Appropriate patient selection or health care rationing? Lessons from surgical aortic valve replacement in the Placement of Aortic Transcatheter Valves I trial

Wilson Y. Szeto, MD,^a Lars G. Svensson, MD, PhD,^{b,c} Jeevanantham Rajeswaran, PhD,^{b,d} John Ehrlinger, PhD,^d Rakesh M. Suri, MD,^c Craig R. Smith, MD,^e Michael Mack, MD,^f D. Craig Miller, MD,^g Patrick M. McCarthy, MD,^h Joseph E. Bavaria, MD,ⁱ Lawrence H. Cohn, MD,^j Paul J. Corso, MD,^k Robert A. Guyton, MD,^l Vinod H. Thourani, MD,^l Bruce W. Lytle, MD,^c Mathew R. Williams, MD,^m John G. Webb, MD,ⁿ Samir Kapadia, MD,^o E. Murat Tuzcu, MD,^o David J. Cohen, MD,^p Hartzell V. Schaff, MD,^q Martin B. Leon, MD,^{b,r} and Eugene H. Blackstone, MD,^{b,c,d} on behalf of the Placement of Aortic Transcatheter Valves Trial Investigators

ABSTRACT

Objectives: The study objectives were to (1) compare the safety of high-risk surgical aortic valve replacement in the Placement of Aortic Transcatheter Valves (PARTNER) I trial with Society of Thoracic Surgeons national benchmarks; (2) reference intermediate-term survival to that of the US population; and (3) identify subsets of patients for whom aortic valve replacement may be futile, with no survival benefit compared with therapy without aortic valve replacement.

Methods: From May 2007 to October 2009, 699 patients with high surgical risk, aged 84 ± 6.3 years, were randomized in PARTNER-IA; 313 patients underwent surgical aortic valve replacement. Median follow-up was 2.8 years. Survival for therapy without aortic valve replacement used 181 PARTNER-IB patients.

Results: Operative mortality was 10.5% (expected 9.3%), stroke 2.6% (expected 3.5%), renal failure 5.8% (expected 12%), sternal wound infection 0.64% (expected 0.33%), and prolonged length of stay 26% (expected 18%). However, calibration of observed events in this relatively small sample was poor. Survival at 1, 2, 3, and 4 years was 75%, 68%, 57%, and 44%, respectively, lower than 90%, 81%, 73%, and 65%, respectively, in the US population, but higher than 53%, 32%, 21%, and 14%, respectively, in patients without aortic valve replacement. Risk factors for death included smaller body mass index, lower albumin, history of cancer, and prosthesis–patient mismatch. Within this high-risk aortic valve replacement group, only the 8% of patients with the poorest risk profiles

Survival after AVR in PARTNER-IA referenced to expected survival in an age-, sex-, and race-matched US population (dash-dot-dash line).

Central Message

PARTNER selection criteria for surgical AVR, with a few caveats, may be more appropriate indications for surgery than those of the past.

Perspective

PARTNER-IA patients experienced average early results and prolonged hospitalization, suggesting that contemporary benchmarks need to be updated for high-risk patients. Unlike in past surgical series, PARTNER-IA patients had worse survival, suggesting they were less selected. PARTNER selection criteria for surgical AVR, with a few caveats, may be more appropriate indications for surgery than those of the past.

See Editorial Commentary page 569.

From the ^aDivision of Cardiovascular Surgery, University of Pennsylvania Health System, Philadelphia, Pa; ^bPlacement of Aortic Transcatheter Valves Publications Office; ^cDepartment of Quantitative Health Sciences, Cleveland Clinic, Cleveland, Ohio; ^dDepartment of Thoracic and Cardiovascular Surgery, Cleveland Clinic, Cleveland, Ohio; ^eDepartment of Surgery, Columbia University Medical Center/New York Presbyterian Hospital, New York, NY; ^fCardiovascular Surgery, Baylor Scott & White Health, Plano, Tex; ^gDepartment of Cardiovascular Surgery, Falk Cardiovascular Research Center, Stanford University School of Medicine, Stanford, Calif; ^hCardiac Surgery, Northwestern Memorial Hospital, Chicago, Ill; ⁱDivision of Thoracic Surgery, University of Pennsylvania Health System, Philadelphia, Pa; ^jDepartment of Surgery, Brigham and Women's Hospital, Boston, Mass; ^kDepartment of Cardiac Surgery, Medstar Washington Hospital Center, Washington, DC; ^lDepartment of Surgery, Division of Cardiothoracic Surgery, Emory University Hospital, Atlanta, Ga; ^mDepartment of Cardiothoracic Surgery & Department of Medicine, New York University, Langone Medical Center, New York, NY; ⁿDivision of Cardiology, Department of Medicine, St Paul's Hospital, University of British Columbia, Vancouver, British Columbia, Canada; ^oDepartment of Cardiovascular Medicine, Cleveland Clinic, Cleveland, Ohio; ^pDivision of Cardiology, St. Luke's Mid-America Heart Institute, Kansas City, Mo; ^qCardiac

Surgery, Mayo Clinic, Rochester, Minn; and ^rCenter for Interventional Vascular Therapy, Division of Cardiology, Department of Medicine, Columbia University Medical Center/New York Presbyterian Hospital, New York, NY.

Trial Registration: <http://clinicaltrials.gov/ct2/show/NCT00530894>; NCT00530894.

Data used for this study were from an October 20, 2012, locked data extract from Edwards Lifesciences to the PARTNER Publications Office. Data analysis was performed by investigators at the Cleveland Clinic, with no sponsor involvement in the proposal and design for this substudy, analysis, interpretation, or decision to publish.

Read at the 95th Annual Meeting of The American Association for Thoracic Surgery, Seattle, Washington, April 25-29.

Received for publication Jan 7, 2015; revisions received April 22, 2015; accepted for publication May 6, 2015; available ahead of print Aug 1, 2015.

Address for reprints: Eugene H. Blackstone, MD, Cleveland Clinic Heart and Vascular Institute, Clinical Investigations, 9500 Euclid Ave, JJ4, Cleveland, OH 44195 (E-mail: blackse@ccf.org).

0022-5223/\$36.00

Copyright © 2015 by The American Association for Thoracic Surgery
<http://dx.doi.org/10.1016/j.jtcvs.2015.05.073>

Abbreviations and Acronyms

AVR	= aortic valve replacement
CABG	= coronary artery bypass grafting
PARTNER	= Placement of Aortic Transcatheter Valves
STS	= Society of Thoracic Surgeons
TAVR	= transcatheter aortic valve replacement

had estimated 1-year survival less than that of similar patients treated without aortic valve replacement.

Conclusions: PARTNER selection criteria for surgical aortic valve replacement, with a few caveats, may be more appropriate, realistic indications for surgery than those of the past, reflecting contemporary surgical management of severe aortic stenosis in high-risk patients at experienced sites. (*J Thorac Cardiovasc Surg* 2015;150:557-68)

Supplemental material is available online.

Surgical aortic valve replacement (AVR) is being challenged by transcatheter technology for patients considered at high surgical risk. Simultaneously, there is increasing pressure on institutions to improve quality outcomes—measured by patient safety indicators and process-of-care metrics—while reducing costs of medical care. Surgeons contemplating operations on high-risk elderly patients with complex comorbid disease in addition to severe aortic stenosis risk failing these quality metrics; therefore, they may refer them for transcatheter AVR (TAVR) or deem them inoperable.¹

The Placement of Aortic Transcatheter Valves (PARTNER) trial provides insight into outcomes after surgical AVR in high-risk patients at the extreme of traditional indications for surgical AVR.² Using the trial, we sought answers to 3 questions:

1. Are national surgical outcomes after high-risk AVR accurately predicted by benchmarks?^{3,4} We hypothesized that contemporary benchmarks underestimate risk at the extreme few percent of nationwide practice.
2. Is intermediate-term survival after high-risk AVR commensurate with that of the matched general population? We hypothesized that survival is shorter, contrasting with past reports on survival after AVR in the elderly.^{5,6}
3. Is there a subset of elderly patients whose risk of mortality after AVR is exceptionally high? We hypothesized

that there are identifiable subsets of patients for whom high-risk surgical AVR is not indicated because their survival is worse than treatment without AVR.

