EDITORIAL

Transcatheter Aortic Valves — Where Do We Go from Here?

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Aortic-valve replacement is the most effective treatment to alleviate symptoms and improve survival in patients with critical aortic stenosis. The incidence of aortic stenosis multiplies with age, and as the life span of our population increases, a larger number of elderly patients will require aortic-valve replacement. However, a substantial number of these patients will have coexisting conditions that preclude surgery. Since outcomes with medical management are uniformly poor, a less invasive and safer alternative to surgical aortic-valve replacement is needed for this expanding group of patients. Transcatheter aortic-valve implantation (TAVI) has emerged as an alternative treatment for aortic stenosis in patients who are considered to have a high or prohibitive surgical risk. TAVI can be performed either by a retrograde approach, in which a catheter is inserted through the common femoral artery, or by an antegrade, transapical approach, in which a catheter is inserted through the apex of the left ventricle with the use of an anterolateral thoracotomy. Single-center, nonrandomized trials have shown the feasibility of TAVI in patients who are not suitable candidates for surgical replacement of the aortic valve[1,2]; however, there has been a paucity of data from randomized trials comparing TAVI with medical management in this population.

In this issue of the *Journal,* Leon and his coauthors report the results of the Placement of Aortic Transcatheter Valves (PARTNER) trial, a prospective, randomized, multicenter trial to determine the optimal method of treating patients with critical aortic stenosis who are considered not to be suitable candidates for surgery.[3] Patients who underwent TAVI with the use of the retrograde approach, as compared with patients receiving medical management, had a significantly lower rate of death at 1 year, fewer hospital readmissions, and a reduction in cardiac symptoms (lower New York Heart Association functional class). These improved outcomes were achieved, however, at the cost of a significant increase in the rate of major strokes and vascular events.

Now that there are evidence-based clinical data to substantiate the benefits of TAVI in patients who are not suitable candidates for surgery, there will be a temptation to expand this technology to all patients with aortic stenosis. What should be the current role of TAVI in the treatment of aortic stenosis? Where do we go from here? In order to answer these questions, a number of issues must be resolved.

First, what criteria will be used to determine who is not a candidate for surgical aortic-valve replacement, and who will be the "gatekeeper"? Unlike the decision of whether to perform a percutaneous or surgical revascularization, this decision-making process must involve surgeons. Advanced age alone cannot be used as an exclusion criterion for surgery, since aortic-valve replacement is currently being performed with increasing frequency in octogenarians and even nonagenarians, with excellent results. It is important to define the criteria for high risk or inoperable aortic stenosis, since there are discrepancies among various risk-scoring systems in the prediction of the risk of death. The logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE) has been shown to consistently overestimate the risk of death, whereas most people consider the Society of Thoracic Surgeons (STS) score to be more accurate.[4,5] An analysis of data from the STS National Database on 108,687 isolated aortic-valve replacements shows that overall mortality is now 2.6%, and the incidence of stroke is 1.3%.[6] Among patients 80 to 85 years of age, 30-day mortality is less than 5% and the rate of stroke is less than

2.5%. These values should be the yardstick by which other strategies to treat aortic stenosis should be measured.

Second, who should perform TAVI, and where should it be performed? TAVI should be performed by physicians with strong expertise in catheter techniques. There is a definite learning curve involved with this technique, since studies have shown that the rates of death and stroke associated with the procedure are reduced, and survival is improved, with increasing experience.[1,2] Physicians who wish to perform TAVI should be required to perform a certain number of procedures before operating independently. If TAVI is performed in the catheterization laboratory, the equipment necessary to perform a major surgical procedure should be available, since there is always the risk that conversion to an open procedure will be required. Furthermore, consideration should be given to whether a patient who is deemed to be at extremely high risk or to have inoperable aortic stenosis should undergo an emergency open procedure if complications occur.

Before the role of TAVI, as performed with the use of the retrograde technique, is expanded, important technical issues must be addressed. There is a risk with the transfemoral approach that an embolism may form from atherosclerotic material and pass from the aorta into the cerebral circulation, resulting in a major stroke. Vascular complications due to iliofemoral dissection or perforation are common. Although the transapical approach decreases the incidence of strokes, it requires a thoracotomy and has been associated with apical false aneurysms requiring surgical repair, during which time the patient is on cardiopulmonary bypass.[7] Furthermore, the long-term durability of these prostheses is unknown. They have been associated with a high incidence of paravalvular leaks (65 to 85%). Although most prostheses have remained stable, the follow-up period has been only 1 to 2 years.[8,9]

The PARTNER trial measured success primarily by 30-day and 1-year survival; however, the primary goal of aortic-valve replacement in high-risk patients is not only to improve survival, but also to enhance quality of life. Future investigations will need to include not only long-term outcomes, but also — and most important — health-related quality of life indexes, such as the ability to live at home rather than at a rehabilitation facility. TAVI is sure to increase the incidence of aortic-valve replacements in patients who are not candidates for surgical aortic-valve replacement, but only long-term trials evaluating quality-of-life indexes will determine whether this therapy is justified.

Despite the promising results of the PARTNER trial, surgical aortic-valve replacement remains the standard for the treatment of aortic stenosis. TAVI should be reserved for patients at inordinately high risk who are not suitable candidates for surgery and who have decreased life expectancy. Given the unknown durability of these prostheses and the high incidence of regurgitation, TAVI should not be performed in patients with long life expectancies. Prospective, adequately powered, randomized trials comparing TAVI with surgical aortic-valve replacement in both high-risk and low-risk patients will be necessary to further define the role of TAVI in the treatment of aortic stenosis. Only then can we determine where we go from here.

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

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Transcatheter Aortic-Valve Implantation for Aortic Stenosis in Patients Who Cannot Undergo Surgery

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ABSTRACT

BACKGROUND

Many patients with severe aortic stenosis and coexisting conditions are not candidates for surgical replacement of the aortic valve. Recently, transcatheter aortic-valve implantation (TAVI) has been suggested as a less invasive treatment for high-risk patients with aortic stenosis.

METHODS

We randomly assigned patients with severe aortic stenosis, whom surgeons considered not to be suitable candidates for surgery, to standard therapy (including balloon aortic valvuloplasty) or transfemoral transcatheter implantation of a balloon-expandable bovine pericardial valve. The primary end point was the rate of death from any cause.

RESULTS

A total of 358 patients with aortic stenosis who were not considered to be suitable candidates for surgery underwent randomization at 21 centers (17 in the United States). At 1 year, the rate of death from any cause (Kaplan–Meier analysis) was 30.7% with TAVI, as compared with 50.7% with standard therapy (hazard ratio with TAVI, 0.55; 95% confidence interval [CI], 0.40 to 0.74; P<0.001). The rate of the composite end point of death from any cause or repeat hospitalization was 42.5% with TAVI as compared with 71.6% with standard therapy (hazard ratio, 0.46; 95% CI, 0.35 to 0.59; P<0.001). Among survivors at 1 year, the rate of cardiac symptoms (New York Heart Association class III or IV) was lower among patients who had undergone TAVI than among those who had received standard therapy (25.2% vs. 58.0%, P<0.001). At 30 days, TAVI, as compared with standard therapy, was associated with a higher incidence of major strokes (5.0% vs. 1.1%, P=0.06) and major vascular complications (16.2% vs. 1.1%, P<0.001). In the year after TAVI, there was no deterioration in the functioning of the bioprosthetic valve, as assessed by evidence of stenosis or regurgitation on an echocardiogram.

