 1:1 ratio to undergo early surgery or receive conservative care. Randomization was performed with the use of a Web-based interactive-response system. Assignment to each treatment group was computergenerated and stratified according to the participating center by means of a permuted-block sequence with variable block size.

The protocol specified that patients who were assigned to the early-surgery group should undergo aortic-valve replacement within 2 months after randomization. Patients who were assigned to the conservative-care group were referred for aortic-valve replacement 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.

END POINTS

The primary end point was a composite of death during surgery or within 30 days after surgery (often called operative mortality) or death from cardiovascular causes during the entire follow-up interval (continuing until 10 years after the last patient was enrolled). Prespecified secondary end points included death from any cause, clinical thromboembolic events, repeat aortic-valve surgery, and hospitalization for heart failure during follow-up. Specific definitions of the trial end points are provided in the Supplementary Appendix (available at NEJM.org).

STATISTICAL ANALYSIS

Details about assumptions of the event rate and power analyses have been published previously.[5] The statistical methods that were used for comparative treatment analyses that included data from the extended follow-up period were similar to those used in the original RECOVERY trial.[5] Analyses were performed on an intention-to-treat basis, in which the treatment groups were defined according to the original randomization. Because randomization was stratified according to the participating center, we analyzed the outcomes with the use of stratified Cox proportional-hazards regression with Firth correction. Estimates of the cumulative incidence of events 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 that are presented here have not been adjusted for multiplicity, so inferences drawn from these intervals should not be used for hypothesis testing. No data were missing for the principal analyses. No interim analyses were planned during the extended follow-up period. For the primary end-point analysis, we also performed a competing-risk analysis in which death from noncardiovascular causes 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.

Sensitivity analyses were conducted with the use of as-treated analyses (in which patients were compared on the basis of the treatment that they actually received) and per-protocol analyses (which included only patients who actually received their randomly assigned treatment). We also assessed the consistency of treatment effects across the two prespecified subgroups defined according to peak aortic velocity and cause of aortic stenosis, using Cox regression models with tests for interactions. All reported P values are two-sided, and a P value of less than 0.05 was considered to indicate statistical significance. SAS software, version 9.4 (SAS Institute), was used for the statistical analyses.

RESULTS

PATIENTS

From July 2010 through April 2015, a total of 145 asymptomatic patients with very severe aortic stenosis were randomly assigned to undergo early surgery (73 patients) or receive conservative care (72 patients) (Fig. 1). After randomization, 2 patients who had been assigned to the conservative-care group crossed over to early surgery, and 4 patients who had been assigned to the early-surgery group crossed over to conservative care and underwent surgical aortic-valve replacement later, after the development of symptoms. The baseline clinical and echocardiographic characteristics of the patients are summarized in Table 1. These characteristics of the patients appeared to be well balanced between the two groups, although a higher percentage of patients with diabetes or bicuspid aortic valves were assigned to the early-surgery group and a higher percentage of patients with degenerative valve disease or rheumatic valve disease were assigned to the conservative-care group.

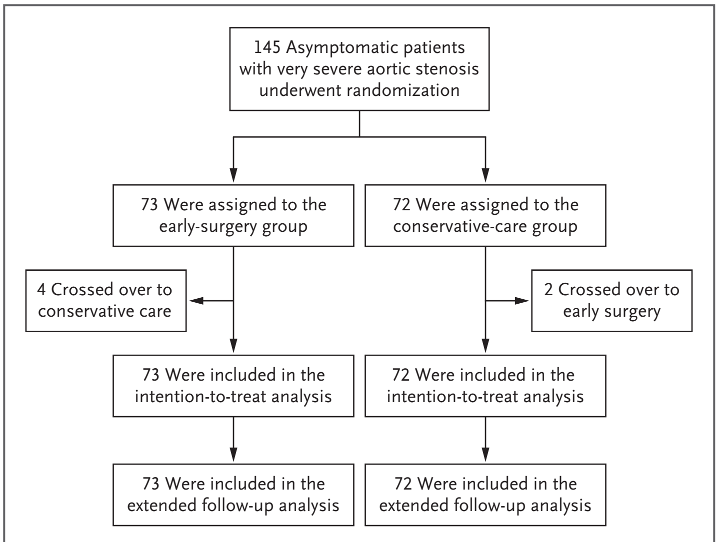

Figure 1. Randomization and Follow-up of the Patients.