MATERIALS AND METHODS**Study Population and Design**

From May 2007 to October 2009, 699 patients with severe symptomatic aortic stenosis who were deemed high risk for surgical AVR by a heart team were enrolled in PARTNER-IA. “High risk for surgical AVR” was determined in part by a Society of Thoracic Surgeons (STS) predicted hospital mortality of 10% or greater and operative mortality of 15% or greater, based on an STS algorithm generated from data gathered nationwide from 1994 through 1997.⁷ Other patient selection criteria included those for symptoms, comorbidities, aortic valve area, and likelihood of survival for 12 months ([Appendix E1](#)).

Patients were randomized 1:1 to surgical AVR or TAVR. Of the 351 patients randomized to surgical AVR, 313 actually underwent AVR (as-treated cohort) by 22 experienced cardiac surgical teams, 28 withdrew, refusing therapy, and 10 deteriorated to an inoperable state ([Figure E1](#)).⁸

The patients were elderly (mean age, 84 ± 6.3 years) and symptomatic, with 95% in New York Heart Association class III or IV ([Table 1](#)). Aortic stenosis was severe, with a valve area averaging 0.64 ± 0.19 cm², and mean and peak valve gradients of 43 ± 14 mm Hg and 73 ± 24 mm Hg, respectively. The patients had many comorbidities: coronary artery disease in 77%, peripheral arterial disease in 67%, prior stroke in 35%, diabetes in 41%, chronic pulmonary disease in 47%, renal disease in 22%, and cancer in 14%. Iliofemoral arteries were deemed not conducive to transfemoral TAVR in 29% of patients.

Surgical Aortic Valve Replacement

The technique for AVR was at the discretion of the surgeon, including invasiveness (full sternotomy [78%], less invasive [22%]), myocardial management, cannulation technique, and core systemic cooling temperature ([Table 2](#)). The use of Edwards Lifesciences (Irvine, Calif) stented bovine pericardial bioprostheses was strongly encouraged by protocol (87% of prostheses implanted). In 233 patients (75%), a 21-mm or 23-mm prosthetic valve was implanted; 12% of patients received a 19-mm valve.

End Points

Procedure safety. The primary safety end points comprised national quality benchmarks for surgical AVR: in-hospital stroke, renal failure, deep sternal wound infection, postoperative length of stay less than 6 days, postoperative length of stay more than 14 days, and operative mortality (death during hospitalization or within 30 days of operation regardless of venue), defined according to the STS National Database (http://www.sts.org/sites/default/files/documents/STSAAdultCVDDataSpecificationsV2_81.pdf).

Intermediate-term survival. Intermediate-term procedure effectiveness (benefit) was evaluated by survival. Median follow-up was 2.8 years; 25% of survivors were followed for more than 3 years, and 10% were followed for more than 4 years. A total of 681 patient years of data were available for analyses of all-cause mortality.

Data Analysis

Data used were from an October 20, 2012, locked data extract from Edwards Lifesciences to the PARTNER Publications Office. Data analysis was performed by PARTNER Publications Office statisticians, with no sponsor involvement in the proposal development, study design, data analysis and interpretation, or decision to publish. The institutional review board at each participating site approved the trial, and all patients provided written informed consent. Data were analyzed using SAS software version 9.2 (SAS Institute Inc, Cary, NC) and R software version 3.0.2.⁹

TABLE 1. Preprocedural patient characteristics

Characteristic	n*	No. (%) or mean $\pm$ SD
Demographics		
Female	313	134 (43)
Age (y)	313	84 $\pm$ 6.3
Body mass index (kg/m ²)	311	27 $\pm$ 5.7
Candidate for TF access	313	
No		92 (29)
Yes		221 (71)
Symptoms		
NYHA functional class	313	
I		0 (0)
II		16 (5.1)
III		134 (43)
IV		163 (52)
Baseline echocardiographic measurements		
AV peak velocity (cm/s)	300	422 $\pm$ 70
AV area (cm ²)	297	0.64 $\pm$ 0.19
AV area index (mL/m ²)	295	0.35 $\pm$ 0.10
AV mean gradient (mm Hg)	302	43 $\pm$ 14
AV peak gradient (mm Hg)	302	73 $\pm$ 24
Ejection fraction (%)	304	53 $\pm$ 12
Cardiac comorbidity		
Coronary artery disease	313	241 (77)
Previous myocardial infarction	310	90 (29)
Atrial fibrillation	313	69 (22)
Noncardiac comorbidity		
Peripheral arterial disease	313	210 (67)
Cerebral vascular disease including carotid arterial disease	313	108 (35)
Carotid arterial disease	313	75 (24)
Prior stroke	313	54 (17)
Stroke or TIA within last 6-12 mo	313	9 (2.9)
Diabetes	313	128 (41)
Smoking	313	156 (50)
Chronic pulmonary disease	313	147 (47)
Hypertension	313	294 (94)
Hyperlipidemia	313	263 (84)
Renal disease	313	69 (22)
Hepatic disease	313	9 (2.9)
Cancer	310	43 (14)
Albumin (g/dL)	247	3.7 $\pm$ 0.52
Previous procedures		
Percutaneous coronary intervention	312	101 (32)
CABG	313	140 (45)
1 previous operation	313	112 (36)
2 previous operations	313	24 (7.7)
3 previous operations	313	3 (0.96)
Missing	313	1 (0.31)
Pacemaker	313	70 (22)
Predicted operative mortality		
By benchmark available at time of enrollment (%)	313	12 $\pm$ 3.4

AV, Aortic valve; CABG, coronary artery bypass grafting; NYHA, New York Heart Association; SD, standard deviation; TF, transfemoral; TIA, transient ischemic attack.

*Patients with data available.

TABLE 2. Details of surgical aortic valve replacement

Detail	n*	No. (%) or mean $\pm$ SD
Incision	312	
Full sternotomy		243 (78)
Partial sternotomy		51 (16)
Thoracotomy		18 (5.8)
Aortic valve prosthesis		
Valve size (mm)	310	
19		37 (12)
21		124 (40)
23		109 (35)
25		37 (12)
27		3 (0.97)
Prosthesis type	313	
Edwards Lifesciences (Irvine, Calif)		273 (87)
St Jude Medical Inc (St Paul, Minn)		3 (0.95)
CarboMedics Inc mechanical (Austin, Tex)		4 (1.3)
Medtronic (Minneapolis, Minn)		12 (3.8)
Sorin (Milan, Italy)		7 (2.2)
Unspecified porcine		1 (0.32)
Unspecified		13 (4.2)
Concomitant procedure		
Unanticipated CABG	313	21 (6.7)
Support		
Aortic clamp time (min)	294	74 $\pm$ 29
Cardiopulmonary bypass time (min)	283	105 $\pm$ 41

CABG, Coronary artery bypass grafting; SD, standard deviation. *Patients with data available.

Procedure safety referenced to contemporaneous Society of Thoracic Surgeons benchmarks. Hospital morbidity and operative mortality were compared with contemporaneous STS benchmarks generated from national surgical experience from 2002 through 2006.^{3,4} For this, PARTNER database variables were transformed as necessary into STS Version 2.61 variables (Table E1) and STS-certified equations solved for expected risks. Confidence intervals for observed-to-expected ratios were estimated by the bootstrap percentile method,¹⁰ and comparisons between observed and expected frequencies used the chi-square goodness-of-fit test.

Survival referenced to population life tables. Survival was estimated nonparametrically by the Kaplan-Meier estimator and parametrically by a multiphase hazard model.¹¹ The parametric model resolved distinct phases of instantaneous risk of death (hazard function) by temporal decomposition, a method chosen because nonproportional hazards were evident. For each patient, expected survival was estimated from 2008 US life tables based on age, sex, and race.¹² These were averaged across time as a population reference.

