

## ORIGINAL ARTICLE

## Five-Year Outcomes of Transcatheter or Surgical Aortic-Valve Replacement

R.R. Makkar, V.H. Thourani, M.J. Mack, S.K. Kodali, S. Kapadia, J.G. Webb, S.-H. Yoon, A. Trento, L.G. Svensson, H.C. Herrmann, W.Y. Szeto, D.C. Miller, L. Satler, D.J. Cohen, T.M. Dewey, V. Babaliaros, M.R. Williams, D.J. Kereiakes, A. Zajarias, K.L. Greason, B.K. Whisenant, R.W. Hodson, D.L. Brown, W.F. Fearon, M.J. Russo, P. Pibarot, R.T. Hahn, W.A. Jaber, E. Rogers, K. Xu, J. Wheeler, M.C. Alu, C.R. Smith, and M.B. Leon, for the PARTNER 2 Investigators\*

## ABSTRACT

**BACKGROUND**

There are scant data on long-term clinical outcomes and bioprosthetic-valve function after transcatheter aortic-valve replacement (TAVR) as compared with surgical aortic-valve replacement in patients with severe aortic stenosis and intermediate surgical risk.

**METHODS**

We enrolled 2032 intermediate-risk patients with severe, symptomatic aortic stenosis at 57 centers. Patients were stratified according to intended transfemoral or transthoracic access (76.3% and 23.7%, respectively) and were randomly assigned to undergo either TAVR or surgical replacement. Clinical, echocardiographic, and health-status outcomes were followed for 5 years. The primary end point was death from any cause or disabling stroke.

**RESULTS**

At 5 years, there was no significant difference in the incidence of death from any cause or disabling stroke between the TAVR group and the surgery group (47.9% and 43.4%, respectively; hazard ratio, 1.09; 95% confidence interval [CI], 0.95 to 1.25;  $P=0.21$ ). Results were similar for the transfemoral-access cohort (44.5% and 42.0%, respectively; hazard ratio, 1.02; 95% CI, 0.87 to 1.20), but the incidence of death or disabling stroke was higher after TAVR than after surgery in the transthoracic-access cohort (59.3% vs. 48.3%; hazard ratio, 1.32; 95% CI, 1.02 to 1.71). At 5 years, more patients in the TAVR group than in the surgery group had at least mild paravalvular aortic regurgitation (33.3% vs. 6.3%). Repeat hospitalizations were more frequent after TAVR than after surgery (33.3% vs. 25.2%), as were aortic-valve reinterventions (3.2% vs. 0.8%). Improvement in health status at 5 years was similar for TAVR and surgery.

**CONCLUSIONS**

Among patients with aortic stenosis who were at intermediate surgical risk, there was no significant difference in the incidence of death or disabling stroke at 5 years after TAVR as compared with surgical aortic-valve replacement. (Funded by Edwards Lifesciences; PARTNER 2 ClinicalTrials.gov number, NCT01314313.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Makkar at Cedars-Sinai Medical Center, 8700 Beverly Blvd., Los Angeles, CA 90048, or at [raj.makkar@cshs.org](mailto:raj.makkar@cshs.org).

\*A complete list of the PARTNER 2 Investigators is provided in the Supplementary Appendix, available at [NEJM.org](http://NEJM.org).

This article was published on January 29, 2020, at [NEJM.org](http://NEJM.org).

DOI: 10.1056/NEJMoa1910555

Copyright © 2020 Massachusetts Medical Society.

**T**RANSCATHETER AORTIC-VALVE REPLACEMENT (TAVR) is an alternative to surgery in patients with symptomatic aortic stenosis, on the basis of clinical evidence from multiple randomized trials.<sup>1,12</sup> However, there are limited data on long-term clinical outcomes and bioprosthetic-valve function after TAVR as compared with surgical aortic-valve replacement.<sup>13-16</sup> The Placement of Aortic Transcatheter Valves (PARTNER) 2 cohort A trial is a randomized trial comparing the outcomes of TAVR and surgery in more than 2000 patients with severe aortic stenosis at intermediate risk for surgery. This report from the PARTNER 2 cohort A trial is a 5-year follow-up analysis of clinical outcomes, valve function, and quality-of-life measures in patients undergoing TAVR or surgery.

## METHODS

### PATIENTS AND TRIAL DESIGN

Details of the trial design have been published previously.<sup>6</sup> From December 2011 through November 2013, a total of 2032 patients with severe, symptomatic aortic stenosis at intermediate surgical risk were enrolled at 57 centers in the United States and Canada. Intermediate-risk status was determined by a multidisciplinary heart team and included a predicted 30-day surgical mortality of 4% to 8%, as calculated with a risk model developed by the Society of Thoracic Surgeons (STS).<sup>17</sup> Complete inclusion and exclusion criteria are provided in the Supplementary Appendix, available with the full text of this article at NEJM.org. Written informed consent was obtained from all the patients.

Patients were stratified according to the intended access route if assigned to TAVR (transfemoral or transthoracic) on the basis of imaging studies, including computed tomography (CT), and were then randomly assigned (in a 1:1 ratio) to undergo either TAVR or surgery. Patients and their treating physicians were aware of the treatment assignments.

### DEVICE AND PROCEDURES

The second-generation balloon-expandable SAPIEN XT heart-valve system (Edwards Lifesciences) and the TAVR procedure have been described previously.<sup>18</sup> In patients assigned to TAVR, transfemoral access was preferred; in those requiring transthoracic access, either transapical or direct aortic

access was used. Patients who were assigned to surgery were required to be good candidates for aortic-valve replacement with the use of a bioprosthetic valve. An Edwards Lifesciences surgical bioprosthesis was recommended; mechanical valve prostheses were not allowed. Standard surgical techniques were applied by experienced valve surgeons who had fulfilled qualification standards; limited thoracotomy approaches were allowed, according to surgeon preference. The use of concomitant procedures during surgery was also at the discretion of the surgeon. Patients with concomitant noncomplex coronary artery disease undergoing revascularization could be treated with percutaneous coronary intervention (PCI) in the TAVR group or coronary-artery bypass grafting (CABG) in the surgery group at the discretion of the heart team.