CONCLUSIONS

In patients with severe aortic stenosis who were not suitable candidates for surgery, TAVI, as compared with standard therapy, significantly reduced the rates of death from any cause, the composite end point of death from any cause or repeat hospitalization, and cardiac symptoms, despite the higher incidence of major strokes and major vascular events. (Funded by Edwards Lifesciences; ClinicalTrials.gov number, NCT00530894.)

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Aortic stenosis is an insidious disease with a long latency period[1] followed by rapid progression after the appearance of symptoms,[2-5] resulting in a high rate of death (approximately 50% in the first 2 years after symptoms appear) among untreated patients.[1,6-8] Surgical replacement of the aortic valve reduces symptoms and improves survival in patients with aortic stenosis,[9-11] and in the absence of serious coexisting conditions, the procedure is associated with low operative mortality.[12,13] However, in clinical practice, at least 30% of patients with severe symptomatic aortic stenosis do not undergo surgery for replacement of the aortic valve, owing to advanced age, left ventricular dysfunction, or the presence of multiple coexisting conditions.[14-17] For these patients, who are at high surgical risk,[18,19] a less invasive treatment may be a worthwhile alternative.

Transcatheter aortic-valve implantation (TAVI) is a new procedure, in which a bioprosthetic valve is inserted through a catheter and implanted within the diseased native aortic valve. Since 2002, when the procedure was first performed,[20,21] there has been rapid growth in its use throughout the world for the treatment of severe aortic stenosis in patients who are at high surgical risk.[22-32] The most recent clinical studies showed that the rate of death from any cause at 1 year among patients treated with TAVI was approximately 25%.[27-29,31] Thus far, all the studies of TAVI have been observational registry studies, without standardization of end-point definitions[33,34] (and unpublished data) and without control populations. There is a paucity of rigorous, evidence-based clinical data to substantiate the incremental benefits of TAVI as compared with current standard therapies.

The Placement of Aortic Transcatheter Valves (PARTNER) trial was a multicenter, randomized clinical trial comparing TAVI with standard therapy in high-risk patients with severe aortic stenosis, including a prespecified cohort of patients who were not considered to be suitable candidates for surgery. In this article, we report the outcomes with TAVI as compared with standard therapy among the patients in the PARTNER trial who were not suitable candidates for surgery.

Methods

Patient Selection

We enrolled in the PARTNER trial patients with severe aortic stenosis and cardiac symptoms for whom conventional surgery to replace the aortic valve was associated with high risk. Severe aortic stenosis was defined as an aortic-valve area of less than 0.8 cm^2, a mean aortic-valve gradient of 40 mm Hg or more, or a peak aortic-jet velocity of 4.0 m per second or more. All the patients had New York Heart Association (NYHA) class II, III, or IV symptoms. Patients were divided into two cohorts: those who were considered to be candidates for surgery despite the fact that they were at high surgical risk, as defined by a Society of Thoracic Surgeons (STS) risk score of 10% or higher[35] (on a scale of 0% to 100%, with higher scores indicating greater surgical risk) or by the presence of coexisting conditions that would be associated with a predicted risk of death by 30 days after surgery of 15% or higher, and those who were not considered to be suitable candidates for surgery because they had coexisting conditions that would be associated with a predicted probability of 50% or more of either death by 30 days after surgery or a serious irreversible condition. At least two surgeon investigators had to agree that the patient was not a suitable candidate for surgery. In this article, we report the results for the patients with aortic stenosis who were not considered to be suitable candidates for surgery. The randomized trial involving patients at high surgical risk who were nevertheless considered to be candidates for surgery (also NCT00530894) is ongoing.

Pertinent exclusion criteria were a bicuspid or noncalcified aortic valve, acute myocardial infarction, substantial coronary artery disease requiring revascularization, a left ventricular ejection fraction of less than 20%, a diameter of the aortic annulus of less than 18 mm or more than 25 mm, severe (>3+) mitral or aortic regurgitation, a transient ischemic attack or stroke within the previous 6 months, and severe renal insufficiency. The complete list of inclusion and exclusion criteria is provided in Table 1 in the Supplementary Appendix, available with the full text of this article at NEJM.org.

After investigators screened the patients for eligibility, Web-based conference calls were conducted by the executive committee to further review and approve the selection of all patients before randomization. Of the 3105 patients with aortic stenosis who were screened by the investigators and the executive committee, approximately 12% ultimately underwent randomization as part of the PARTNER trial and were assigned to the

cohort of patients who were not considered to be suitable candidates for surgery.

STUDY DEVICE AND PROCEDURE

The Edwards SAPIEN heart-valve system (Edwards Lifesciences) consists of a trileaflet bovine pericardial valve and a balloon-expandable, stainless-steel support frame. The heart valve is shown in Figure 1 in the Supplementary Appendix. The TAVI procedure was performed in a sterile environment (catheterization laboratory or operating room), with the patient under general anesthesia; the procedure was performed with the use of transesophageal echocardiography. A standard balloon aortic valvuloplasty was performed, followed by transfemoral insertion of either a 22- or 24-French sheath, depending on the selected size of the valve (23 mm or 26 mm). The bioprosthetic heart valve, crimped onto a balloon catheter, was advanced across the native aortic valve. During rapid right ventricular pacing, balloon inflation of the crimped heart valve and support frame simultaneously deployed the bioprosthetic valve and expanded the frame, which was secured to the underlying aortic-valve annulus and leaflets (see videos 1 and 2, available at NEJM.org). Adjunctive pharmacologic therapy included heparin during the procedure and dual antiplatelet therapy (aspirin and clopidogrel) for 6 months after the procedure.

STUDY DESIGN AND OVERSIGHT

The PARTNER study incorporated two parallel prospective, multicenter, randomized, active-treatment–controlled clinical trials. The overall study design is shown in Figure 2 in the Supplementary Appendix. Patients were randomly assigned with the use of a computer-generated scheme, blocked separately at each participating site and for each of the trial cohorts. The PARTNER study was approved by the institutional review board at each participating site, and all patients provided written informed consent.

The trial was designed by the sponsor (Edwards Lifesciences) and members of the executive committee, which included the two academic coprincipal investigators, three interventional cardiologists, and three cardiac surgeons. The sponsor funded the studies and participated in the selection and management of the sites and the collection and monitoring of the data. The executive committee met in person every 6 to 8 weeks to monitor all aspects of the conduct of the trial. The coprincipal investigators and the executive committee had unrestricted access to the data after the database was locked, made the decision to submit the manuscript for publication, prepared all drafts of the manuscript, and attest to the integrity of the trial and the completeness and accuracy of the reported data, as well as to the fidelity of the report to the trial protocol. The protocol, including the statistical analysis plan, is available at NEJM.org.

DATA MANAGEMENT

All serious adverse events were adjudicated by an independent clinical events committee. A data and safety monitoring board met frequently and had access to all study data and treatment assignments when requested; the board recommended after each meeting that the study be continued without modification. All data were sent for analysis to independent consulting biostatisticians. Independent core laboratories analyzed all echocardiograms and electrocardiograms. The members of the committees, the institutions, and the research organizations participating in the PARTNER trial are listed in Table 2 in the Supplementary Appendix.