Risk factors for all-cause mortality. Incremental risk factors were identified simultaneously within each hazard phase, with a *P* value criterion for retention of variables in the model of .05. Variable selection from 102 possible risk factors (Appendix E2) used bagging (bootstrap aggregation),^{13,14} a method suited to screening a large number of variables compared with number of events. For this, 1000 bootstrap datasets were generated, and variables were selected using automated forward stepwise selection. Variables selected in at least 50% of models were retained in the final analysis. Results are illustrated using Random Forests for Survival, a nonparametric machine-learning method that permits graphic display of risk-adjusted relationships of continuous variables to survival (partial dependency plots) without model assumptions.^{15,16}

TABLE 3. Observed versus expected outcomes after surgical aortic valve replacement, based on contemporary Society of Thoracic Surgeons benchmarks^{3,4}

Outcome	Observed no. (%)	Expected no. (%)	Observed/expected (68% CL)	P value
Operative mortality*	33 (10)	29 (9.3)	1.14 (1.01-1.29)	.4
Stroke	8 (2.6)	11 (3.5)	0.73 (0.55-0.94)	.4
Renal failure	18 (5.8)	38 (12)	0.48 (0.38-0.60)	.0008
Deep sternal wound infection	2 (0.64)	1.03 (0.33)	1.94 (0.91-3.1)	.3
Postoperative length of stay >14 d	83 (26)	56 (18)	1.48 (1.36-1.62)	<.0001

CL, Confidence limit. *In-hospital mortality plus any death occurring out-of-hospital within 30 days of surgery.

Survival referenced to therapy without valve replacement. In the PARTNER-I randomized trial, 181 patients who were considered inoperable were randomized to management without valve replacement (PARTNER-IB) (Figure E1).¹⁷ A parsimonious survival model for patients in PARTNER-IB was developed using all preprocedural and valve-related characteristics listed in Appendix E2 and bootstrap aggregation methodology as described previously. A multivariable hazard model was also developed for the surgical AVR group based on pre-AVR factors alone. Finally, a semisaturated model was generated for patients in PARTNER-IB that included not only their parsimonious risk factors but also those identified as pre-AVR risk factors (Table E2). This model was solved for each surgical AVR patient and averaged to estimate risk-adjusted survival had surgical AVR not been performed.

Missing values. To account for missing values for some variables in multivariable modeling, we performed 5-fold multiple imputation using a Markov chain Monte Carlo technique¹⁸ to yield final regression coefficient estimates, the variance-covariance matrix, and *P* values.

Presentation. Continuous variables are summarized as mean $\pm$ standard deviation or as equivalent 15th, 50th (median), and 85th percentiles when distribution of values is skewed. Categorical variables are summarized by frequencies and percentages.

RESULTS

Procedure Safety Referenced to Contemporaneous Society of Thoracic Surgeons Benchmarks

In-hospital mortality was 9.6% (*n* = 30), 30-day mortality was 8.0% (*n* = 25), and operative mortality (in-hospital or within 30 days) was 10.5% (*n* = 33). In-hospital stroke was 2.6% (*n* = 8), and combined in-hospital death or stroke was 12% (*n* = 37). Postoperative myocardial infarction occurred in 1 patient (0.32%), new-onset renal failure requiring dialysis occurred in 18 patients (5.8%), bleeding events requiring transfusion occurred in 58 patients (19%), and deep sternal wound infection occurred in 2 patients (0.64%). A new permanent pacemaker was implanted in 12 patients (4.9%).

In general, occurrences of operative mortality (Figure E2), stroke (Figure E3), and deep sternal wound infection were consistent with contemporaneous STS benchmarks (Table 3). Operative mortality was lower than recorded at the time of trial entry using noncontemporaneous benchmarks (Figure E4). Renal failure occurred less often than expected (Figure E5), but postoperative length of stay was longer (Figure E6). However, calibration of observed-to-expected risk for these outcomes was poor.

Metrics not benchmarked by the STS include home discharge in 78% of patients and New York Heart

Association functional class I or II in 86% of patients at 6 months after surgery (Table E3).

Survival Referenced to Matched US Population

Survival at 1, 2, 3, and 4 years after surgical AVR was 75%, 68%, 57%, and 44%, respectively (Figure 1). After a phase of high risk of death immediately after AVR, instantaneous risk became briefly similar to that of the matched US population before accelerating well above it (Figure 1, inset). The combined effect of these was that overall survival remained well below that of the matched US population through the end of follow-up.

Risk Factors for Death After Surgical Aortic Valve Replacement

Incremental risk factors for death in the high early hazard phase (Table 4) were low albumin, particularly less than 3 g/dL (Figure 2, A), and longer aortic clamp time (Figure 2, B); prior coronary artery bypass grafting (CABG) was associated with a lower risk of early death (Figure 3, A). Risk factors for mid-term death were small body mass index, particularly less than 22 kg/m² (Figure 2, C), history of cancer (Figure 3, B), and severe (<0.65 cm²/m²) prosthesis-patient mismatch (Figure 3, C). Effective orifice area, from which prosthesis-patient mismatch is derived, less than 1 cm²/m² was associated with a near-linear decrease in 1-year survival (Figure 2, D). Although older age was not identified as a reliable risk factor in the parametric analysis, Random Forests analysis suggested that 1-year mortality became progressively higher beyond age 88 years (Figure E7).

Survival Referenced to Therapy Without Valve Replacement

Survival predicted for surgical AVR patients compared with survival without AVR showed no survival benefit at 6 months (79% vs 70%) because of the high early risk after surgery, but there was a substantial mid-term survival benefit: 75% versus 53% at 1 year, 68% versus 32% at 2 years, 57% versus 21% at 3 years, and 44% versus 14% at 4 years (Figure E8, A and B).

Predicted survival after surgical AVR varied widely depending on patient risk factor profiles (Figure E9), with some combinations of risk factors predicting less than 50% survival at 1 year and less than 10% at 4 years. In contrast,

FIGURE 1. Survival after AVR in PARTNER-IA, referenced to expected survival in an age-, sex, and race-matched US population. Each symbol represents a death. Vertical bars are confidence limits of nonparametric Kaplan-Meier estimates equivalent to ± 1 standard error, and the solid line enclosed within a dashed 68% confidence band equivalent to ± 1 standard error represents parametric estimates. Numbers below the horizontal axis are patients remaining at risk. Dash-dot-dash line represents age-, sex-, and race-matched expected survival in the US population. Inset shows instantaneous risk of death (hazard function) referenced to an age-, sex, and race-matched US population. AVR, Aortic valve replacement.

other profiles predicted 95% survival at 1 year and 80% at 4 years. In total, only 8% of patients undergoing surgical AVR were predicted to have worse 1-year survival than patients deemed inoperable, and an even smaller proportion were predicted to have worse survival thereafter (Figures 4 and E10).

DISCUSSION

Principal Findings

Contrary to our first hypothesis, mortality and morbidity after AVR in these high-risk elderly patients were commensurate with contemporaneous STS benchmarks, except for prolonged length of stay.^{3,4} This contrasts with estimated mortality at PARTNER trial enrollment that relied on an

older benchmark.⁷ However, we caution that the sites selected for the trial tended to have risk-adjusted STS mortalities below the national average, so underestimation of risk by contemporary STS models may still exist. This caution is particularly important in light of longer than expected postoperative length of stay and the lack of close calibration of estimates within the high-risk range.