Of the 145 patients who underwent randomization, 73 were assigned to the early-surgery group and 72 to the conservative-care group; all these patients were included in the intention-to-treat analysis. Four patients in the early-surgery group who crossed over to conservative care underwent surgery later, after the development of symptoms. Two patients (1 in each group) who were lost to follow-up had their data censored at their last follow-up assessment and were included in the extended follow-up analysis up to that time.

AORTIC-VALVE REPLACEMENT PROCEDURES

In the early-surgery group, surgical aortic-valve replacement was performed successfully in all 73 patients, with 36 patients (49%) receiving a mechanical valve and 37 (51%) receiving a biologic prosthesis. All the patients except those who crossed over to conservative care underwent surgery within 2 months after randomization; overall, 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 receive conservative care, 61 (85%) underwent either surgical aortic-valve replacement (59 patients) or transcatheter aortic-valve replacement (2 patients) during follow-up (Fig. S1 in the Supplementary Appendix), mainly owing to the development of symptoms (in 49 patients). The indications for aortic-valve replacement are listed in Table S1. Urgent surgery was performed in 11 of 59 patients (19%) who had been admitted from the emergency department. There was no operative mortality among the patients who underwent later aortic-valve replacement. The median time from randomization to aortic-valve replacement was 1048 days (interquartile range, 339 to 1700). Additional information about surgical procedures and results is provided in Table S2 and in the Supplementary Surgical Results section in the Supplementary Appendix.

FOLLOW-UP AND END POINTS

Data collection ended in May 2025, when the last enrolled patient had completed 10 years (120 months) of follow-up; the overall median follow-up was 144 months (interquartile range, 124 to 160). The median follow-up was 12.0 years (interquartile range, 10.4 to 13.4) in the early-surgery group and 11.2 years (interquartile range, 8.9 to 12.8) in the conservative-care group. Two patients, one in each treatment group, were lost to follow-up and thus had their data censored at their last follow-up assessment; these patients had their data included in the analyses up to that time.

In an intention-to-treat analysis, 2 of 73 patients (3%) in the early-surgery group and 17 of 72 patients (24%) in the conservative-care group died from cardiovascular causes (a primary end-point event) (hazard ratio, 0.10; 95% confidence interval [CI], 0.02 to 0.43; P=0.002) (Table 2). The number needed to treat to prevent one death from cardiovascular causes within 10 years was 6 patients. The cumulative incidence of operative mortality or death from cardiovascular causes (the primary end point), as calculated with the use of a Kaplan–Meier analysis, was 1% at both 5 years and 10 years in the early-surgery group, as compared with 7% at 5 years and 19% at 10 years in the conservative-care group (Fig. 2A).

Death from any cause occurred in 11 patients (15%) in the early-surgery group and in 23 (32%) in the conservative-care group (hazard ratio, 0.42; 95% CI, 0.21 to 0.86). The number needed to treat to prevent one death from any cause within 10 years was 7 patients. The cumulative incidence of death from any cause was 4% at 5 years and 11% at 10 years in the early-surgery group and 11% at 5 years and 25% at 10 years in the conservative-care group (Fig. 2B). Details of the deaths are provided in Table S3.

The incidence of other prespecified secondary end points is shown in Table 2. The incidence of hospitalization for heart failure was 19% in the conservative-care group; no patients in the early-surgery group were hospitalized for heart failure. In the conservative-care group, there were

10 deaths from any cause (all due to cardiovascular causes) before aortic-valve replacement and 13 deaths from any cause (7 due to cardiovascular causes) after aortic-valve replacement. The cumulative incidence of the composite of death from any cause or aortic-valve replacement in the conservative-care group was 74% at 5 years and 97% at 10 years (Fig. S2).