Recommended pharmacotherapy in the TAVR group before the procedure included aspirin (81 mg daily) and clopidogrel (75 mg daily) and after the procedure included aspirin indefinitely and clopidogrel for at least 1 month. For patients in the surgery group, the same postprocedure drug regimen was recommended. In patients receiving long-term oral anticoagulation, clopidogrel was added at the physician's discretion (see the Supplementary Appendix).

### TRIAL OVERSIGHT

The trial was designed and monitored by the sponsor (Edwards Lifesciences) and the physician executive committee. The trial protocol, which is available at NEJM.org, was approved by the institutional review board at each site. All the patients were reviewed before randomization by a multidisciplinary case-review committee. Data collection and storage were conducted by the sponsor with the use of an electronic data-capture system. All echocardiograms were interpreted at a central core laboratory. All adverse events occurring during the first 2 years of the trial were adjudicated by an independent clinical-events committee. The committee continued to adjudicate all deaths, strokes, and rehospitalizations occurring between 2 and 5 years after the procedure, whereas other clinical events were site-reported. Statistical analysis for the 5-year manuscript was performed by the sponsor. The first author and last two authors had unrestricted access to the data after the database was locked, wrote the first draft of the manuscript

(with assistance from other authors), made the decision to submit the manuscript for publication, and vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol.

## END POINTS

The primary end point of the trial was a nonhierarchical composite of death from any cause or disabling stroke at 2 years in the intention-to-treat population. Disabling stroke was defined as a score on the modified Rankin scale of 2 or more (with scores ranging from 0 [no symptoms] to 6 [death]) and an increase of at least 1 point from baseline to 30 or 90 days after the stroke. The key end points reported in this analysis are 5-year incidences of death from any cause, disabling stroke, repeat hospitalization (procedure-, valve-, or heart failure–related), and aortic-valve reintervention, as well as New York Heart Association (NYHA) functional class, quality-of-life measures, and echocardiographic assessments of aortic-valve area, aortic-valve gradients, and paravalvular regurgitation. Patients were followed yearly for clinical end points. Echocardiographic results were reported from core laboratory assessments. Details of end-point definitions and clinical follow-up are provided in the Supplementary Appendix, including Table S1.

## STATISTICAL ANALYSIS

All clinical outcomes were analyzed in the intention-to-treat population (i.e., all the patients who underwent randomization, regardless of the treatment received). The as-treated population (patients in whom the intended procedure was initiated) was used for sensitivity analyses. Echocardiographic analyses were performed in patients who received the intended valve therapy. The transfemoral-access cohort and the transthoracic-access cohort were prespecified analysis subgroups for the primary end point. Because the statistical analysis plan did not include corrections for multiple comparisons with respect to tests for secondary or other outcomes in the 5-year follow-up data, results are reported as point estimates and 95% confidence intervals. Because the margins of the confidence intervals were not adjusted for multiple comparisons, the intervals should not be used to infer definitive treatment effects for secondary outcomes.

The chi-square test or Fisher's exact test was

used to compare categorical variables. Continuous variables, which are presented as means with standard deviations, were compared with the use of Student's *t*-test. Analysis of the primary end point and other time-to-event end points used Kaplan–Meier estimates; comparisons were made with the log-rank test. Interaction analyses were performed in the same subgroups as prespecified for the 2-year analysis.<sup>6</sup> To account for the possibility of nonproportional hazards, restricted mean survival time (restricted to 5 years) and restricted mean event-free time for the end point of death or disabling stroke were calculated.

Ordinal categories that were based on previously established thresholds for clinically relevant changes in the Kansas City Cardiomyopathy Questionnaire–Overall Summary (KCCQ–OS) score were defined as death, worsened (decrease from baseline of >5 points), no change (change of –5 to <5 points), mildly improved (increase of 5 to <10 points), moderately improved (increase of 10 to <20 points), and substantially improved (increase of ≥20 points).<sup>19,20</sup> The relative effect of TAVR as compared with surgery on health status was then compared with the use of ordinal logistic regression. Absolute mean changes in the KCCQ–OS score from baseline to 5 years are also presented. Statistical analyses were performed with the use of SAS software, version 9.4 (SAS Institute).

## RESULTS

### PARTICIPANTS, PROCEDURES, AND FOLLOW-UP

Among 2032 patients who were enrolled, 1550 (76.3%) were suitable candidates for transfemoral access, and the remaining 482 (23.7%) were included in the transthoracic-access cohort. Patient characteristics at baseline are shown in Table 1. The mean age was 81.6 years, and the mean STS risk score 5.8%; 45.5% of the patients were female. A total of 700 patients (69.2%) in the TAVR group and 679 (66.5%) in the surgery group had coronary artery disease, with similar incidences in the two groups of previous CABG (23.6% and 25.6%, respectively) and previous PCI (27.1% and 27.6%).

A total of 994 of 1011 patients in the TAVR group and 944 of 1021 in the surgery group underwent the assigned procedure (Fig. S1 in the Supplementary Appendix). Concomitant planned or unplanned procedures during surgery were performed in 86 of 944 patients in the surgery