Two videos showing deployment of the valve and animation of the TAVI procedure are available at NEJM.org

STUDY END POINTS

The primary end point was the rate of death from any cause over the duration of the trial. All patients were followed for at least 1 year, and crossover from the standard-therapy group to the TAVI group was not permitted. The coprimary end point was the rate of a hierarchical composite of the time to death from any cause or the time to the first occurrence of repeat hospitalization (after the index procedure) due to valve-related or procedure-related clinical deterioration. This composite end point was also reported with the use of more conventional Kaplan–Meier nonhierarchical analytical methods. Prespecified secondary end points included the rate of death from cardiovascular causes, NYHA functional class, the rate of repeat hospitalization due to valve-related or procedure-related clinical deterioration, the distance covered during a 6-minute walk test,[36] valve performance (assessed by echocardiography), and the rates of myocardial infarction, stroke, acute kidney injury, vascular complications, and bleeding. A major stroke was defined as a focal or global neurologic deficit associated with a score of 2 or higher on the modified Rankin scale, which has a range of 0 to 6, with 0 indicating no symptoms and 6 indicating death. Specific definitions of other im-

portant end points are provided in Table 3 in the Supplementary Appendix. All patients were followed during the index hospitalization; at 30 days, 6 months, and 1 year; and yearly thereafter.

STATISTICAL ANALYSIS

We estimated that with a sample of 350 patients, the study would have at least 85% power to show the superiority of TAVI over standard treatment with respect to the primary end point, assuming that 1-year mortality would be 37.5% in the standard-treatment group and 25% in the TAVI group. In calculating the size of the sample, we also assumed that deaths would follow a constant hazard distribution, that follow-up would continue for 12 months after the last patient was enrolled, and that the rate of loss to follow-up would be 10%.

The analysis of the coprimary end point — the hierarchical composite of death or repeat hospitalization — was performed with the use of a nonparametric method described by Finkelstein and Schoenfeld.[37] With this method, multiple pairwise comparisons are performed for all patient pairs, first with respect to the time to death and then with respect to the time to repeat hospitalization, if necessary. On the basis of a simulation with the use of SAS software, we estimated that with a total sample of 350 patients, the power for this coprimary end point would be more than 95%. The Hochberg procedure was used to make multiple corrections of the primary and coprimary end points.

Categorical variables were compared with the use of Fisher's exact test. A generalized linear model was used to calculate risk ratios in the subgroup analysis and to test for interactions. Continuous variables, which are presented as means (±SD), were compared with the use of Student's t-test. All the analyses were performed with data from the intention-to-treat population, which included all patients who underwent randomization, regardless of the treatment actually received. Survival curves for time-to-event variables were constructed on the basis of all available follow-up data with the use of Kaplan–Meier estimates and were compared with the use of the log-rank test. A two-sided alpha level of 0.05 was used for all superiority testing. All statistical analyses were performed with the use of SAS software, version 9.2.

RESULTS

PATIENTS AND ENROLLMENT

Between May 11, 2007, and March 16, 2009, a total of 358 patients with severe aortic stenosis who were not suitable candidates for surgery were enrolled at 21 sites (17 in the United States) and were randomly assigned to TAVI (179 patients) or standard therapy (179 patients). All the patients were followed for at least 1 year (median follow-up period, 1.6 years; maximum, 2.8 years). The numbers of patients who underwent randomization and follow-up are shown in Figure 3 in the Supplementary Appendix.

The baseline characteristics of the patients in the two groups were generally well balanced (Table 1). The overall patient population was at high risk (STS score, 11.6±6.0%). However, there were many patients with low STS scores but with coexisting conditions that contributed to the surgeons' determination that the patient was not a suitable candidate for surgery, including an extensively calcified (porcelain) aorta (15.1%), chest-wall deformity or deleterious effects of chest-wall irradiation (13.1%), oxygen-dependent respiratory insufficiency (23.5%), and frailty, as determined by the surgeons according to prespecified criteria (23.1%).

PROCEDURAL OUTCOMES

Of the 179 patients assigned to TAVI, 6 (3.4%) did not receive a transcatheter heart valve (2 patients died before the scheduled implantation, transfemoral access was unsuccessful in 2 patients, and the intraprocedural annulus measurement was too large in 2 patients). After randomization, the median time to TAVI was 6 days (interquartile range, 3 to 11). During the TAVI procedure or in the first 24 hours after the procedure, 2 patients (1.1%) died, 3 (1.7%) had major strokes, 1 (0.6%) had a valve embolization, and 2 (1.1%) underwent multiple (≥2) valve implantations; no patient underwent urgent cardiac surgery to manage complications. In the first 30 days after the procedure, 11 of the 173 patients who underwent TAVI (6.4%) died.

Of the 179 patients assigned to standard therapy, balloon aortic valvuloplasty was performed in 114 patients (63.7%) during the 30 days after randomization and in an additional 36 patients

Table 1. Baseline Characteristics of the Patients and Echocardiographic Findings.*

Characteristic	TAVI (N=179)	Standard Therapy (N=179)	P Value
Age — yr	83.1±8.6	83.2±8.3	0.95
Male sex — no. (%)	82 (45.8)	84 (46.9)	0.92
STS score†	11.2±5.8	12.1±6.1	0.14
Logistic EuroSCORE‡	26.4±17.2	30.4±19.1	0.04
NYHA class — no. (%)			0.68
II	14 (7.8)	11 (6.1)	
III or IV	165 (92.2)	168 (93.9)	
Coronary artery disease — no. (%)	121 (67.6)	133 (74.3)	0.20
Previous myocardial infarction — no./total no. (%)	33/177 (18.6)	47/178 (26.4)	0.10
Previous intervention — no./total no. (%)			
CABG	58/155 (37.4)	73/160 (45.6)	0.17
PCI	47/154 (30.5)	39/157 (24.8)	0.31
Balloon aortic valvuloplasty	25/154 (16.2)	39/160 (24.4)	0.09
Cerebral vascular disease — no./total no. (%)	48/175 (27.4)	46/167 (27.5)	1.00
Peripheral vascular disease — no./total no. (%)	54/178 (30.3)	45/179 (25.1)	0.29
COPD — no. (%)			
Any	74 (41.3)	94 (52.5)	0.04
Oxygen-dependent	38 (21.2)	46 (25.7)	0.38
Creatinine >2 mg/dl (177 μmol/liter) — no./total no. (%)	10/178 (5.6)	17/178 (9.6)	0.23
Atrial fibrillation — no./total no. (%)	28/85 (32.9)	39/80 (48.8)	0.04
Permanent pacemaker — no./total no. (%)	35/153 (22.9)	31/159 (19.5)	0.49
Pulmonary hypertension — no./total no. (%)	50/118 (42.4)	53/121 (43.8)	0.90
Frailty — no./total no. (%)§	21/116 (18.1)	33/118 (28.0)	0.09
Extensively calcified aorta — no. (%)	34 (19.0)	20 (11.2)	0.05
Deleterious effects of chest-wall irradiation — no. (%)	16 (8.9)	15 (8.4)	1.00
Chest-wall deformity — no. (%)	15 (8.4)	9 (5.0)	0.29
Liver disease — no./total no. (%)	6/177 (3.4)	6/178 (3.4)	1.00
Echocardiographic findings			
Aortic-valve area — cm^2	0.6±0.2	0.6±0.2	0.97
Mean aortic-valve gradient — mm Hg	44.5±15.7	43.0±15.3	0.39
Mean LVEF — %	53.9±13.1	51.1±14.3	0.06
Moderate or severe mitral regurgitation — no./total no. (%)¶	38/171 (22.2)	38/165 (23.0)	0.90

* Plus–minus values are means ±SD. CABG denotes coronary-artery bypass grafting, COPD chronic obstructive pulmonary disease, LVEF left ventricular ejection fraction, NYHA New York Heart Association, PCI percutaneous coronary intervention, and TAVI transcatheter aortic-valve implantation.