Supporting our second hypothesis is the finding that intermediate-term survival of these AVR patients was distinctly below that of the age-, sex-, and race-matched US population, with approximately 20% mortality within 6 months of surgery and accelerating risk among survivors thereafter. This differs from previous studies demonstrating

TABLE 4. Incremental risk factors for death after surgical aortic valve replacement

Risk factor	Coefficient $\pm$ SE	P value	Hazard ratio (68% CI)	Reliability (%)*
Early decreasing hazard				
Previous CABG (less risk)	-0.57 ± 0.29	.03	0.57 (0.42-0.76), Figure 3, A	88
Lower albumin†	7.0 ± 3.4	.05	Figure 2, A	51
Longer aortic clamp time‡	0.95 ± 0.36	.009	Figure 2, B	60
Intermediate-term hazard				
Smaller BMI§	0.99 ± 0.39	.01	Figure 2, C	64
History of cancer	0.86 ± 0.31	.006	2.4 (1.7-3.2), Figure 3, B	59
Severe prosthesis–patient mismatch	0.77 ± 0.27	.004	2.2 (1.6-2.8), Figure 3, C	86

BMI, Body mass index; CABG, coronary artery bypass grafting; CI, confidence interval; SE, standard error. *Percent of times variables appeared in 1000 bootstrap models. †(1/albumin), inverse transformation. ‡Log (aortic clamp time/75), logarithmic transformation. §(25/BMI)², inverse squared transformation.

FIGURE 2. Random Forest for Survival partial dependency plots of 1-year predicted survival. Random Forest for Survival is a completely nonparametric method for survival analysis that, in this case, was based on all 102 variables used in the multivariable parametric analysis.^{15,16,E11} Each graph presents a risk-adjusted estimate of the independent effect of a continuous variable identified as a risk factor in the parametric analysis; however, these depictions make no model assumptions. Circles and solid lines represent risk-adjusted estimates, and dashed lines indicate the 68% confidence band equivalent to ± 1 standard error. A, Albumin (g/dL). B, Aortic clamp time (min). C, Body mass index (kg/m²). D, Effective prosthetic aortic valve orifice area at hospital discharge by echocardiography (cm²/m²).

that elderly patients selected for surgical AVR experience mortality commensurate with that of their population counterparts, but younger patients have distinctly worse survival (Figure E11).^{5,6,19-21} A reasonable explanation for this paradox is that elderly patients with severe aortic stenosis undergoing surgical AVR reported in these studies were an even more selected population than the patients meeting selection criteria for PARTNER-IA, perhaps partly accounting for the many patients whose aortic stenosis has gone surgically untreated.²²

Finally, as we hypothesized, several risk factors predict worse survival after high-risk AVR than treatment without valve replacement in inoperable patients: albumin less than 3 g/dL,²³ cardiac cachexia with body mass index less than 22 kg/m²,^{24,25} and cancer. This highlights an important observation made during review of this article. Patients were deemed high surgical risk for 2 reasons: (1) surgical challenges, such as reoperation and porcelain aorta; and (2) comorbidities. Patients likely to do well long-term are those

with surgical challenges that are overcome; those likely to do less well are those with important comorbid disease and combinations thereof. Although surgical AVR may be considered futile for the latter patients, TAVR may be appropriate if performed with outcomes commensurate with contemporary national benchmarks and survival superior to that of inoperable PARTNER-IB patients.

Surgical Aortic Valve Replacement in High-Risk Patients

Despite PARTNER-IA being composed of high-risk patients, good intermediate-term survival was observed after AVR. Thus, the classic indication for surgery—that benefit should exceed risk in terms of mortality—would suggest that, with the exceptions noted in the previous section, high-risk patients with severe aortic stenosis otherwise meeting PARTNER inclusion and exclusion criteria (Appendix E1) can be considered possible candidates for surgical AVR and TAVR.

FIGURE 3. Unadjusted Kaplan-Meier estimates of survival after surgical AVR. Each symbol represents a death. Vertical bars are 68% confidence limits equivalent to ± 1 standard error. Numbers below the horizontal axis are patients remaining at risk. A, Survival stratified by prior CABG (*squares*) or not (*circles*). B, Survival stratified by history of cancer (*squares*) or not (*circles*). C, Survival stratified by degree of prosthesis–patient mismatch: none/mild (*circles*), moderate (*squares*), severe (*triangles*). AVR, Aortic valve replacement; CABG, coronary artery bypass grafting.

Comorbidities													
Patient	Age (y)	BMI (kg/m ²)	NYHA	Mixed AR/AS	CABG	Pacemaker	BAV	Cancer	HCT (%)	Albumin (g/dL)	Stroke Volume Index (mL/m ²)	WBC	LV Mass Index (g/m ²)
A	70	36	II	No	No	No	No	Yes	39	2.9	28	17	192
B	90	27	III	No	No	No	No	Yes	35	3.04	30	4.9	70
C	86	21	II	Yes	Yes	No	No	Yes	29	3.5	39	4.9	141

FIGURE 4. Profile of patients who are likely to have worse 1-, 2-, and 3-year survival after surgical AVR than after contemporary standard therapy (“natural history”). These curves are solutions from the multivariable equations in Table E2. Values for the 3 patients illustrated are in the above table. A, A 70-year-old obese patient with low albumin and considerable left ventricular hypertrophy. Note that after a prolonged early phase of surgical risk, long-term risk is better than standard therapy and survival curves cross. B, A 90-year-old patient with moderate symptoms, albumin 3.04 g/dL, and a left ventricular mass index of only 70 g/m². Note that to 4 years, survival after surgical AVR is predicted to be worse than after standard therapy. C, An 86-year-old patient with cardiac cachexia, mixed severe aortic stenosis and aortic regurgitation, and ischemic heart disease previously treated with CABG. This patient is predicted to do well after surgery, but then to have elevated mid-term risk. Survival with standard therapy also is reasonable. Thus, subjecting the patient to surgical AVR is not expected to increase the patient’s longevity. AVR, Aortic valve replacement; BMI, body mass index; NYHA, New York Heart Association; AR, aortic regurgitation; AS, aortic stenosis; CABG, coronary artery bypass grafting; BAV, balloon aortic valvotomy; HCT, hematocrit; WBC, white blood cell; LV, left ventricle.

Severe prosthesis–patient mismatch was associated with elevated mid-term death, as shown by others.^{26–28} However, some have questioned the clinical relevance in elderly high-risk patients with limited functional capacity and physiologic requirements.²⁷ In the PARTNER-I surgical AVR cohort, severe mismatch occurred in one third of patients. Explanation for such a high prevalence is multifactorial. First, this was a high-risk cohort of patients, many with a small and heavily calcified aortic annulus. Second, stented bioprostheses from a single vendor were predominately used, by protocol. Newer stented and stentless bioprostheses with improved hemodynamic characteristics were implanted in only 13% of patients. Third, root enlargement enabling implantation of larger prostheses was not allowed by study protocol. Fourth, many patients had “low flow,” which may have resulted in inaccurate estimation of prosthetic valve effective orifice area. Thus, in high-risk elderly patients, strategies to avoid mismatch should be considered during surgical AVR.

Previous CABG was associated with lower early mortality after AVR, despite increased surgical complexity, although coexisting coronary artery disease has been associated with elevated risk,^{29,30} and previous CABG or percutaneous coronary intervention is its surrogate. Risk assessment models take these into consideration when calculating operative risk.⁴ However, as surgical AVR has matured, it can be performed safely in the setting of previous CABG.^{31–33}

Findings Placed in the Context of Today’s Health Care Climate (Appendix E3^{E1–E15})

Indication for surgical AVR in patients with severe aortic stenosis is based classically on a positive benefit-to-risk ratio of prolonged life expectancy of greater quality than that of natural history.³⁴ In real life, however, decisions for or against surgery are also influenced by referring physicians and cardiologists, and, increasingly, institutional quality rankings and alignment of physicians with institutions.^{35,E1,E2}