**Table 1. Characteristics of the Patients at Baseline.\***

Characteristic	TAVR (N=1011)	Surgery (N=1021)
Age — yr	81.5±6.7	81.7±6.7
Male sex — no. (%)	548 (54.2)	560 (54.8)
Body-mass index†	28.6±6.2	28.3±6.2
STS risk score‡	5.8±2.1	5.8±1.9
NYHA class III or IV — no./total no. (%)	782/1011 (77.3)	776/1020 (76.1)
Coronary artery disease — no. (%)	700 (69.2)	679 (66.5)
Previous myocardial infarction — no. (%)	185 (18.3)	179 (17.5)
Previous CABG — no. (%)	239 (23.6)	261 (25.6)
Previous PCI — no. (%)	274 (27.1)	282 (27.6)
Previous balloon aortic valvuloplasty — no. (%)	51 (5.0)	50 (4.9)
Cerebral vascular disease — no. (%)	325 (32.1)	317 (31.0)
Peripheral vascular disease — no. (%)	282 (27.9)	336 (32.9)
Diabetes mellitus — no. (%)	381 (37.7)	349 (34.2)
COPD — no. (%)		
Any	321 (31.8)	306 (30.0)
Oxygen-dependent	34 (3.4)	32 (3.1)
Renal insufficiency — no. (%)§	51 (5.0)	53 (5.2)
Atrial fibrillation — no. (%)	313 (31.0)	359 (35.2)
Permanent pacemaker — no. (%)	118 (11.7)	123 (12.0)
Frail condition — no./total no. (%)		
5-Meter walk-test time >7 sec	416/936 (44.4)	418/901 (46.4)
Serum albumin <3.5 g/dl	150/988 (15.2)	140/951 (14.7)
Liver disease — no. (%)	19 (1.9)	26 (2.5)
Aortic-valve area — cm <sup>2</sup>	0.7±0.2	0.7±0.2
Aortic-valve gradient — mm Hg	44.9±13.4	44.6±12.5
Left ventricular ejection fraction — %	56.2±10.8	55.3±11.9
Left ventricular mass index — g/m <sup>2</sup>	119.8±31.5	120.6±32.6
Moderate or severe mitral regurgitation — no./total no. (%)	151/899 (16.8)	171/894 (19.1)

\* Plus-minus values are means ±SD. Data on left ventricular ejection fraction were missing for 348 patients assigned to transcatheter aortic-valve replacement (TAVR) and for 347 assigned to surgical aortic-valve replacement. CABG denotes coronary-artery bypass grafting, COPD chronic obstructive pulmonary disease, NYHA New York Heart Association, and PCI percutaneous coronary intervention.

† The body-mass index is the weight in kilograms divided by the square of the height in meters.

‡ Scoring on the risk model of the Society of Thoracic Surgeons (STS) uses an algorithm that is based on the presence of coexisting illnesses in order to predict 30-day operative mortality. The STS score equals the predicted mortality expressed as a percentage.

§ Renal insufficiency was defined as a serum creatinine level of more than 2 mg per deciliter (177 μmol per liter).

group, including aortic endarterectomy, aortic-root enlargement or replacement, and mitral-valve or tricuspid-valve repair or replacement. Coronary revascularization was performed in 39 of 994 patients in the TAVR group (who underwent PCI) and in 137 of 944 patients in the surgery group (who underwent CABG).

Data were available at 5 years for 920 patients (91.0%) in the TAVR group and for 831 (81.4%) in the surgery group. Baseline characteristics of patients with missing 5-year follow-up as compared with those with complete follow-up are presented in Table S2. Patients with complete follow-up were more likely than those with missing

follow-up to be male, to be in NYHA class III or IV, and to have diabetes and were less likely to have moderate or severe mitral regurgitation. To account for varying percentages of patients with missing 5-year data for specific end points in the TAVR and surgery groups (NYHA class, 15.7% vs. 23.4%; KCCQ-OS score, 19.6% vs. 23.7%; and echocardiographic findings, 30.4% vs. 35.7%), sensitivity analyses to account for missing data were performed with the use of multiple imputation or linear mixed-effects models and paired analyses (see the Supplementary Appendix).

#### DEATH AND STROKE

At 5 years, there was no evidence of a significant difference in the incidence of the composite end point of death from any cause or disabling stroke between the TAVR group and the surgery group (47.9% and 43.4%, respectively; hazard ratio, 1.09; 95% confidence interval [CI], 0.95 to 1.25;  $P=0.21$ ) (Table 2 and Fig. 1). Results of a sensitivity analysis performed with the use of multiple imputation were consistent with these findings (Table S3). In the transfemoral-access cohort, the incidence of death or disabling stroke was similar in the TAVR group and the surgery group (44.5% and 42.0%, respectively; hazard ratio, 1.02; 95% CI, 0.87 to 1.20) (Fig. S2A). However, the incidence of death or disabling stroke was higher after TAVR than after surgery in the transthoracic-access cohort (59.3% vs. 48.3%; hazard ratio, 1.32; 95% CI, 1.02 to 1.71) (Fig. S2B). Apart from access route, there was no heterogeneity of treatment effect for death or disabling stroke for any subgroup tested (Fig. S3).

The incidences of death from any cause in the TAVR and surgery groups were 46.0% and 42.1%, respectively, in the overall population, 42.7% and 40.5% in the transfemoral-access cohort, and 56.9% and 47.3% in the transthoracic-access cohort (Table 2 and Table S4). Adjudicated causes of death are presented in Table S5. The incidence of disabling stroke was similar in the TAVR group and the surgery group, regardless of cohort. Results of a sensitivity analysis that were restricted to the as-treated population were consistent with the intention-to-treat results (Table S6). Post hoc landmark analyses of events occurring between 2 and 5 years after the procedure are presented in Figure S4 and Table S7. The 5-year restricted mean survival time was similar for TAVR and surgery (46.3 months and 46.6

months, respectively), as was the restricted mean event-free time for the end point of death or disabling stroke (45.0 months and 44.8 months) (Table S8).

#### OTHER CLINICAL OUTCOMES

Rehospitalization occurred more frequently after TAVR than after surgery at 5 years (33.3% vs. 25.2%; hazard ratio, 1.28; 95% CI, 1.07 to 1.53) (Table 2 and Fig. S5); reasons for rehospitalization are shown in Table S9. Aortic-valve reintervention was uncommon in both groups but was more frequent among patients in the TAVR group than among those in the surgery group (3.2% vs. 0.8%; hazard ratio, 3.28; 95% CI, 1.32 to 8.13) (Table 2 and Table S10). Reinterventions after TAVR were due to progressive stenosis (10 of 21 cases) or aortic regurgitation (11 of 21 cases), and most patients (18 of 21) were treated with either repeat TAVR or balloon valvuloplasty. Endocarditis was the main cause of the reintervention in patients in the surgery group (4 of 6 cases), most of whom were treated with repeat surgery. In-hospital mortality from valve reintervention was 5% (1 of 21 patients) in the TAVR group and 50% (3 of 6 patients) in the surgery group.