† The Society of Thoracic Surgeons (STS) score measures patient risk at the time of cardiovascular surgery on a scale that ranges from 0% to 100%, with higher numbers indicating greater risk. An STS score higher than 10% indicates very high surgical risk.

‡ The logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE), which measures patient risk at the time of cardiovascular surgery, is calculated with the use of a logistic-regression equation. Scores range from 0% to 100%, with higher scores indicating greater risk. A logistic EuroSCORE higher than 20% indicates very high surgical risk.

§ Frailty was determined by the surgeons according to prespecified criteria.

¶ Moderate or severe mitral regurgitation was defined as regurgitation of grade 3+ or higher.

(20.1%) more than 30 days after randomization. Despite the fact that all the patients in this cohort of the PARTNER study were determined not to be suitable candidates for surgery, 12 of the patients who were assigned to standard therapy (6.7%) underwent aortic-valve replacement, 5 (2.8%) underwent placement of a conduit from the left ventricular apex to the descending aorta plus aortic-valve replacement, and 4 (2.2%) underwent TAVI at a nonparticipating site outside the United States. The 1-year rates of death among patients in the standard-therapy group who underwent aortic-valve replacement, conduit plus aortic-valve replacement, or TAVI at a nonparticipating site outside the United States were 33%, 80%, and 0%, respectively.

RATES OF DEATH, REPEAT HOSPITALIZATION, AND STROKE

At 30 days after randomization, the rate of death from any cause was 5.0% in the TAVI group as compared with 2.8% in the standard-therapy group (P=0.41) (Table 2). At the 1-year follow-up, the rate of death from any cause (the primary end point), as calculated with the use of a Kaplan–Meier analysis, was 30.7% in the TAVI group, as compared with 50.7% in the standard-therapy group (hazard ratio, 0.55; 95% confidence interval [CI], 0.40 to 0.74; P<0.001) (Fig. 1A). The rate of death from cardiovascular causes at 1 year (Kaplan–Meier analysis) was also lower in the TAVI group than in the standard-therapy group (20.5% vs. 44.6%; hazard ratio, 0.39; 95% CI, 0.27 to 0.56; P<0.001) (Fig. 1B). The specific cardiovascular and noncardiovascular causes of death are shown in Table 4 in the Supplementary Appendix.

The superiority of TAVI with respect to the coprimary end point (the rate of the hierarchical composite of death from any cause or repeat hospitalization) was confirmed by the Finkelstein–Schoenfeld analysis (P<0.001). In addition, the rate of the nonhierarchical composite of death from any cause or repeat hospitalization at the 1-year follow-up (Kaplan–Meier analysis) was 42.5% with TAVI as compared with 71.6% with standard therapy (hazard ratio, 0.46; 95% CI, 0.35 to 0.59; P<0.001) (Fig. 1C).

Major strokes were observed more frequently in the TAVI group than in the standard-therapy group at 30 days (5.0% vs. 1.1%, P=0.06) and at 1 year (7.8% vs. 3.9%, P=0.18). However, the rate of the composite of major stroke or death from any cause (Kaplan–Meier analysis) was still significantly lower in the TAVI group than in the standard-therapy group (33.0% vs. 51.3% at 1 year; hazard ratio, 0.58; 95% CI, 0.43 to 0.78; P<0.001) (Fig. 1D). A more detailed analysis of the neurologic events is shown in Table 5 in the Supplementary Appendix.

Subgroup analyses with interaction testing were performed to determine whether the reduction in the primary end point (the rate of death from any cause) after TAVI was consistent across 10 important subgroups (Fig. 2). No significant interactions were observed.

OTHER CLINICAL OUTCOMES

The frequencies of other important clinical events at 30 days and at 1 year are shown in Table 2. Major vascular complications and major bleeding events were more frequent in the TAVI group than in the standard-therapy group. At 30 days, 6 months, and 1 year, symptoms were significantly reduced in the TAVI group (P<0.001 for all three comparisons) (Fig. 3). At 1 year, 74.8% of the surviving patients who had undergone TAVI, as compared with 42.0% of the surviving patients who had received standard therapy, were asymptomatic or had mild symptoms (NYHA class I or II) (P<0.001). The 6-minute walk test could be performed in only a subgroup of patients, owing to the presence of coexisting conditions in many of the patients. At 1 year, a paired analysis of the distance covered during a 6-minute walk test showed that there was significant improvement after TAVI (P=0.002) and no change after standard therapy (P=0.67).

ECHOCARDIOGRAPHIC FINDINGS

Echocardiographic findings are shown in Table 6 in the Supplementary Appendix. Among patients who underwent TAVI, the mean aortic-valve area increased from 0.6±0.2 cm^2 at baseline to 1.5±0.5 cm^2 at 30 days (P<0.001), and the mean aortic-valve gradient decreased from 44.5±15.7 mm Hg to 11.1±6.9 mm Hg (P<0.001). At the 1-year follow-up assessment, the improvement in aortic-valve area and mean gradient was maintained.

Moderate or severe paravalvular aortic regurgitation was present in 11.8% of the patients in the TAVI group at 30 days and in 10.5% at 1 year. There were no substantial changes (i.e., changes of more than one grade) in paravalvular aortic regurgitation in the TAVI group during the 1-year follow-up period. The incidence of moderate or severe transvalvular aortic regurgitation was 1.3%

Table 2. Clinical Outcomes at 30 Days and 1 Year.*

Outcome	30 Days			1 Year		
	TAVI (N=179)	Standard Therapy (N=179)	P Value†	TAVI (N=179)	Standard Therapy (N=179)	P Value†
	no. of patients (%)			*no. of patients (%)*		
Death						
From any cause	9 (5.0)	5 (2.8)	0.41	55 (30.7)	89 (49.7)	<0.001
From cardiovascular cause‡	8 (4.5)	3 (1.7)	0.22	35 (19.6)	75 (41.9)	<0.001
Repeat hospitalization§	10 (5.6)	18 (10.1)	0.17	40 (22.3)	79 (44.1)	<0.001
Death from any cause or repeat hospitalization§	19 (10.6)	22 (12.3)	0.74	76 (42.5)	126 (70.4)	<0.001
Stroke or TIA						
All	12 (6.7)	3 (1.7)	0.03	19 (10.6)	8 (4.5)	0.04
TIA	0	0	—	1 (0.6)	0	1.00
Stroke						
Minor	3 (1.7)	1 (0.6)	0.62	4 (2.2)	1 (0.6)	0.37
Major	9 (5.0)	2 (1.1)	0.06	14 (7.8)	7 (3.9)	0.18
Death from any cause or major stroke	15 (8.4)	7 (3.9)	0.12	59 (33.0)	90 (50.3)	0.001
Myocardial infarction						
All	0	0	—	1 (0.6)	1 (0.6)	1.00
Periprocedural	0	0	—	0	0	—
Vascular complications						
All	55 (30.7)	9 (5.0)	<0.001	58 (32.4)	13 (7.3)	<0.001
Major	29 (16.2)	2 (1.1)	<0.001	30 (16.8)	4 (2.2)	<0.001
Acute kidney injury						
Creatinine >3 mg/dl (265 μmol/liter)¶	0	1 (0.6)	1.00	2 (1.1)	5 (2.8)	0.45
Renal-replacement therapy‖	2 (1.1)	3 (1.7)	1.00	3 (1.7)	6 (3.4)	0.50
Major bleeding	30 (16.8)	7 (3.9)	<0.001	40 (22.3)	20 (11.2)	0.007
Cardiac reintervention						
Balloon aortic valvuloplasty	1 (0.6)**	2 (1.1)	1.00	1 (0.6)	66 (36.9)††	<0.001
Repeat TAVI‡‡	3 (1.7)	NA	—	3 (1.7)	NA	—
Aortic-valve replacement	0	3 (1.7)	0.25	2 (1.1)**	17 (9.5)	<0.001
Endocarditis	0	0	—	2 (1.1)	1 (0.6)	0.31
New atrial fibrillation	1 (0.6)	2 (1.1)	1.00	1 (0.6)	3 (1.7)	0.62
New pacemaker	6 (3.4)	9 (5.0)	0.60	8 (4.5)	14 (7.8)	0.27