Cardiac surgeons and institutions are being pressured to reduce short-term risk of CABG and AVR to less than 1% risk-adjusted mortality, and comply with all process measures to achieve STS “3-star” status. To achieve this with a mature technology such as AVR, and with an increasing number of institutions near or at 100% compliance with process measures, requires streamlined processes, experienced surgeons, and higher costs. It also requires risk-adjusted benchmarks that are accurate at the extreme end of the age and comorbidity ranges so as not to penalize those operating on high-risk patients. This is because sicker patients in other settings often have benefited the most long-term from complex procedures, despite higher early risk.^{E3,E4} Yet, the Northern New England Group showed that better unadjusted results of operations such as CABG for ischemic heart disease were largely related to patient selection, namely, performing fewer emergency operations.^{E5,E6} Thus, for this and other reasons, “salvage operations” are becoming rare, and

high-risk patients are being bridged with various mechanical devices rather than undergoing operations that could negatively affect a surgeon's or institution's reputation.^{E7} This behavior may reflect lack of understanding of the risk-adjustment process or the belief that present benchmark algorithms do not adequately account for rare conditions that elevate actual risk above the benchmarks, leading to poor calibration and penalty for performing operations in these patients. If surgeons and hospitals are not incentivized to offer high-risk surgical operations, but instead penalized for doing them, availability of care yielding long-term patient survival benefit may be restricted.^{E8,E9}

Prior studies of long-term survival after AVR suggest that “rationing” of care for high-risk patients with aortic stenosis has occurred under the rubric of “careful patient selection.” Evidence of this is that, paradoxically, the older the patient who has undergone AVR, the more likely he or she will survive as long as expected for the general population.^{5,6} This paradox suggests that physicians and surgeons recommending AVR have selected patients they believed had a reasonable chance of low operative risks and prolonged survival after AVR. These patients then become benchmarks for quality outcomes, such as those from the STS National Cardiac Database, introducing a bias into quality benchmarks that may underestimate risk for higher-risk patients.^{3,4} This is being addressed by gathering data on patients undergoing TAVR from the STS database.

If high-risk patients can undergo AVR with safety comparable to national benchmarks, then at what level of operative risk, life expectancy, and quality of life should AVR be considered prohibitive?^{E9} Our risk-adjusted analysis indicates that most patients enrolled in the high-risk arm of PARTNER-IA experienced a survival benefit from surgical AVR versus no valve replacement. This suggests that PARTNER selection criteria were appropriate, with the exception of cachectic, malnourished patients. These criteria for surgical AVR were more liberal than has been practiced in “real world” health care environments and suggest that the expected higher risk should be accepted. However, results of contemporary medical therapy and TAVR also must be considered to avoid futile or harmful valve replacement. Indeed, with the maturation of TAVR and technologic developments leading to reduction of paravalvular leak and improvement in periprocedural outcomes, appropriateness of AVR versus TAVR for high-risk patients should be further assessed.

Study Limitations

PARTNER-IA was not a randomized trial of no valve replacement versus surgical AVR for high-risk patients; however, PARTNER-IB showed that, on average, survival after TAVR was considerably better than no valve

replacement in inoperable patients,¹⁷ and parallel studies have shown that AVR and TAVR have similar outcomes.² Granted, PARTNER-IB patients were deemed inoperable, so they represent an even more high-risk population with aortic stenosis than in PARTNER-IA. However, this does not mean they have nothing in common. We believe they provided a reference group that has allowed us to identify patients in the surgical series who are predicted to have worse survival after surgical AVR than if they had not undergone an operation. Most such patients also are predicted to have a survival benefit from TAVR.¹⁷

The trial was not designed to assess a priori targets of quality metrics, but procedure safety indicators that could be translated into STS outcomes were collected. Although many metrics met STS benchmarks, there was considerable scatter in calibration. This may reflect the small effective sample size (number of events) for these metrics or possible deficiencies of the STS models for extreme risk profiles.

The trial limited the type of prosthesis that could be used. Use of more efficient contemporary bioprostheses may have reduced prosthesis patient mismatch. Likewise, more frequent use of less-invasive incisions may have reduced morbidity.

The scope of this study is also limited to procedure safety and time-related mortality; it does not address patient frailty—incompletely assessed in PARTNER-I—or subsequent ventricular remodeling, patient-reported disease-specific functional health status and quality of life, patient-specific utilities, or health care costs, all of which must be considered in a complete risk-benefit-value assessment.^{E10}

Finally, there were many exclusion criteria for PARTNER-IA (Appendix E1), so that although we believe the evidence points to more selection bias in past surgical practice, PARTNER-IA patients do not represent an unselected population.

CONCLUSIONS

Despite surgical AVR being performed in institutions whose results generally outpace national benchmarks, PARTNER-IA patients experienced average early results and prolonged hospitalization, suggesting that contemporary benchmarks may not discriminate across high-risk profiles and require future updating from results of TAVR procedures. Unlike past surgical series, in which survival of elderly patients was commensurate with a matched US population, PARTNER-IA patients had worse survival, suggesting they were a less-selected population, thus providing expanded indications for surgical AVR. After a period of higher early mortality, most PARTNER-IA patients experienced better mid-term survival than inoperable PARTNER-IB patients, suggesting that PARTNER selection criteria for surgical AVR, with a few caveats, may be more appropriate, realistic indications for surgery than those of the past, reflecting contemporary surgical management of severe aortic stenosis in high-risk patients at experienced sites.

Conflict of Interest Statement

Dr Szeto is an investigator for Edwards Lifesciences; Dr Svensson is on executive committees for Edwards Lifesciences PARTNER and Prospective, Nonrandomized, Multi-center Clinical Evaluation of Edwards Pericardial Bioprostheses With a New Tissue Treatment Platform (COMMENCE) trials; Dr Suri is a member of the Clinical Steering Committee at Abbott and St Jude Medical, consults with Sorin and Abbott, has a patent application with Sorin, and does research with Sorin, Edwards Lifesciences, Abbott, and St Jude Medical; Dr Smith is a PARTNER trial investigator for Edwards Lifesciences; Dr Mack is a PARTNER trial executive committee member for Edwards Lifesciences; Dr Miller consults with Abbott Vascular Structural Heart, GenTAC, Medtronic Cardiovascular Division, and Edwards Lifesciences PARTNER trial, and is an investigator for the PARTNER trial; Dr McCarthy consults with Edwards Lifesciences; Dr Bavaria is an investigator for Edwards Lifesciences, Medtronic CoreValve, St Jude Portico, and Boston Scientific, and an executive committee member for Boston Scientific; Dr Guyton consults with Medtronic; Dr Thourani consults with Edwards Lifesciences; Dr Williams consults with Edwards Lifesciences; Dr Webb consults with Edwards Lifesciences and is an executive committee member and investigator for the PARTNER trial; Dr Cohen consults with Medtronic and is an investigator for Medtronic, Edwards Lifesciences, and Boston Scientific; Dr Blackstone is on executive committees for Edwards Lifesciences PARTNER and COMMENCE trials and leads the Cleveland Clinic PARTNER Publications Office. All other authors have nothing to disclose with regard to commercial support.

You can watch a Webcast of this AATS meeting presentation by going to: http://webcast.aats.org/2015/Video/Monday/04-27-15_4E_1400_Szeto.mp4.