#### ECHOCARDIOGRAPHIC FINDINGS

In both treatment groups, initial gains in aortic-valve areas and reductions in mean gradients were sustained for 5 years (Fig. 2A and 2B). Among surviving patients with echocardiograms, mild or greater paravalvular aortic regurgitation was observed in 33.3% of the patients in the TAVR group and in 6.3% of those in the surgery group (Fig. 2C and Fig. S6). Results of sensitivity analyses of the echocardiographic findings to account for missing data with the use of multiple imputation are presented in Table S11. Moderate or severe paravalvular aortic regurgitation after TAVR was associated with an increased risk of death at 5 years in the overall population (Fig. 2D) and in the transfemoral-access cohort (Fig. S7). Changes in left ventricular dimensions and ejection fraction are presented in Table S12 and Figures S8 and S9.

#### FUNCTIONAL AND HEALTH STATUS

Among surviving patients with available data, both TAVR and surgery led to improvements in health status at 5 years (NYHA functional class I or II, 89.0% and 92.7%, respectively; average



**Table 2. Clinical End Points at 2 and 5 Years (Intention-to-Treat Population).\***

End Point	At 2 Years			At 5 Years		
	TAVR (N = 1011)	Surgery (N = 1021)	Hazard Ratio (95% CI)	TAVR (N = 1011)	Surgery (N = 1021)	Hazard Ratio (95% CI)
Death from any cause or disabling stroke	192 (19.3)	202 (21.1)	0.89 (0.73–1.09)	456 (47.9)	388 (43.4)	1.09 (0.95–1.25)
Death		<i>no. of patients (%)</i>			<i>no. of patients (%)</i>	
From any cause	166 (16.7)	170 (18.0)	0.92 (0.74–1.13)	436 (46.0)	370 (42.1)	1.09 (0.95–1.25)
From cardiac causes	97 (10.1)	105 (11.4)	0.87 (0.66–1.15)	245 (29.4)	223 (27.8)	1.02 (0.85–1.23)
Not from cardiac causes	69 (7.4)	65 (7.4)	0.99 (0.70–1.38)	191 (23.6)	147 (19.8)	1.20 (0.97–1.49)
Neurologic event						
Any event	121 (12.7)	104 (11.1)	1.13 (0.87–1.47)	166 (19.5)	134 (16.0)	1.20 (0.95–1.50)
Transient ischemic attack	34 (3.7)	21 (2.5)	1.54 (0.89–2.65)	45 (5.3)	32 (4.3)	1.33 (0.84–2.09)
Any stroke	91 (9.5)	85 (8.9)	1.04 (0.78–1.40)	128 (15.3)	107 (12.5)	1.15 (0.89–1.49)
Disabling stroke	59 (6.2)	61 (6.4)	0.93 (0.65–1.33)	83 (9.8)	75 (8.6)	1.05 (0.77–1.44)
Nondisabling stroke	33 (3.4)	27 (2.9)	1.20 (0.72–2.00)	43 (5.1)	33 (3.9)	1.27 (0.81–2.00)
Rehospitalization	186 (19.9)	158 (17.5)	1.12 (0.91–1.39)	281 (33.3)	209 (25.2)	1.28 (1.07–1.53)
Death from any cause or rehospitalization	306 (30.7)	283 (29.8)	1.03 (0.87–1.21)	559 (58.1)	460 (51.0)	1.16 (1.02–1.31)
Death from any cause or any stroke	223 (22.4)	225 (23.4)	0.94 (0.78–1.13)	488 (51.1)	406 (45.2)	1.13 (0.99–1.29)
Death from any cause, any stroke, or rehospitalization	346 (34.7)	328 (34.1)	1.00 (0.86–1.17)	597 (61.8)	490 (53.5)	1.16 (1.03–1.31)
Myocardial infarction	43 (4.7)	37 (4.3)	1.10 (0.71–1.70)	84 (11.1)	62 (8.2)	1.26 (0.91–1.75)
New atrial fibrillation	112 (11.5)	275 (27.5)	0.37 (0.30–0.46)	141 (15.8)	291 (30.4)	0.43 (0.35–0.53)
New permanent pacemaker implantation	114 (11.8)	97 (10.3)	1.17 (0.89–1.53)	138 (15.5)	113 (13.0)	1.20 (0.94–1.54)
Endocarditis	15 (1.7)	13 (1.5)	1.07 (0.51–2.25)	30 (3.9)	19 (2.5)	1.46 (0.82–2.60)
Aortic-valve reintervention	6 (0.7)	4 (0.5)	1.40 (0.40–4.98)	21 (3.2)	6 (0.8)	3.28 (1.32–8.13)
Surgical aortic-valve replacement	2 (0.2)	4 (0.5)	0.47 (0.09–2.59)	3 (0.3)	5 (0.6)	0.56 (0.13–2.35)
Balloon aortic valvuloplasty	1 (0.1)	0	NA	1 (0.1)	0	NA
Valve-in-valve	3 (0.3)	0	NA	17 (2.7)	1 (0.2)	15.88 (2.12–119.27)

\* All percentages are Kaplan–Meier estimates at the specific time point and thus do not equal the number of patients divided by the total number of patients in the treatment group. NA denotes not applicable.