* NA denotes not applicable, TAVI transcatheter aortic-valve implantation, and TIA transient ischemic attack.
† P values are for between-group comparisons of the frequency of the event at each time point.
‡ Deaths from unknown causes were assumed to be deaths from cardiovascular causes.
§ Repeat hospitalizations were included if they were due to aortic stenosis or complications of the valve procedure (e.g., TAVI).
¶ Patients who received renal-replacement therapy were not included.
‖ Patients who received renal-replacement therapy after randomization were included.
** One patient in the TAVI group did not receive TAVI (because of failed access) and subsequently underwent balloon aortic valvuloplasty, followed by aortic-valve replacement.
†† A total of 30 patients underwent a repeat balloon aortic valvuloplasty after the index balloon aortic valvuloplasty procedure that had been performed in the first 30 days after randomization, and 36 patients underwent a first balloon aortic valvuloplasty more than 30 days after randomization.
‡‡ Three patients underwent a repeat TAVI within 24 hours after the index TAVI procedure; four patients in the standard-therapy group who underwent TAVI at a nonparticipating site outside the United States are not included here.

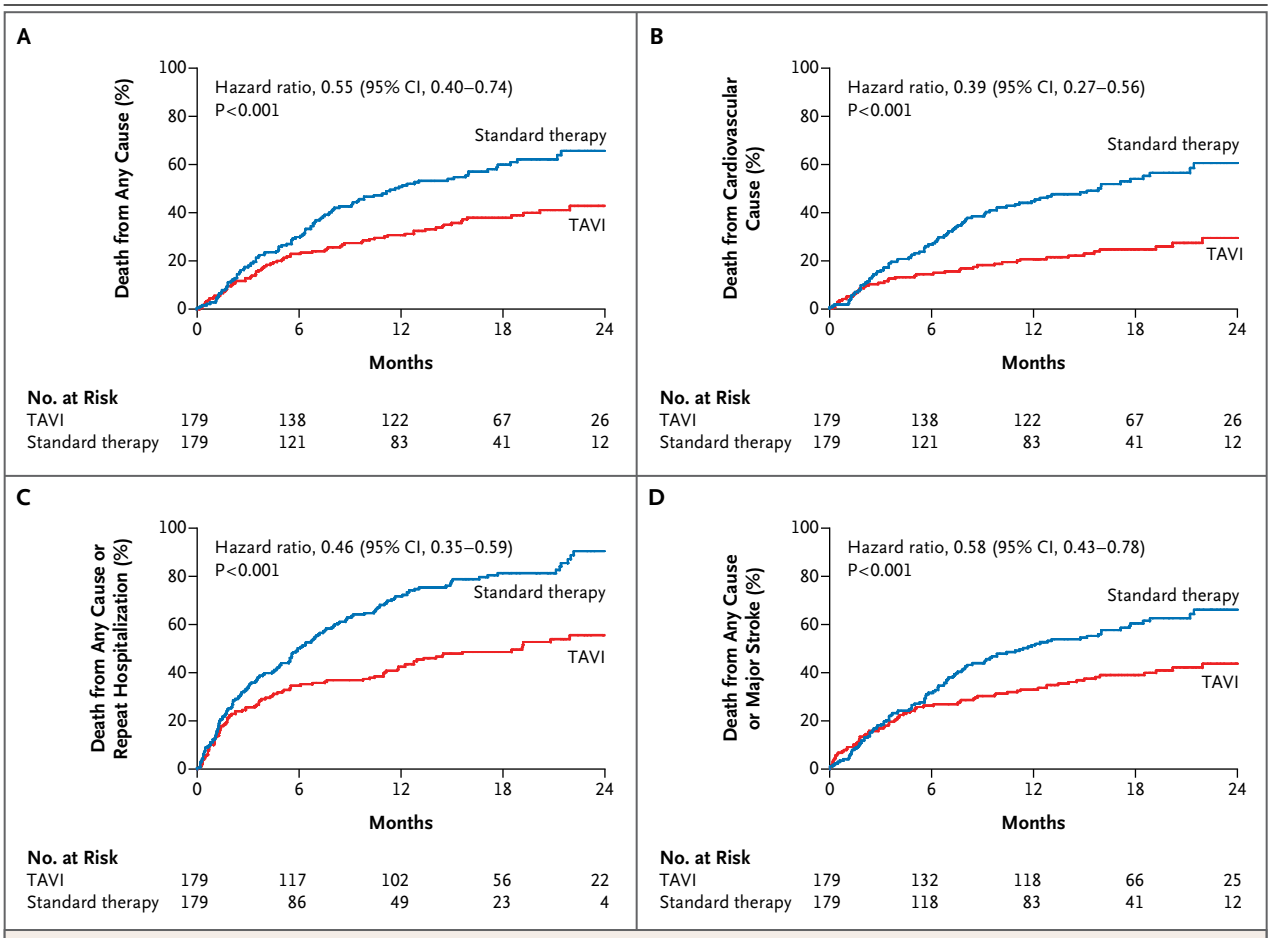

Figure 1. Time-to-Event Curves for the Primary End Point and Other Selected End Points.

Event rates were calculated with the use of Kaplan–Meier methods and compared with the use of the log-rank test. Deaths from unknown causes were assumed to be deaths from cardiovascular causes.

at 30 days and 4.2% at 1 year among patients in the TAVI group, as compared with 16.9% and 15.2%, respectively, among patients in the standard-therapy group. Three patients in the TAVI group (1.7%) had to undergo an additional procedure (repeat TAVI) to treat clinically significant aortic regurgitation (paravalvular in two patients and transvalvular in one).