SENSITIVITY AND SUBGROUP ANALYSES

The results of per-protocol analyses that excluded four patients in the early-surgery group and three patients in the conservative-care group who had a protocol deviation are shown in Figure S3 and Table S4. The results of the as-treated analysis comparing patients who were actually treated with early surgery and those who were actually treated with conservative care appeared to be consistent with results of the intention-to-treat analyses for the primary end point (Table S5 and Fig. S4). The association of aortic-valve replacement with the primary end point and with death from any cause was also evaluated in an as-treated analysis. Not undergoing aortic-valve replacement appeared to be associated with higher cardiovascular mortality than undergoing aortic-value replacement (Table S6). Early aortic-valve replacement performed within 2 months after randomization appeared to be associated with lower cardiovascular mortality than later aortic-valve replacement. The treatment effects for the primary outcome and all-cause mortality in the two prespecified subgroups are shown in Table S7.

Table 1. Clinical and Echocardiographic 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-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)
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)
EuroSCORE II score — %‡	0.9±0.4	0.9±0.3
Echocardiographic findings		
Cause of aortic stenosis — no. (%)		
Bicuspid aortic valve	39 (54)	49 (67)
Degenerative valve disease	26 (36)	22 (30)
Rheumatic valve 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 ejection fraction — %	64.8±4.1	64.8±5.2

* Plus–minus values are means ±SD. PCI denotes percutaneous coronary intervention.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ Scores on the European System for Cardiac Operative Risk Evaluation (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.

DISCUSSION

In this extended follow-up of the RECOVERY trial involving asymptomatic patients with very severe aortic stenosis, early surgical aortic-valve replacement led to a lower incidence of a composite primary end point of operative mortality or death from cardiovascular causes over a period of 10 years as compared with conservative care. The absence of convergence of the Kaplan–Meier curves for the primary composite end point during this longer period of follow-up underscores the sustained benefits of early surgery in our patient population.

Randomized trials comparing early aortic-valve replacement with conservative care in asymptomatic patients with severe aortic stenosis have shown conflicting results. Several factors may explain these discrepancies. First, long-term follow-up is necessary for comparing survival rates between treatment groups. Because aortic stenosis is a slowly progressive chronic disease,[3] a persistent and increasing effect size over time, coupled with a greater number of events during follow-up, may result in further separation between the

Table 2. Primary and Secondary End Points.*

End Point	Conservative Care (N=72)	Early Surgery (N=73)	Hazard Ratio (95% CI)†	Difference in Cumulative Incidence at 10 Yr (95% CI)
	number (percent)			*percentage points*
Primary end point: operative mortality or death from cardiovascular causes‡	17 (24)	2 (3)		
Competing-risk analysis			0.10 (0.02 to 0.43)§	−16 (−24 to −7)
Proportional-hazards analysis			0.12 (0.03 to 0.46)	−17 (−27 to −8)
Secondary end points				
Death from any cause	23 (32)	11 (15)	0.42 (0.21 to 0.86)	−14 (−26 to −2)
Clinical thromboembolic event	7 (10)	3 (4)	0.39 (0.10 to 1.48)	−9 (−17 to 0.3)
Stroke	5 (7)	3 (4)	—	—
Myocardial infarction	2 (3)	0	—	—
Repeat aortic-valve surgery	4 (6)	3 (4)	0.67 (0.15 to 2.99)	−0.4 (−8 to 7)
Hospitalization for heart failure	14 (19)	0	0.03 (0.00 to 0.49)	−16 (−24 to −7)

* Percentages were calculated as the number of end points observed divided by the number of patients in the group. Event rates are based on Kaplan–Meier estimates in time-to-first-event analyses (i.e., the cumulative incidence); thus, the rate is not the same as the ratio of the numerator to the denominator. Differences were calculated as the cumulative incidence in the early-surgery group minus the cumulative incidence in the conservative-care group. There was no adjustment for multiplicity, and the widths of the confidence intervals should not be used in place of hypothesis testing.