References

- Moscucci M, Eagle KA, Share D, Smith D, De Franco AC, O'Donnell M, et al. Public reporting and case selection for percutaneous coronary interventions: an analysis from two large multicenter percutaneous coronary intervention databases. *J Am Coll Cardiol*. 2005;45:1759-65.
- Smith CR, Leon MB, Mack MJ, Miller DC, Moses JW, Svensson LG, et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. *N Engl J Med*. 2011;364:2187-98.
- O'Brien SM, Shahian DM, Filardo G, Ferraris VA, Haan CK, Rich JB, et al. The Society of Thoracic Surgeons 2008 cardiac surgery risk models: part 2—isolated valve surgery. *Ann Thorac Surg*. 2009;88:S23-42.
- Shahian DM, O'Brien SM, Filardo G, Ferraris VA, Haan CK, Rich JB, et al. The Society of Thoracic Surgeons 2008 cardiac surgery risk models: part 3—valve plus coronary artery bypass grafting surgery. *Ann Thorac Surg*. 2009;88:S43-62.
- Blackstone EH, Cosgrove DM, Jamieson WR, Birkmeyer NJ, Lemmer JH Jr, Miller DC, et al. Prosthesis size and long-term survival after aortic valve replacement. *J Thorac Cardiovasc Surg*. 2003;126:783-96.
- Beach JM, Mihaljevic T, Rajeswaran J, Marwick T, Edwards ST, Nowicki ER, et al. Ventricular hypertrophy and left atrial dilatation persist and are associated with reduced survival after valve replacement for aortic stenosis. *J Thorac Cardiovasc Surg*. 2014;147:362-9.
- Edwards FH, Peterson ED, Coombs LP, DeLong ER, Jamieson WR, Shroyer ALW, et al. Prediction of operative mortality after valve replacement surgery. *J Am Coll Cardiol*. 2001;37:885-92.
- Svensson LG, Blackstone EH, Rajeswaran J, Brozzi N, Leon MB, Smith CR, et al. Comprehensive analysis of mortality among patients undergoing TAVR: results of the PARTNER trial. *J Am Coll Cardiol*. 2014;64:158-68.
- R Development Core Team. *R: a language and environment for statistical computing*. Vienna, Austria: Foundation for Statistical Computing; 2013. Available at: <http://www.R-project.org>.
- Efron B, Tibshirani RJ. *An Introduction to the Bootstrap*. New York: Chapman and Hall/CRC; 1994.
- Blackstone EH, Naftel DC, Turner ME Jr. The decomposition of time-varying hazard into phases, each incorporating a separate stream of concomitant information. *J Am Stat Assoc*. 1986;81:615-24.
- Arias E. United States life tables, 2008. *Natl Vital Stat Rep*. 2012;61:1-63.
- Breiman L. Bagging predictors. *Machine Learning*. 1996;24:123-40.
- Sauerbrei W, Schumacher M. A bootstrap resampling procedure for model building: application to the Cox regression model. *Stat Med*. 1992;11:2093-109.
- Ishwaran H, Kogalur UB, Blackstone EH, Lauer MS. Random survival forests. *Ann Appl Stat*. 2008;2:841-60.
- Ishwaran H, Kogalur UB. *Random forests for survival, regression, and classification (RF-SRC)*. R package version 1.6.0. Available at: <http://cran.r-project.org/web/packages/randomForestSRC/index.html>.
- Leon MB, Smith CR, Mack M, Miller DC, Moses JW, Svensson LG, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med*. 2010;363:1597-607.
- Rubin DB. *Multiple Imputation for Non-response in Surveys*. New York: Wiley; 1987.
- Di Eusanio M, Fortuna D, Cristell D, Pugliese P, Nicolini F, Pacini D, et al. Contemporary outcomes of conventional aortic valve replacement in 638 octogenarians: insights from an Italian Regional Cardiac Surgery Registry (RERIC). *Eur J Cardiothorac Surg*. 2012;41:1247-53.
- Mihaljevic T, Nowicki ER, Rajeswaran J, Blackstone EH, Lagazzi L, Thomas J, et al. Survival after valve replacement for aortic stenosis: implications for decision making. *J Thorac Cardiovasc Surg*. 2008;135:1270-9.
- Dewey TM, Brown D, Ryan WH, Herbert MA, Prince SL, Mack MJ. Reliability of risk algorithms in predicting early and late operative outcomes in high-risk patients undergoing aortic valve replacement. *J Thorac Cardiovasc Surg*. 2008;135:180-7.
- Nkomo VT, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enriquez-Sarano M. Burden of valvular heart diseases: a population-based study. *Lancet*. 2006;368:1005-11.
- Rady MY, Ryan T, Starr NJ. Clinical characteristics of preoperative hypoalbuminemia predict outcome of cardiovascular surgery. *JPN J Parenter Enteral Nutr*. 1997;21:81-90.
- Engelman DT, Adams DH, Byrne JG, Aranki SF, Collins JJ Jr, Couper GS, et al. Impact of body mass index and albumin on morbidity and mortality after cardiac surgery. *J Thorac Cardiovasc Surg*. 1999;118:866-73.
- Smith RL II, Herbert MA, Dewey TM, Brinkman WT, Prince SL, Ryan WH, et al. Does body mass index affect outcomes for aortic valve replacement surgery for aortic stenosis? *Ann Thorac Surg*. 2012;93:742-7.
- Hong S, Yi G, Youn YN, Lee S, Yoo KJ, Chang BC. Effect of the prosthesis-patient mismatch on long-term clinical outcomes after isolated aortic valve replacement for aortic stenosis: a prospective observational study. *J Thorac Cardiovasc Surg*. 2013;146:1098-104.
- LaPar DJ, Ailawadi G, Bhamidipati CM, Stukenborg G, Crosby IK, Kern JA, et al. Small prosthesis size in aortic valve replacement does not affect mortality. *Ann Thorac Surg*. 2011;92:880-8.
- Chen J, Lin Y, Kang B, Wang Z. Indexed effective orifice area is a significant predictor of higher mid- and long-term mortality rates following aortic valve replacement in patients with prosthesis-patient mismatch. *Eur J Cardiothorac Surg*. 2014;45:234-40.
- Nowicki ER, Birkmeyer NJ, Weintraub RW, Leavitt BJ, Sanders JH, Dacey LJ, et al. Multivariable prediction of in-hospital mortality associated with aortic and mitral valve surgery in Northern New England. *Ann Thorac Surg*. 2004;77:1966-77.
- Tjang YS, van Hees Y, Korfer R, Grobbee DE, van der Heijden GJ. Predictors of mortality after aortic valve replacement. *Eur J Cardiothorac Surg*. 2007;32:469-74.
- Vohra HA, Pousios D, Whistance RN, Haw MP, Barlow CW, Ohri SK, et al. Aortic valve replacement in patients with previous coronary artery bypass grafting: 10-year experience. *Eur J Cardiothorac Surg*. 2012;41:e1-6.
- Redlich K, Khaladj N, Peterss S, Pichlmaier M, Shrestha M, Hoy L, et al. Conventional aortic valve replacement in patients with concomitant coronary artery disease and previous coronary artery bypass grafting in the era of interventional approaches. *Eur J Cardiothorac Surg*. 2011;40:455-62.

33. Dobrilovic N, Fingleton JG, Maslow A, Machan J, Feng W, Casey P, et al. Midterm outcomes of patients undergoing aortic valve replacement after previous coronary artery bypass grafting. *Eur J Cardiothorac Surg*. 2012;42:819-25.
34. Kouchoukos NT, Blackstone EH, Hanley FL, Kirklin J. Aortic valve disease. In: *Cardiac Surgery*. 4th ed. Philadelphia: Elsevier; 2012:612-4.
35. Sade RM. Should the use of transcatheter aortic valve implantation be rationed? *J Thorac Cardiovasc Surg*. 2012;143:769-70.

Key Words: aortic stenosis, aortic valve replacement, Society of Thoracic Surgeons

Discussion

Dr David Fullerton (*Aurora, Colo*). Congratulations, Dr Szeto, on an interesting study and a sophisticated analysis. Your data demonstrate that the most widely used predictive model for assessment of risk, the STS risk calculator, did a pretty good job in this case of being true to the ultimate outcomes; in other words, it was an accurate tool for generating an observed/expected ratio for outcomes. But given that the current climate is one in which our hospitals, the public, and our patients demand very low operative mortality and at the same time they don't really understand observed/expected ratios, they focus on an absolute number and demand that the absolute number be very low.

Your study demonstrated that this cohort of patients, a very high-risk group, have a very high risk of dying. Just to be a little bit provocative, do your data suggest that it is now time to simply stop operating on these people, no longer consider TAVR as a challenge or a competitive therapy to the treatment of aortic stenosis but instead a complementary tool by which these people can be treated?