DISCUSSION

The main results from the PARTNER trial in the cohort of patients with aortic stenosis who were not suitable candidates for surgery can be summarized as follows. First, standard medical therapy (including balloon aortic valvuloplasty, which was performed in 83.8% of the patients in the standard-therapy group) did not alter the natural history of severe aortic stenosis; at the end of 1 year, the rate of death from any cause was 50.7%, and the rate of death from cardiovascular causes was 44.6%. Second, transfemoral TAVI was superior to standard therapy, markedly reducing the rate of death from any cause (the primary end point), the rate of death from cardiovascular causes, and the rate of repeat hospitalization. In the first year, only five patients needed to be treated with TAVI to prevent one death, and only three patients needed to be treated to prevent either a death or repeat hospitalization. Third, the rate of death at 30 days among patients who underwent TAVI (5.0% in the intention-to-treat population, and 6.4% among patients who underwent TAVI) did not differ significantly from that among patients who received standard therapy in this cohort of patients who were not suitable candidates for surgery, despite the use of early-generation systems for TAVI and minimal operator experience with

Subgroup	TAVI	Standard Therapy	Relative Risk (95% CI)	NNT	P Value for Interaction
	no. of events/total no. (%)				
Overall	55/179 (30.7)	89/179 (49.7)	0.62 (0.47–0.81)	5	
Age					0.54
≤85 yr	28/96 (29.2)	46/90 (51.1)	0.57 (0.39–0.83)	5	
>85 yr	27/83 (32.5)	43/89 (48.3)	0.67 (0.46–0.96)	6	
Sex					0.80
Female	30/97 (30.9)	46/95 (48.4)	0.64 (0.44–0.92)	6	
Male	25/82 (30.5)	43/84 (51.2)	0.60 (0.40–0.88)	5	
Body-mass index					0.20
≤25	32/83 (38.6)	46/87 (52.9)	0.73 (0.52–1.02)	7	
>25	23/96 (24.0)	43/92 (46.7)	0.51 (0.34–0.78)	4	
STS score					0.44
≤11	22/93 (23.7)	32/76 (42.1)	0.56 (0.36–0.88)	5	
>11	33/86 (38.4)	56/102 (54.9)	0.70 (0.51–0.96)	6	
LV ejection fraction					0.50
≤55%	30/82 (36.6)	58/95 (61.1)	0.60 (0.43–0.83)	4	
>55%	24/91 (26.4)	28/77 (36.4)	0.73 (0.46–1.14)	10	
Pulmonary hypertension					0.47
No	18/69 (26.1)	30/66 (45.5)	0.57 (0.36–0.92)	5	
Yes	29/82 (35.4)	42/85 (49.4)	0.72 (0.50–1.03)	7	
Moderate or severe mitral regurgitation					0.09
No	43/133 (32.3)	59/127 (46.5)	0.70 (0.51–0.95)	7	
Yes	9/38 (23.7)	23/38 (60.5)	0.39 (0.21–0.73)	3	
COPD (oxygen-dependent)					0.70
No	41/141 (29.1)	64/133 (48.1)	0.60 (0.44–0.83)	5	
Yes	14/38 (36.8)	25/46 (54.3)	0.68 (0.41–1.11)	6	
Prior CABG or PCI					0.60
No	20/72 (27.8)	32/68 (47.1)	0.59 (0.38–0.93)	5	
Yes	23/84 (27.4)	50/92 (54.3)	0.50 (0.34–0.75)	4	
Peripheral vascular disease					0.10
No	35/124 (28.2)	70/134 (52.2)	0.54 (0.39–0.75)	4	
Yes	20/54 (37.0)	19/45 (42.2)	0.88 (0.54–1.43)	19	

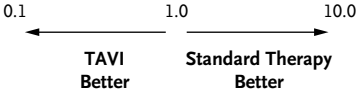

Figure 2. Subgroup Analyses of the Primary End Point of Death from Any Cause.

Relative risks and 95% confidence intervals are shown for the primary end point of death from any cause at 1 year among patients randomly assigned to transcatheter aortic-valve implantation (TAVI) or standard therapy. The P value for interaction represents the likelihood of an interaction between the variable and the relative treatment effect. The body-mass index is the weight in kilograms divided by the square of the height in meters. The Society of Thoracic Surgeons (STS) score measures patient risk at the time of cardiovascular surgery on a scale that ranges from 0% to 100%, with higher scores indicating greater risk. Moderate or severe mitral regurgitation was defined as regurgitation of grade 3+ or higher. CABG denotes coronary-artery bypass grafting, COPD chronic obstructive pulmonary disease, LV left ventricular, NNT number needed to treat, and PCI percutaneous coronary intervention.

the TAVI procedure before the trial was initiated. Fourth, TAVI was also associated with a significant reduction in symptoms, as assessed with the use of the NYHA classification system and the results of a 6-minute walk test. Fifth, there were more neurologic events (including all strokes and major strokes), major vascular complications, and major bleeding events in the TAVI group than in the standard-therapy group. Sixth, echocardiographic findings after TAVI indicated that the hemodynamic performance of the bioprosthetic valve was excellent and that there was no evidence of deterioration in the first year. TAVI was accompanied by the frequent occurrence of paravalvular regurgitation, which was usually mild, remained stable during the 1-year follow-up period, and rarely required further treatment for worsening symptoms.

The early clinical outcomes (at ≤30 days) after transfemoral TAVI were similar to those seen in other recent studies of the same balloon-expandable bovine pericardial heart valve.[28,29,31,32] Un-

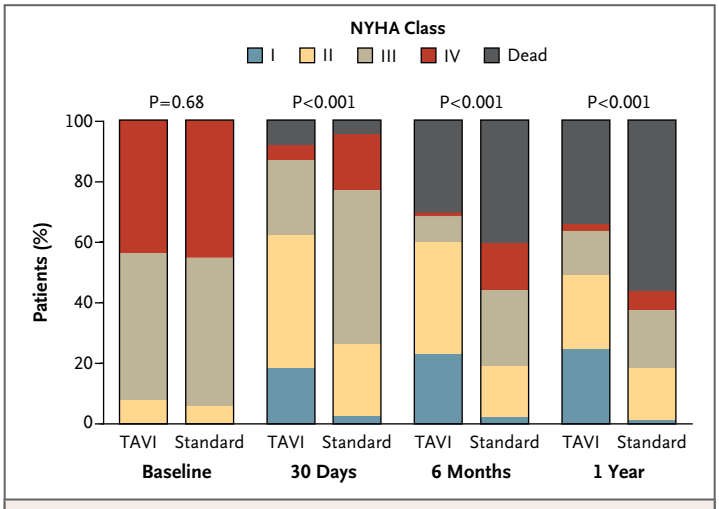

Figure 3. Symptom Status over Time.

Symptom status according to New York Heart Association (NYHA) class is shown at baseline and at 30 days, 6 months, and 1 year among patients randomly assigned to transcatheter aortic-valve implantation (TAVI) or standard therapy (Standard).

doubtedly, the large femoral access sheaths that are required to insert this TAVI system contributed to the frequent occurrence of vascular complications and bleeding events. Ongoing studies are assessing the use of a lower-profile valve and support frame, which may reduce vascular complications, allow patients who have smaller iliofemoral arteries than did patients in this study to undergo this procedure, and facilitate percutaneous access and closure.

Strokes remain a troublesome adverse effect following TAVI; strokes occur more frequently among patients who undergo TAVI than among patients who receive standard therapy. Recently, diffusion-weighted magnetic resonance imaging studies have shown that there are new perfusion deficits in many patients after TAVI, presumably due to atherothrombotic emboli.[38,39] The combination of smaller, less traumatic TAVI systems than the ones currently in use and novel cerebral protection devices is being evaluated in an effort to reduce the frequency of embolic neurologic events associated with TAVI. Additional randomized clinical trials are needed to compare the frequency of procedural strokes after TAVI with the frequency after surgical aortic-valve replacement.