† Hazard ratios were calculated with the use of a stratified Cox proportional-hazards model with Firth correction, except for the competing-risk analysis, in which a Fine and Gray model was used.

‡ Operative mortality was defined as death during surgery or within 30 days after surgery.

§ P=0.002.

treatment groups.[9,10] In the AVATAR (Aortic Valve Replacement versus Conservative Treatment in Asymptomatic Severe Aortic Stenosis) trial,[11] which had a median follow-up of 32 months, and the EARLY TAVR (Evaluation of TAVR [transcatheter aortic-valve replacement] Compared to Surveillance for Patients with Asymptomatic Severe Aortic Stenosis) trial,[4] which had a median follow-up of approximately 46 months, no significant between-group differences were observed with respect to all-cause mortality. However, the extended follow-up of the AVATAR trial,[6] which had a median follow-up of 63 months, showed that all-cause mortality was significantly lower in the early-surgery group than in the conservative-treatment group. In addition, the present trial, which had a median follow-up of 144 months, showed that all-cause mortality appeared to be lower in the early-surgery group than in the conservative-care group. Second, the percentage of patients undergoing aortic-valve replacement and the timing of aortic-valve replacement in the conservative-care group may affect survival. In the present trial, not undergoing aortic-valve replacement appeared to be associated with a risk of death from cardiovascular causes, with this risk increasing with a longer time interval from randomization to aortic-valve replacement. In the AVATAR trial,[6] which showed shorter survival in the conservative-treatment group than in the early-surgery group, aortic-valve replacement was performed in 44% of the patients assigned to the conservative-treatment group. Conversely, in the EARLY TAVR trial, in which survival in the clinical surveillance group was similar to that in the TAVR group, 87% of the patients assigned to the clinical surveillance group underwent aortic-valve replacement at the median of 11.1 months.[4]

Waiting for symptoms to develop remains a justifiable strategy in asymptomatic patients with severe aortic stenosis (peak aortic jet velocity, <5 m per second) for several reasons.[1,2,12] First, the potential benefit of aortic-valve replacement in preventing sudden death among asymptomatic patients may not be greater than the procedural risk of aortic-valve replacement.[13,14] However, among patients undergoing early aortic-valve replacement in four randomized clinical trials,[4-6,15-17] periprocedural mortality (within 30 days after surgery) was reported to be 0%, 0.2%, 0.9%, and 1.4%. Second, concerns persist regarding the long-term outcomes of early aortic-valve replacement. Prosthetic valves are associated with complications such as thromboembolism, anticoagulation-related bleeding, and bioprosthetic-valve failure, which become more evident over time.[7,8] In the present trial, the incidence of repeat aortic-valve surgery appeared to be similar in the two treatment groups, and the early-surgery group had a lower incidence of a primary composite end-point event, as well as apparently lower all-cause mortality, than the conservative care group — findings that were sustained over a 10-year follow-up period.

Some limitations of the present trial should be noted. First, our definition of very severe aortic stenosis (aortic-valve area of ≤0.75 cm^2 with peak aortic jet velocity of ≥4.5 m per second)[18] could influence the risk–benefit ratio for early surgery, because the risks of sudden cardiac death and of myocardial damage due to pressure overload during watchful waiting increase according to the severity of aortic stenosis.[19] Second, because RECOVERY was an open-label trial examining the efficacy of early surgical aortic-valve replacement, nonfatal outcomes could have been influenced by ascertainment bias, and whether transcatheter aortic-valve replacement would have long-term results similar to those for early surgical aortic-valve replacement is unclear.

Third, exercise stress testing was not routinely performed to confirm the absence of symptoms. Fourth, the participating centers were selected on the basis of their level of expertise with aortic-valve replacement, and the results of this analysis may not be generalizable to all centers. Fifth, our trial included relatively young patients with few coexisting conditions, a population that differs from patients with severe aortic stenosis who are commonly encountered in the real world. In older patients with coexisting conditions, the effect of competing risks is greater, which may reduce the long-term benefits of early aortic-valve replacement.[7,20] Sixth, the small number of primary end-point events is an important limitation of this trial. Finally, part of this extended follow-up study was conducted during the coronavirus disease 2019 pandemic, which may have affected outcomes.