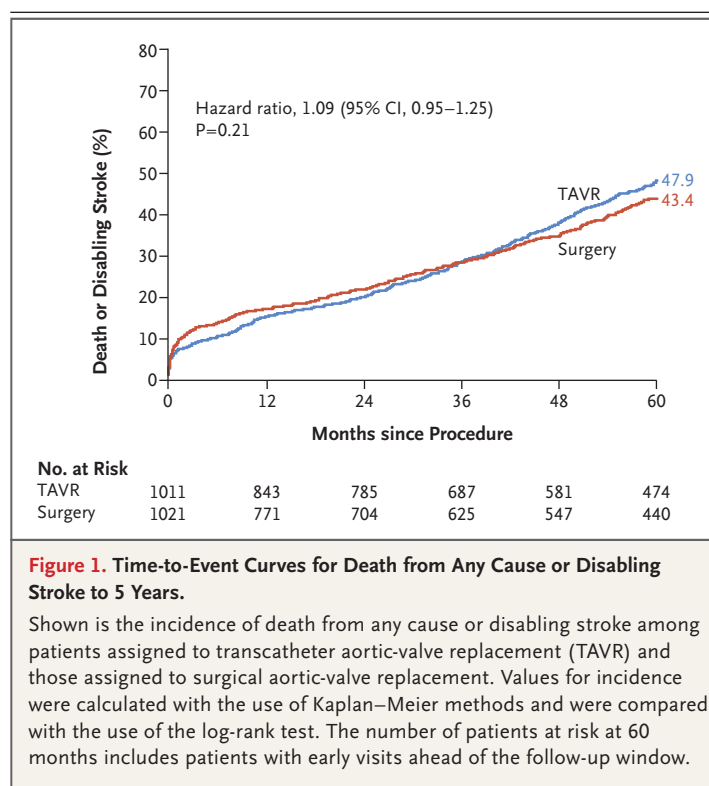
increase from baseline in the KCCQ-OS score, 19.6 points and 20.5 points) (Fig. 3A and 3B). When patients were stratified according to established thresholds for clinically relevant changes in the KCCQ-OS score, there was no evidence of a substantial difference between the TAVR group and the surgery group at 5 years (Fig. S10). Results of sensitivity analyses to account for missing data with the use of multiple imputation (for data on the NYHA class) and linear mixed-effects models (for data on the KCCQ-OS score) are shown in Tables S13 and S14.

## DISCUSSION

The PARTNER 2 cohort A trial compared TAVR with surgical aortic-valve replacement in patients with severe, symptomatic aortic stenosis at intermediate surgical risk. The main findings from the 5-year follow-up of the trial can be summarized as follows. First, there was no significant difference between the two groups in the primary end point of death from any cause or disabling stroke up to 5 years. Second, valve hemodynamics after TAVR were similar to those after surgery (with larger valve areas and similar valve gradients), but TAVR was associated with higher incidences of mild and moderate or severe paravalvular aortic regurgitation. Third, TAVR and surgery resulted in similar improvements in functional status and disease-specific quality-of-life measures through 5 years. Fourth, valve-related reintervention and rehospitalization were more frequent among patients undergoing TAVR than among those undergoing surgery.

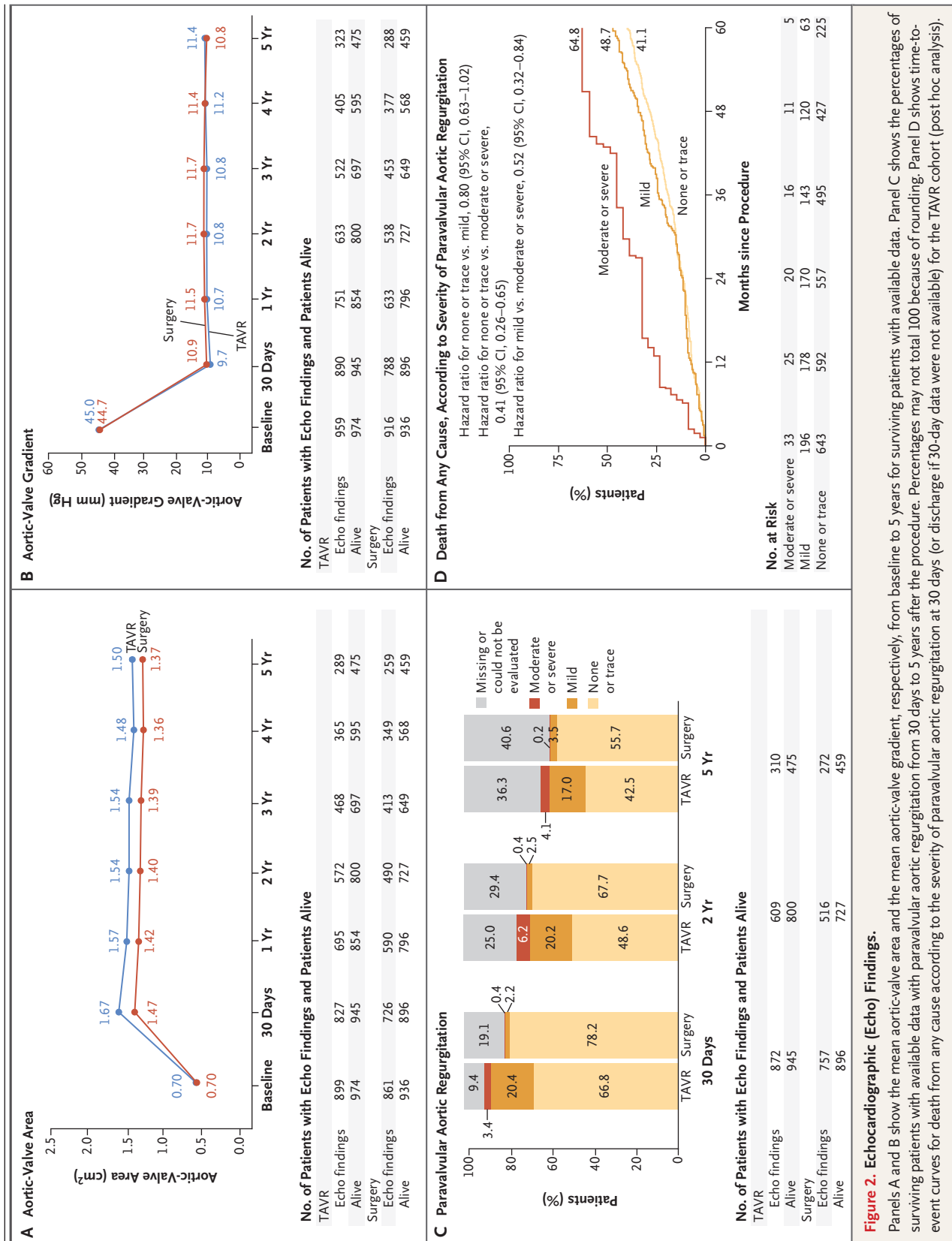
A key subgroup analysis showed that the outcomes of TAVR through transthoracic access, but not through transfemoral access, were inferior to those of open-heart surgery. The progressive divergence of time-to-event curves for death or disabling stroke in the transthoracic-access cohort suggests that considerations beyond procedural factors, including a delayed effect of paravalvular regurgitation on left ventricular function, may play a role. In contemporary practice with smaller-diameter TAVR systems, transfemoral access is used in more than 95% of patients undergoing TAVR. In addition, other transvascular-access routes (axillary, carotid, and caval) are being used preferentially instead of transthoracic access in many centers.<sup>21-23</sup>