Our study has several limitations. The protocol-mandated selection criteria excluded important patient subgroups, such as patients requiring treatment of coronary stenoses and patients with severe peripheral vascular disease. An assessment of the durability and the long-term clinical safety and effectiveness of the bioprosthetic valves will require more prolonged follow-up of patients who participated in the PARTNER trial and in other clinical trials of TAVI. Because TAVI was a relatively new procedure in the United States at the time the PARTNER trial was conducted, there was still a learning curve for most of the surgeons and interventional cardiologists who performed TAVI in the United States, and this relative inexperience was compounded by the use of an earlier-generation delivery system that was more likely to cause complications.

On the basis of a rate of death from any cause at 1 year that was 20 percentage points lower with TAVI than with standard therapy, balloon-expandable TAVI should be the new standard of care for patients with aortic stenosis who are not suitable candidates for surgery (like the patients enrolled in this study). These results cannot be extrapolated to other patients with aortic stenosis. Additional randomized trials are needed to compare TAVI with aortic-valve replacement among high-risk patients with aortic stenosis for whom surgery is a viable option and among low-risk patients with aortic stenosis.

Sponsored by Edwards Lifesciences.

Dr. Leon reports receiving consulting fees from Medtronic and owning stock options in Sadra Medical; Dr. Moses, receiving buyout of options in Heart Leaflet Technologies from Bracco; Dr. Wang, receiving grant support from Edwards Lifesciences; Dr. Mack, receiving lecture fees from Edwards Lifesciences and consulting fees from Medtronic; Dr. Miller, receiving consulting fees from Medtronic and St. Jude Medical; Dr. Webb, receiving grant support, consulting fees, and travel reimbursement from Edwards Lifesciences; Dr. Pocock, receiving grant support and consulting fees from Edwards Lifesciences; Dr. Makkar, receiving consulting fees, grant support, and lecture fees from Abbott, Medtronic, and Lilly, consulting fees and grant support from Johnson & Johnson and Daiichi Sankyo, and grant support from St. Jude Medical; Dr. Fontana, receiving consulting fees and lecture fees from Sorin Medical, consulting fees from and stock options in Entourage Medical Technologies, and consulting fees from St. Jude Medical; Dr. Block, receiving board membership fees from Medtronic and CoreValve, consulting fees from and stock options in Medtronic and Direct Flow Medical, and lecture fees from Edwards Lifesciences; Dr. Pichard, being employed as director of the Catheterization Laboratory at Washington Hospital Center and receiving lecture fees from St. Jude Medical; Dr. Bavaria, receiving grant support from Edwards Lifesciences; Ms. Akin, being employed by, owning stock options in, and receiving travel reimbursement from Edwards Lifesciences; Dr. Anderson, receiving consulting fees from and stock options in Edwards Lifesciences; and Dr. Douglas, receiving grant support from Edwards Lifesciences. No other potential conflict of interest relevant to this article was reported.

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

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CORRESPONDENCE

Transcatheter Aortic-Valve Implantation for Aortic Stenosis

TO THE EDITOR: Although Leon et al. (Oct. 21 issue)[1] report that transcatheter aortic-valve implantation (TAVI) is better than standard therapy, a look at the Placement of Aortic Transcatheter Valves (PARTNER) trial shows that this conclusion is unfounded. What the authors call "standard therapy" was — in 84% of the patients — a wholly discredited procedure that was largely discontinued years ago. This discredited procedure, aortic valvuloplasty, has been relegated to class III — that is, "not useful and may be harmful" — since 1998.[2] Aortic valvuloplasty fell out of favor years ago because of "dismal" (40%) event-free 1-year survival.[3]

The unexpectedly high rate of death in the control group was undoubtedly due to the use of this outdated, dangerous procedure. It is notable that the lowest 1-year rates of death (33%) in the PARTNER study were among the 12 patients in the standard-therapy group who underwent surgical aortic-valve replacement. The standard therapy in patients with aortic stenosis who are not surgical candidates is medical therapy alone. Unfortunately, the PARTNER study did not include a valid control group, and thus we do not know how TAVI compares with standard therapy.

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Dr. Redberg reports being a member of the Cardiovascular Device expert panel. No other potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: In the study by Leon et al., despite randomization, the patients assigned to TAVI had a significantly better logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE) than those receiving standard therapy (26.4±17.2 vs. 30.4± 19.1, P=0.04). This difference raises the question of whether the better outcome (reduced rates of death from any cause) in the patients who underwent TAVI reflects the positive effect of the experimental treatment or the better baseline conditions of this patient group.

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No potential conflict of interest relevant to this letter was reported.

THIS WEEK'S LETTERS

TO THE EDITOR: The PARTNER trial investigators report on a tremendous advance in the care of patients with aortic stenosis who are at high surgical risk.

Major societies of cardiology have recognized the need for cost-effectiveness analyses of TAVI.[1,2] Preliminary studies have suggested that TAVI may be cost-effective[3]; however, large studies are lacking. Although the subgroup analysis in this study suggested that TAVI improved symptoms and functional capacity, the results of quality-of-life assessments were not reported. Given the demonstrated increase in periprocedural strokes and bleeding complications, future investigations should consider the cost-effectiveness of TAVI and the patient's quality of life after this procedure, especially in patients at elevated, but not prohibitive, surgical risk. The decreases in mortality after TAVI reported by the authors are remarkable. However, in the targeted population of elderly persons with multiple coexisting conditions, limited life expectancy, and disproportionate health care expenditures,[4] a careful consideration of the cost-effectiveness and quality-of-life benefits of TAVI is warranted, especially in the context of recent domestic health care reform initiatives.

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No potential conflict of interest relevant to this letter was reported.

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THE AUTHORS REPLY: In response to Redberg: the 358 patients in the PARTNER trial had aortic stenosis, severe cardiac symptoms (93% of the patients had New York Heart Association class III or IV symptoms), and multiple coexisting conditions (mean Society of Thoracic Surgeons [STS] score, 11.6%). These conditions were considered "inoperable" by surgeons and cardiologists.

In these "sickest of the sick" patients with inoperable aortic stenosis, balloon aortic valvuloplasty is entirely appropriate as an important component of standard therapy. Balloon aortic valvuloplasty is a class IIb recommendation in the most recent guidelines of the American College of Cardiology and American Heart Association (AHA)[1] and the European Society of Cardiology,[2] and it is considered reasonable therapy in patients with aortic stenosis as a bridge to aortic-valve replacement or as palliation in patients who cannot undergo aortic-valve replacement because of coexisting conditions.

In the PARTNER study, balloon aortic valvuloplasty was safe (one death and two strokes occurred within 7 days after balloon aortic valvuloplasty in 150 patients). Balloon aortic valvuloplasty was a successful bridge to aortic-valve replacement in 11 of the 12 patients with initially inoperable aortic stenosis who subsequently underwent aortic-valve replacement. As compared with standard therapy in patients who underwent balloon aortic valvuloplasty, among patients who did not undergo this procedure there was an absolute reduction of 20 percentage points in mortality at 3 months and a significant mortality benefit over the course of the trial ($P=0.04$ by the log-rank test). Therefore, as compared with patients who underwent TAVI, the patients with inoperable aortic stenosis who underwent balloon aortic valvuloplasty and received optimal medical therapy composed an entirely valid control group in the randomized PARTNER trial.