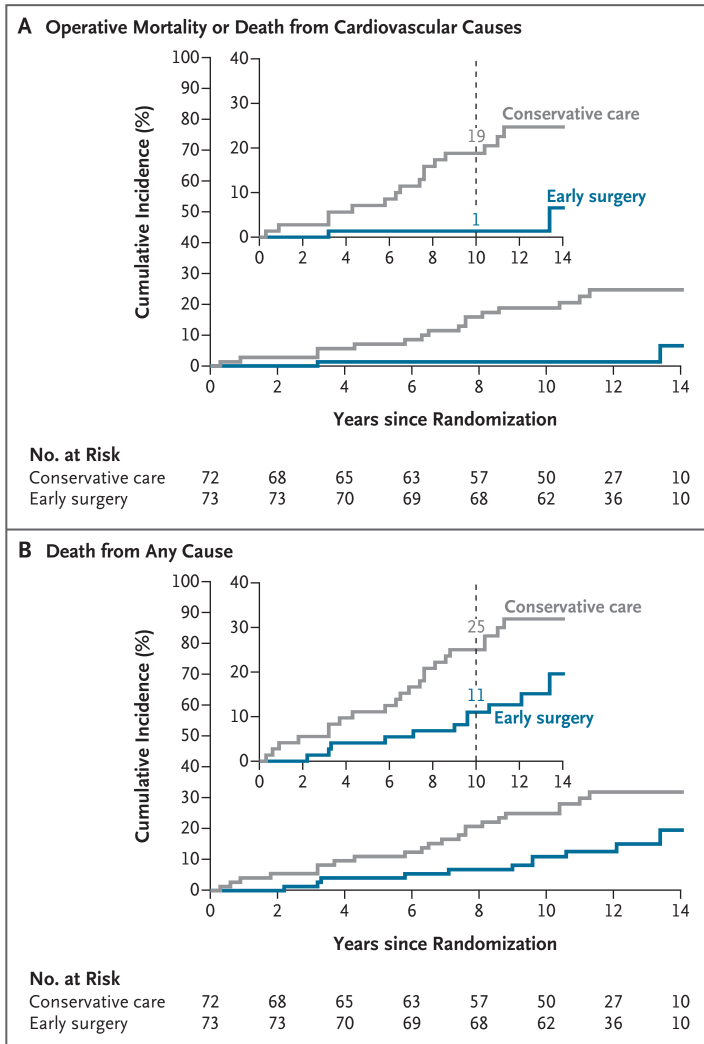

Figure 2. Time-to-Event Curves for the Primary Composite End Point and for Death from Any Cause.

Shown are Kaplan–Meier estimates of the cumulative incidence of death during surgery or within 30 days after surgery (called operative mortality) or death from cardiovascular causes (the primary composite end point) (Panel A) and of death from any cause (a secondary end point) (Panel B) among patients who had been randomly assigned to either undergo early surgery or receive conservative care. The cumulative incidence of each end point in the two groups is shown at 10 years (dashed line). In both panels, the inset shows the same data on an expanded y axis.

The final results of the RECOVERY trial showed that among asymptomatic patients with very severe aortic stenosis, early surgical aortic-valve replacement was associated with a significantly lower risk of a composite of operative mortality and death from cardiovascular causes than conservative care at 10 years.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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

AUTHOR INFORMATION

[1] Division of Cardiology, Asan Medical Center, College of Medicine, University of Ulsan, Seoul, South Korea; [2] Division of Cardiology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea; [3] Department of Thoracic and Cardiovascular Surgery, Asan Medical Center, College of Medicine, University of Ulsan, Seoul, South Korea; [4] Cardiovascular Center, Seoul National University Hospital, Seoul, South Korea; [5] Department of Biostatistics, Asan Medical Center, College of Medicine, University of Ulsan, Seoul, South Korea; [6] Division of Cardiology, Severance Hospital, Seoul, South Korea.

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