In landmark analyses from 2 to 5 years after



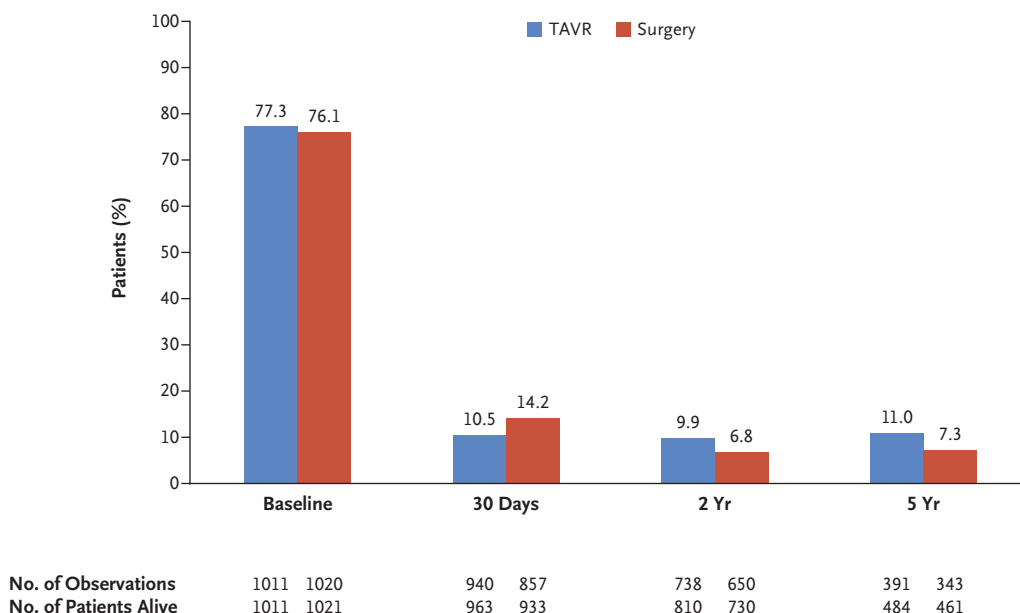
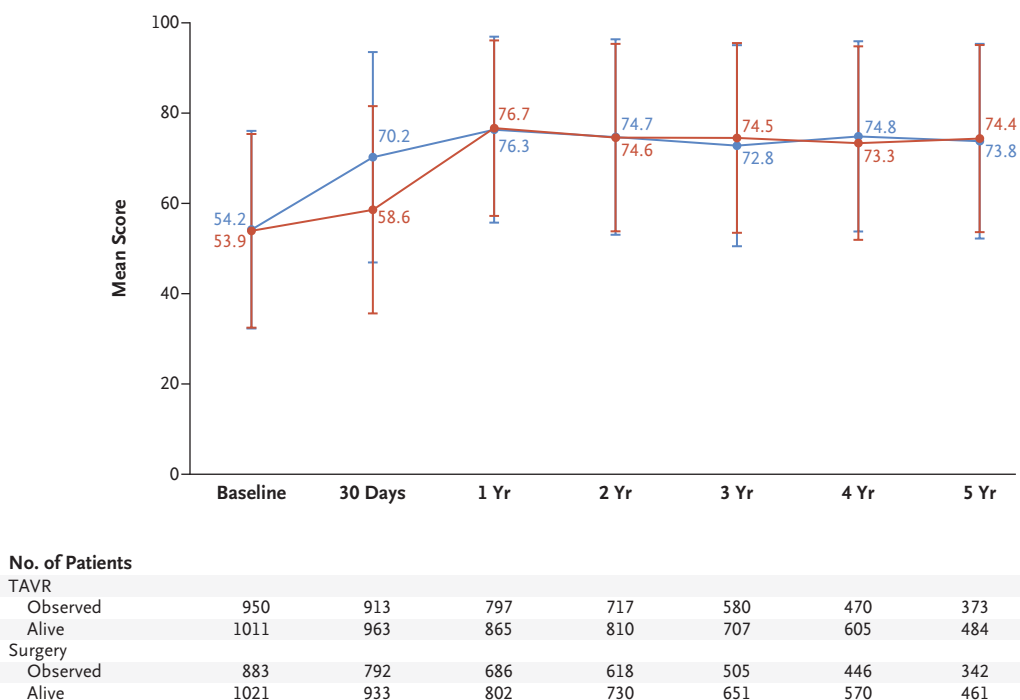
the procedure, we observed a higher incidence of death from any cause or disabling stroke and a higher incidence of death from any cause with TAVR than with surgery. Possible explanations for the higher mortality during this time period among patients in the TAVR group than among those in the surgery group may be the negative effect of increased moderate or severe paravalvular regurgitation after TAVR or the higher prevalence of untreated clinically significant coronary disease in the TAVR cohort than in the surgery cohort. Several previous studies have shown an association between moderate or severe paravalvular regurgitation and mortality after TAVR,<sup>24,25</sup> which has led to device refinements and improved valve-sizing techniques with the use of CT imaging.<sup>26-28</sup> The currently used SAPIEN 3 valve, which incorporates an external sealing skirt and is implanted with the use of CT sizing, is associated with markedly lower incidences of postprocedural and 1-year moderate or severe paravalvular aortic regurgitation than were seen with previous-generation devices.<sup>8,24,29-31</sup>

Although aortic-valve reintervention was uncommon, it was more frequent after TAVR than after surgery, and the causes of reintervention

**Figure 2. Echocardiographic (Echo) Findings.**

Panels A and B show the mean aortic-valve area and the mean aortic-valve gradient, respectively, from baseline to 5 years for surviving patients with available data. Panel C shows the percentages of surviving patients with available data with paravalvular aortic regurgitation from 30 days to 5 years after the procedure. Percentages may not total 100 because of rounding. Panel D shows time-to-event curves for death from any cause according to the severity of paravalvular aortic regurgitation at 30 days (or discharge if 30-day data were not available) for the TAVR cohort (post hoc analysis).