In response to Trippoli and Messori: the baseline characteristics of the patients in the PARTNER trial were generally well balanced, but there were some differences, including a higher logistic EuroSCORE (but a similar STS score) and more frequent chronic obstructive pulmonary disease and atrial fibrillation in patients receiving standard therapy and more frequent calcified (porcelain) aorta in patients undergoing TAVI. In a small, randomized trial such as PARTNER (which involved 358 patients), such baseline disparities are commonly observed, and after adjustment for baseline risk imbalances, there were still marked

differences in the mortality end point between the test and control therapies.

In response to Newman and Shimbo: we agree that formal quality-of-life and cost-effectiveness studies are required to best determine the ultimate benefit of TAVI. These studies were embedded in the PARTNER trial design, and the quality-of-life assessment was reported on by Cohen at the recent AHA meeting.[3] In summary, among survivors, significant differences in results of the Kansas City Cardiomyopathy questionnaire and other quality-of-life measures were observed; these results favored TAVI over standard therapy at 1, 6, and 12 months. Cost-effectiveness analyses from the PARTNER study are ongoing. These quality-of-life outcomes suggest that in the PARTNER patient cohort, TAVI not only adds years to life, but also adds life to years.

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Since publication of their article, the authors report no further potential conflict of interest.

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Induced Pluripotent Stem Cells in Long-QT Syndrome

TO THE EDITOR: Moretti et al. (Oct. 7 issue)[1] report that patient-derived pluripotent stem cells recapitulated features of a cardiac disorder through reprogramming. The authors clearly show the directed differentiation of such stem cells into functional cardiac myocytes. With regard to pluripotency, they tested for expression of pluripotency markers, but data on teratoma formation were missing. We would be grateful if the authors would provide information on any correlation between functional differentiation and teratoma formation (e.g., whether stem-cell clones with good differentiation potential have a tendency to fail to form teratomas). Although criteria for the authenticity of such cells may vary in the context of specific applications, there has been discussion of whether standards for characterization of these cell lines require teratoma assays.[2,3] In addition, the need for standards for teratoma assays,[4] especially for human cells, has been proposed. Induced cardiomyocytes[5] may replace induced pluripotent stem cells, but there may be an interesting (positive or negative) correlation between the functional differentiation ability and teratoma-forming ability of human induced pluripotent stem cells.

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THE AUTHORS REPLY: An important issue regarding the derivation of human induced pluripotent

CORRESPONDENCE

Transcatheter Aortic-Valve Replacement

TO THE EDITOR: For decades, inoperable critical aortic stenosis has been considered untreatable. The randomized, controlled trial conducted by the Placement of Aortic Transcatheter Valves (PARTNER) investigators (Oct. 21, 2010, issue and June 9, 2011, issue),[1,2] in which transcatheter aortic-valve implantation is compared with medical therapy, has generated excitement, and on the basis of the trial results, the manufacturer of the SAPIEN valve, Edwards Lifesciences, has applied to the Food and Drug Administration (FDA) for premarket approval of its use. The report of a 20% reduction in mortality for the patients who underwent this procedure[1] as compared with controls appears striking until one considers that most of the patients in the control group underwent balloon aortic valvuloplasty, a little-used procedure associated with high morbidity and mortality.[3] One sixth of the patients in the transcatheter group had major vascular complications, and an alarmingly high percentage of patients — 5% — had clinical strokes.[1] Furthermore, Edwards Lifesciences actively participated in the selection and management of the study sites and in the collection and monitoring of data.[1] These circumstances are likely to have created conditions that were conducive to a successful outcome. Indeed, the 30-day rate of death among patients undergoing transcatheter aortic-valve implantation who were listed in a European registry, which reflects experience in actual clinical practice, was greater than it was in the PARTNER trial (8.5% vs. 5.2%).[4]

Given these safety concerns, the continued collection of data on transcatheter aortic-valve implantation is critical. If use of the SAPIEN valve is approved by the FDA, the agency must require the formation of a public patient registry in which data could be collected on both in-hospital adverse events and clinical outcomes (e.g., stroke, myocardial infarction, death, or the need for pacemakers) for a period of 3 to 5 years. We support the thoughtful consensus document recently released by the American College of Cardiology (ACC) Foundation and the Society of Thoracic Surgeons, which recommends the creation of such a registry and advises that device implantation occur only at specialized regional centers.[4]

Given the potential for serious adverse events associated with transcatheter aortic-valve implantation, the FDA must monitor results regularly and pay close attention to signals indicating that the procedure may be unsafe. Caution is most appropriate for high-risk devices such as the transcatheter aortic valve, which once implanted cannot be removed and may lead to the performance of additional risky procedures, such as pacemaker implantation. Only a concerted effort by professional societies and regulatory bodies to support continued data gathering and analysis will ensure that actions are based on new in-

THIS WEEK'S LETTERS

formation and experience and that such new devices will be put to optimal and appropriate use. The likely approval of the SAPIEN valve by the FDA Circulatory System Devices Panel will provide the ideal (and in our view, imperative) opportunity for implementing such a program.

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Dr. Redberg reports being a member of the FDA Circulatory System Devices Panel and the California Technology Assessment Forum. No other potential conflict of interest relevant to this letter was reported.

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THE AUTHORS REPLY: In the most recent guidelines from the ACC–American Heart Association and the European Union,[1,2] balloon aortic valvuloplasty is a class IIb procedure, appropriate for use in symptom palliation or as a bridge to more definitive therapy, the precise indications considered in the PARTNER trial. In the October 21, 2010, report from the trial, balloon aortic valvuloplasty was not associated with significant complications, served as a bridge to subsequent aortic-valve-replacement procedures for some patients, and reduced early mortality by 20% as compared with patients who did not receive balloon aortic valvuloplasty.

Complications from transcatheter aortic-valve replacement were neither alarming nor unexpected, especially considering the complications associated with the use of large, early-generation devices in a high-risk, elderly, frail population of patients with multiple coexisting conditions and critical aortic stenosis. It is potentially misleading to raise concerns about higher early risk of death in a "real world" registry[3] when 1-year rates of death (the primary end point of the study) and stroke were actually lower in this registry than they were in the PARTNER study.

We and our professional societies agree concerning the need for rational dispersion and careful scrutiny of this new technology. A multidisciplinary heart valve team whose members have advanced skills is required to achieve optimal clinical outcomes. It is certainly reasonable to limit access to transcatheter aortic-valve replacement to clinical sites that have such a team. Monitoring real-world outcomes in rigorous post-approval studies and a public multiyear registry is equally important.

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Since publication of their article, the authors report no further potential conflict of interest.

1. Bonow RO, Carabello BA, Chatterjee K, et al. 2008 Focused update incorporated into the ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1998 Guidelines for the Management of Patients with Valvular Heart Disease): endorsed by the Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. Circulation 2008;118(15):e523-e661.
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Treatment of Hepatitis C by Primary Care Providers

TO THE EDITOR: A careful analysis of the patients with hepatitis C virus (HCV) infection in the study by Arora et al. (June 9 issue)[1] suggests that this is a highly selected, and perhaps biased, patient population, including those at the Extension for Community Healthcare Outcomes (ECHO) site, where 112 of 261 patients (43%) had HCV genotype 2 infection, a group that is known to have a higher response rate than patients with genotype 1. Thus, the incidence of HCV genotype 2 in this study is much greater