Dr Szeto. I think you are absolutely right. This field has changed quite a bit over the last 7 years, as well as patient selection. Cases we used to operate on in 2007 I would beg to argue that we would not be doing today on the basis of the body of evidence that has accumulated over the last 7 years. As you know, the American Heart Association/American College of Cardiology guidelines in 2014 would suggest that TAVR is a class IIA recommendation for high-risk patients. So what you are referring to is should we be rethinking that in this patient cohort maybe TAVR should be a class I recommendation, and I think the data that have accumulated over the last 7 years certainly would support that. These 2 randomized studies were the Edwards Lifesciences (Irvine, Calif) PARTNER I cohort 5-year data and the Medtronic CoreValve (Minneapolis, Minn) high-risk cohort 2-year data that were presented at the American College of Cardiology by Drs Mack and Reardon.

To answer your question, I want to drive home 2 points. First, yes, what we are calling high risk has evolved, and for the high-risk patients, certainly in this profile, I do believe the pendulum is swinging toward TAVR, assuming these are isolated aortic stenosis cases and no other

concomitant clinical circumstances that we may want to talk about, such as mitral regurgitation, coronary disease, and so forth.

Second, we have to be better in terms of the other side of the coin, which is who should not receive an operation, or the concept of futility. In this study, in approximately 1 of 10 patients, surgical AVR was found to be a detriment, meaning patients did worse with surgery than medical therapy, and that's a powerful message I want to drive home.

Dr Fullerton. Thank you.

Dr Michael Reardon (*Houston, Tex*). Congratulations to you and all the PARTNER investigators for the bravery it took to run this trial, the first trial out of the box, on people that were really high-risk patients. I have 1 question for you.

I'm still perplexed about why coronary bypass was protective in the PARTNER trial. In the CoreValve trial you did better with TAVR, which seems to make intrinsic sense to me. Do you have a reason why it was protective in the PARTNER trial?

Dr Szeto. There has been some work presented by Kevin Greason on this at this meeting last year. Conceptually, perhaps from a technical perspective, I think we have improved over time with doing the surgery. But in the past, coronary disease was a surrogate for perhaps not fully revascularized territories within the heart, but perhaps with patent grafts—and, as you know, these patients were very highly selected in the trial—these patients in general with patent grafts were fully revascularized. So perhaps there is an extra level of myocardial protection during their surgery. But you're absolutely right, it's a very interesting factor that came out of this analysis.

Dr J. Bavaria (*Philadelphia, Pa*). Wilson, a couple of questions. You use the words "as treated" in your methods. So the question is, did you use the AVRs that were done in the transcatheter aortic valve implantation group? I know in our series at our institution there were a couple of AVRs that were done in those with transcatheter aortic valve implantation who did great. Were those included?

Dr Szeto. Yes. This was an as-treated group, so patients who had surgical AVR I believe were included, yes.

Dr Bavaria. Even when they were randomized to TAVR?

Dr Szeto. No, I do not believe so, no.

Dr Bavaria. So it's not really an as-treated group; it's kind of a somewhat as-treated group, because that would be interesting to clarify in the article to make sure that that's the case or not the case. The second thing is, was there a difference in your data between patients with sternotomy versus any of the other 2 categories and was it statistically significant if there was a difference?

Dr Szeto. We did not dive into that; the numbers were small. As you can see, the numbers were not enough to power that. But there are certainly some signals to suggest that perhaps they were equivalent. But, no, we did not dive deep into that, and I think that's a good question.

Dr Bavaria. The third question is, your prosthetic–patient mismatch data are really powerful here and more powerful than I have seen in almost any study. Are there any comments you can make to the audience about the importance of prosthetic–patient mismatch in these patients and maybe give us some insight on what was going on with the PARTNER trial surgeons regarding their valve choices and things of that nature?

Dr Szeto. I think prosthetic–patient mismatch is a significant factor. I know there is a lot of debate regarding this. In this study, as you know, a particular device or prosthesis was highly encouraged. Perhaps not the most relevant or the most recent-generation valves were used in the majority of the patients. That's number 1.

Number 2, most of us initially thought that in these elderly patients a smaller valve would probably be okay. We've been through this all the time: This is a small man; he's 80 years old; he's not going to run a marathon; a 21-mm valve is probably okay. I think as surgeons we have to get smarter and savvier than that. We have to do a better operation if we're going to continue to do AVR. So a combination of better technique, better platform, and new technology is very important, and I think prosthetic–patient mismatch is an important, relevant topic.

Dr Manuel Antunes (*Coimbra, Portugal*). I want to go back to that question of operative mortality. In fact, when you compare the curves of expected survival for the general population, what you see is that the curves are parallel and the difference is operative mortality. Now, I would say, and maybe I am naive, but a 10% or almost 11% mortality, even for a very high-risk population, is probably a bit too high for current times. In any case, it seems there is probably room for improvement. We surgeons should work to improve our mortalities, and from my own experience I believe that's possible.

Did you observe any differences, for example, between centers or between surgeons in terms of mortality, because these are not mortalities that we see today in the reports from the large, very busy clinics in the United States.

Dr Szeto. You hit on a key point there. As you said, most of these centers, if not all of them, were high-volume centers of excellence that traditionally outpace the national

benchmarks. So when we first analyzed these data, it was a bit of a surprise to us.

But you're right, this is in contrast to other previous premarket approval studies of prostheses, and the curves are very different, and I think it has a lot to do with not only techniques of the surgeons but also patient selection.

So, again, I think the point is we have to learn and get savvier and more sophisticated with our patient selection moving forward, especially in the high-risk patients. But as we deal with the lower-risk patients, patient selection, has to be more evidence-based and more of a heart team approach and more comprehensive.

Dr Niv Ad (*Falls Church, Va*). On the same line of Dr Antunes, some of the centers that were in the PARTNER trial are with a training program. Were residents allowed to perform AVRs in this trial, because on the TAVR side only world expert surgeons and cardiologists were allowed?

Dr Szeto. The database does not provide the data to answer your question. I can only speak for my center. In patients who were randomized to open surgery, even at institutions like ours at Penn, 2 surgeons routinely performed the operations, which was a marked shift from our educational paradigm. We are a high-volume training program, and it was a rarity that 2 surgeons did cases together. So to answer your question, at least for our centers, there were 2 surgeons for the majority of these cases, for the same reasons that you brought up. This is an important landmark analysis and study, and we wanted to make sure that the data would accurately reflect the highest standards of care.

Dr Harold Roberts (*Aventura, Fla*). I did note that you had a substantial incidence of patient–prosthesis mismatch, and you did state, rather quickly, that the valve choice was Perimount (Edwards Lifesciences). Was it actually Perimount or were you using the newer-generation Magna (Edwards Lifesciences) to produce these often unfavorable hemodynamics?

Dr Szeto. I don't have the figures off the top of my head, but the majority were Edwards stented pericardial valves. I don't know the breakdown between Magna versus Perimount, so I apologize for that.

APPENDIX E1. PATIENT SELECTION CRITERIA^{E12} IN PLACEMENT OF AORTIC TRANSCATHETER VALVES (PARTNER) IA

Inclusion Criteria

1. Comorbidities such that the surgeon and cardiologist Co-Principal Investigators concurred that the predicted risk of operative mortality was 15% or greater or an STS score of 10 or greater based on the 1990s model. A candidate who did not meet the STS score criteria of 10 or greater could be included in the study if a peer review by at least 2 surgeon investigators (not including the enrolling surgeon) concluded and documented that the subject's predicted risk of operative mortality was 15% or more.
2. Senile degenerative aortic valve stenosis with echocardiography-derived criteria: mean gradient greater than 40 mm Hg or jet velocity greater than 4.0 m/s, or AVA less than 0.8 cm² (or EOA index <0.5 cm²/m²). Qualifying AVA baseline measurement must be within 30 days of study valve implantation procedure.
3. Symptomatic because of aortic valve stenosis as demonstrated by NYHA functional class II or greater.