**A NYHA Class III or IV****B KCCQ Overall Summary Score****Figure 3. Functional Status and Quality of Life.**

The percentages of surviving patients with available data in New York Heart Association (NYHA) class III or IV are shown from baseline to 5 years (Panel A). Quality-of-life metrics according to Kansas City Cardiomyopathy Questionnaire—Overall Summary (KCCQ-OS) scores are shown for surviving patients with available data from baseline to 5 years (Panel B). Scores range from 1 to 100, with higher scores indicating better quality of life. The I bars indicate standard deviations.

were distinctly different. Reintervention after TAVR usually occurred after 2 years and was due to progressive aortic-valve stenosis or regurgitation. Most of these patients were treated with repeat TAVR (valve-in-valve), with favorable early outcomes. In contrast, reintervention after surgery was most commonly due to endocarditis and was managed with repeat open-heart surgery, which resulted in a high surgical mortality.

This analysis has several limitations. The device used (SAPIEN XT) is no longer in clinical use, which reduces the clinical applicability of the current trial. Bioprosthetic-valve failure increases with time, and 5-year comparative data may not reflect the true durability of transcatheter or surgical valves at later time points. The mean age of the patients in this trial was 81 years, and it would

be inappropriate to extrapolate these findings to younger patients or patients with lower surgical risk who have higher activity expectations and longer life spans. Missing 5-year data for some of the important secondary end points, such as the echocardiography results, may have biased our findings regarding valve hemodynamics.

Among patients with severe, symptomatic aortic stenosis at intermediate surgical risk, the incidence of the composite end point of death from any cause or disabling stroke at 5 years was similar with TAVR and surgical aortic-valve replacement.

Supported by Edwards Lifesciences.

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.

## APPENDIX

The authors' full names and academic degrees are as follows: Raj R. Makkar, M.D., Vinod H. Thourani, M.D., Michael J. Mack, M.D., Susheel K. Kodali, M.D., Samir Kapadia, M.D., John G. Webb, M.D., Sung-Han Yoon, M.D., Alfredo Trento, M.D., Lars G. Svensson, M.D., Ph.D., Howard C. Herrmann, M.D., Wilson Y. Szeto, M.D., D. Craig Miller, M.D., Lowell Satler, M.D., David J. Cohen, M.D., Todd M. Dewey, M.D., Vasilis Babaliaros, M.D., Mathew R. Williams, M.D., Dean J. Kereiakes, M.D., Alan Zajarias, M.D., Kevin L. Greason, M.D., Brian K. Whisenant, M.D., Robert W. Hodson, M.D., David L. Brown, M.D., William F. Fearon, M.D., Mark J. Russo, M.D., Philippe Pibarot, D.V.M., Ph.D., Rebecca T. Hahn, M.D., Wael A. Jaber, M.D., Erin Rogers, M.Eng., Ke Xu, Ph.D., Jaime Wheeler, M.B.A., C.Ph.T., Maria C. Alu, M.S., Craig R. Smith, M.D., and Martin B. Leon, M.D.

The authors' affiliations are as follows: Cedars-Sinai Medical Center, Los Angeles (R.R.M., S.-H.Y., A.T.), Stanford University, Stanford (D.C.M., W.F.F.), and Edwards Lifesciences, Irvine (E.R., K.X., J.W.) — all in California; the Department of Cardiovascular Surgery, Piedmont Heart Institute (V.H.T.), and Emory University (V.B.) — both in Atlanta; Baylor Scott and White Healthcare, Plano (M.J.M., D.L.B.), and Medical City Dallas Hospital, Dallas (T.M.D.) — both in Texas; Columbia University Medical Center/New York–Presbyterian Hospital (S.K.K., R.T.H., M.C.A., C.R.S., M.B.L.) and NYU Langone Medical Center (M.R.W.) — both in New York; Cleveland Clinic, Cleveland (S.K., L.G.S., W.A.J.); St. Paul's Hospital, Vancouver, BC (J.G.W.), and Institut Universitaire de Cardiologie et de Pneumologie de Québec, Université Laval, Québec, QC (P.P.) — both in Canada; University of Pennsylvania, Philadelphia (H.C.H., W.Y.S.); Medstar Washington Hospital Center, Washington, DC (L.S.); University of Missouri–Kansas City School of Medicine, Kansas City (D.J.C.); Christ Hospital, Cincinnati (D.J.K.); Barnes–Jewish Hospital, Washington University, St. Louis (A.Z.); Mayo Clinic, Rochester, MN (K.L.G.); Intermountain Medical Center, Salt Lake City (B.K.W.); Providence St. Vincent Medical Center, Portland, OR (R.W.H.); and Rutgers–Robert Wood Johnson Medical School, New Brunswick, NJ (M.J.R.).

## REFERENCES

- Leon MB, Smith CR, Mack M, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med* 2010;363:1597-607.
- Smith CR, Leon MB, Mack MJ, et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. *N Engl J Med* 2011;364:2187-98.
- Makkar RR, Fontana GP, Jilaihawi H, et al. Transcatheter aortic-valve replacement for inoperable severe aortic stenosis. *N Engl J Med* 2012;366:1696-704.
- Kodali SK, Williams MR, Smith CR, et al. Two-year outcomes after transcatheter or surgical aortic-valve replacement. *N Engl J Med* 2012;366:1686-95.
- Adams DH, Popma JJ, Reardon MJ, et al. Transcatheter aortic-valve replacement with a self-expanding prosthesis. *N Engl J Med* 2014;370:1790-8.
- Leon MB, Smith CR, Mack MJ, et al. Transcatheter or surgical aortic-valve replacement in intermediate-risk patients. *N Engl J Med* 2016;374:1609-20.
- Reardon MJ, Van Mieghem NM, Popma JJ, et al. Surgical or transcatheter aortic-valve replacement in intermediate-risk patients. *N Engl J Med* 2017;376:1321-31.
- Mack MJ, Leon MB, Thourani VH, et al. Transcatheter aortic-valve replacement with a balloon-expandable valve in low-risk patients. *N Engl J Med* 2019;380:1695-705.
- Popma JJ, Deeb GM, Yakubov SJ, et al. Transcatheter aortic-valve replacement with a self-expanding valve in low-risk patients. *N Engl J Med* 2019;380:1706-15.
- Thyregod HG, Steinbrüchel DA, Ihlemann N, et al. Transcatheter versus surgical aortic valve replacement in patients with severe aortic valve stenosis: 1-year results from the all-comers NOTION randomized clinical trial. *J Am Coll Cardiol* 2015;65:2184-94.
- Nishimura RA, Otto CM, Bonow RO, et al. 2017 AHA/ACC focused update of the 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation* 2017;135(25):e1159-e1195.
- Baumgartner H, Falk V, Bax JJ, et al. 2017 ESC/EACTS guidelines for the management of valvular heart disease. *Eur Heart J* 2017;38:2739-91.
- Mack MJ, Leon MB, Smith CR, et al. 5-Year outcomes of transcatheter aortic valve replacement or surgical aortic valve replacement for high surgical risk patients with aortic stenosis (PARTNER 1): a randomised controlled trial. *Lancet* 2015;385:2477-84.

14. Kapadia SR, Leon MB, Makkar RR, et al. 5-Year outcomes of transcatheter aortic valve replacement compared with standard treatment for patients with inoperable aortic stenosis (PARTNER 1): a randomised controlled trial. *Lancet* 2015; 385:2485-91.
15. Gleason TG, Reardon MJ, Popma JJ, et al. 5-Year outcomes of self-expanding transcatheter versus surgical aortic valve replacement in high-risk patients. *J Am Coll Cardiol* 2018;72:2687-96.
16. Søndergaard L, Ihlemann N, Capodanno D, et al. Durability of transcatheter and surgical bioprosthetic aortic valves in patients at lower surgical risk. *J Am Coll Cardiol* 2019;73:546-53.
17. O'Brien SM, Shahian DM, Filardo G, et al. The Society of Thoracic Surgeons 2008 cardiac surgery risk models: part 2 — isolated valve surgery. *Ann Thorac Surg* 2009;88:Suppl:S23-S42.
18. Webb JG, Altwegg L, Masson JB, Al Bugami S, Al Ali A, Boone RA. A new transcatheter aortic valve and percutaneous valve delivery system. *J Am Coll Cardiol* 2009;53:1855-8.
19. Spertus J, Peterson E, Conard MW, et al. Monitoring clinical changes in patients with heart failure: a comparison of methods. *Am Heart J* 2005;150:707-15.
20. Baron SJ, Arnold SV, Wang K, et al. Health status benefits of transcatheter vs surgical aortic valve replacement in patients with severe aortic stenosis at intermediate surgical risk: results from the PARTNER 2 randomized clinical trial. *JAMA Cardiol* 2017;2:837-45.
21. Dahle TG, Kaneko T, McCabe JM. Outcomes following subclavian and axillary artery access for transcatheter aortic valve replacement: Society of the Thoracic Surgeons/American College of Cardiology TVT Registry report. *JACC Cardiovasc Interv* 2019;12:662-9.
22. Nguyen V, Michel M, Eltchaninoff H, et al. Implementation of transcatheter aortic valve replacement in France. *J Am Coll Cardiol* 2018;71:1614-27.
23. Overtchouk P, Folliguet T, Pinaud F, et al. Transcarotid approach for transcatheter aortic valve replacement with the Sapien 3 prosthesis: a multicenter French registry. *JACC Cardiovasc Interv* 2019;12: 413-9.
24. Thourani VH, Kodali S, Makkar RR, et al. Transcatheter aortic valve replacement versus surgical valve replacement in intermediate-risk patients: a propensity score analysis. *Lancet* 2016;387:2218-25.
25. Kodali S, Pibarot P, Douglas PS, et al. Paravalvular regurgitation after transcatheter aortic valve replacement with the Edwards Sapien valve in the PARTNER trial: characterizing patients and impact on outcomes. *Eur Heart J* 2015;36:449-56.
26. Jilaihawi H, Kashif M, Fontana G, et al. Cross-sectional computed tomographic assessment improves accuracy of aortic annular sizing for transcatheter aortic valve replacement and reduces the incidence of paravalvular aortic regurgitation. *J Am Coll Cardiol* 2012;59:1275-86.
27. Jilaihawi H, Doctor N, Kashif M, et al. Aortic annular sizing for transcatheter aortic valve replacement using cross-sectional 3-dimensional transesophageal echocardiography. *J Am Coll Cardiol* 2013;61:908-16.
28. Willson AB, Webb JG, Labounty TM, et al. 3-Dimensional aortic annular assessment by multidetector computed tomography predicts moderate or severe paravalvular regurgitation after transcatheter aortic valve replacement: a multicenter retrospective analysis. *J Am Coll Cardiol* 2012;59:1287-94.
29. Wendler O, Schymik G, Treede H, et al. SOURCE 3 Registry: design and 30-day results of the European postapproval registry of the latest generation of the SAPIEN 3 transcatheter heart valve. *Circulation* 2017;135:1123-32.
30. Kodali S, Thourani VH, White J, et al. Early clinical and echocardiographic outcomes after SAPIEN 3 transcatheter aortic valve replacement in inoperable, high-risk and intermediate-risk patients with aortic stenosis. *Eur Heart J* 2016;37:2252-62.
31. Webb J, Gerosa G, Lefèvre T, et al. Multicenter evaluation of a next-generation balloon-expandable transcatheter aortic valve. *J Am Coll Cardiol* 2014;64: 2235-43.

Copyright © 2020 Massachusetts Medical Society.