Exclusion Criteria

1. Evidence of an acute MI 1 month or less before the intended treatment (defined as Q-wave MI, or non-Q-wave MI with total CK elevation twice or more than normal in the presence of CK-MB elevation or troponin elevation [WHO definition]).
2. Aortic valve was a congenital unicuspid or congenital bicuspid valve, or was noncalcified.
3. Mixed aortic valve disease (aortic stenosis and aortic regurgitation with predominant aortic regurgitation >3+).
4. Any therapeutic invasive cardiac procedure performed within 30 days of the index procedure, or 6 months if the procedure was a drug-eluting coronary stent implantation.
5. Preexisting prosthetic heart valve in any position, prosthetic ring, severe mitral annular calcification, severe (>3+) mitral regurgitation, or Gorlin syndrome.
6. Blood dyscrasias as defined: leukopenia (WBC <3000 WBC/ μ L), acute anemia (hemoglobin <9 g/dL), thrombocytopenia (platelet count <50,000 cells/ μ L), history of bleeding diathesis or coagulopathy.
7. Untreated clinically significant coronary artery disease requiring revascularization.
8. Hemodynamic instability requiring inotropic therapy or mechanical hemodynamic support devices.
9. Need for emergency surgery for any reason.
10. Hypertrophic cardiomyopathy with or without obstruction.

11. Severe ventricular dysfunction with LVEF less than 20%.
12. Echocardiographic evidence of intracardiac mass, thrombus, or vegetation.
13. Active peptic ulcer or upper gastrointestinal bleeding within the last 3 months.
14. Recent (within 6 months) cerebrovascular accident or transient ischemic attack.
15. Renal insufficiency (creatinine >3.0 mg/dL) or end-stage renal disease requiring chronic dialysis.
16. Life expectancy less than 12 months because of noncardiac comorbid conditions.
17. Significant abdominal or thoracic aorta disease, including aneurysm (defined as maximal luminal diameter $\geq$ 5 cm), marked tortuosity (hyperacute bend), aortic arch atheroma (especially if thick [$>$ 5 mm], protruding, or ulcerated), or narrowing of the abdominal aorta (especially with calcification and surface irregularities).
18. Active bacterial endocarditis or other active infections.

AVA, Aortic valve area; CK, creatine kinase; CK-MB, creatine kinase-MB; EOA, effective orifice area; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; STS, Society of Thoracic Surgeons; WBC, white blood cell; WHO, World Health Organization.

APPENDIX E2. VARIABLES CONSIDERED IN THE ANALYSIS

Preprocedural Patient and Valve-Related Characteristics

Demographics. Age (years), sex, race (white, black, other), height (cm), weight (kg), body mass index (kg/m²), body surface area (m²).

Functional health status. Syncope not related to atrioventricular block, exertional syncope, heart failure, NYHA functional class, STS predicted operative mortality (based on contemporaneous STS risk models^{3,4}) (Table E1).

Aortic valve pathophysiology, including echocardiographic studies. Prior balloon aortic valvotomy, native valve calcified, AV peak velocity (cm/sec), AV time-velocity integral (cm), AV estimated orifice area (cm²), AV area index (cm²/m²), AV mean gradient (mm Hg), AV peak gradient (mm Hg), AV regurgitation severity (none, mild, moderate, severe).

Peripheral arterial disease. Peripheral arterial disease; normal iliac artery greater than 8 mm, noncalcified, nontortuous; iliofemoral disease; iliofemoral vessel characteristics that preclude placement of introducer sheath; severe tortuosity of femoral or iliac vessels; severely calcified iliac artery; peripheral arterial intervention.

Cerebrovascular disease. Cerebral vascular disease including carotid arterial disease, carotid arterial disease,

previous carotid endarterectomy or carotid stent, prior stroke, stroke or transient ischemic attack within last 6 to 12 months, dementia.

Coronary artery disease. Coronary artery disease, angina, Canadian Angina Class, coronary artery stenosis (none, left main trunk >50%, left anterior descending >50%, left circumflex >50%, right coronary artery >50%), saphenous vein conduit stenosis after previous CABG, prior percutaneous coronary intervention, number of prior CABGs.

Ventricular function. Previous myocardial infarction.

Other cardiac comorbidity. MV disease, baseline MV regurgitation severity, mitral valvuloplasty, tricuspid valve disease, history of endocarditis, atrial fibrillation, pacemaker implant, cardiomyopathy, rheumatic fever, other prior cardiovascular interventions.

Left ventricular outflow tract, including proximal aorta. LV outflow tract dimension (cm), aortic root diameter (cm), sinutubular junction diameter (cm), ascending aorta diameter (cm).

Preprocedure echocardiogram: Left ventricular morphology and function. LV end-diastolic dimension (cm), LV end-systolic dimension (cm), ejection fraction (%), LV mass (g), LV mass index (g/m^2), stroke volume (mL), stroke volume index (mL/m^2), cardiac output (L/min), cardiac index ($\text{L}/\text{min}/\text{m}^2$), heart rate (beats/min).

Noncardiac comorbidity. Diabetes (yes/no, type I, type II, mild-to-moderate, with end-organ damage), smoking, pulmonary disease, chronic pulmonary disease, hyperlipidemia, renal disease, gastrointestinal condition, cancer, bilirubin (mg/dL), creatinine (mg/dL), creatinine clearance (Cockcroft-Gault, mL/min), glomerular filtration rate (MDRD, $\text{mL}/\text{min}/1.73 \text{ m}^2$), blood urea nitrogen (mg/dL), hemoglobin (g/dL), hematocrit (%), international normalized ratio, platelet count ($\text{k}/\mu\text{L}$), white blood cell count ($\text{k}/\mu\text{L}$), albumin (g/dL).

Approach. Candidate for transfemoral access (yes/no).

Procedural Characteristics

Procedure. Incision (full sternotomy, partial sternotomy, thoracotomy), AV prosthesis size, prosthesis–patient mismatch (none, moderate, severe).

Concomitant procedures. CABG, other.

Support. Aortic clamp time (min), cardiopulmonary bypass time (min).

AV, Aortic valve; CABG, coronary artery bypass grafting; LV, left ventricular; MDRD, Modification of Diet in Renal Disease; MV, mitral valve; NYHA, New York Heart Association; STS, Society of Thoracic Surgeons.

APPENDIX E3. ADDITIONAL REFERENCES

- E1. Mayer JE Jr. Transcatheter aortic valve implantation should be controlled and monitored by the medical profession. *J Thorac Cardiovasc Surg.* 2012;143:771-3.
- E2. Wheatley GH III. Use of transcatheter valve should not be rationed. *J Thorac Cardiovasc Surg.* 2012;143:774-5.
- E3. Lytle BW, Blackstone EH, Sabik JF, Houghtaling P, Loop FD, Cosgrove DM. The effect of bilateral internal thoracic artery grafting on survival during 20 postoperative years. *Ann Thorac Surg.* 2004;78:2005-14.
- E4. Hochman JS, Sleeper LA, Webb JG, Sanborn TA, White HD, Talley JD, et al. Early revascularization in acute myocardial infarction complicated by cardiogenic shock. SHOCK Investigators. Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock. *N Engl J Med.* 1999;341:625-34.
- E5. O'Connor GT, Plume SK, Olmstead EM, Morton JR, Maloney CT, Nugent WC, et al. A regional intervention to improve the hospital mortality associated with coronary artery bypass graft surgery. The Northern New England Cardiovascular Disease Study Group. *JAMA.* 1996;275:841-6.
- E6. O'Connor GT, Plume SK, Olmstead EM, Coffin LH, Morton JR, Maloney CT, et al. A regional prospective study of in-hospital mortality associated with coronary artery bypass grafting. The Northern New England Cardiovascular Disease Study Group. *JAMA.* 1991;266:803-9.
- E7. Shahian DM, O'Brien SM, Filardo G, Ferraris VA, Haan CK, Rich JB, et al. The Society of Thoracic Surgeons 2008 cardiac surgery risk models: part 1—coronary artery bypass grafting surgery. *Ann Thorac Surg.* 2009;88:S2-22.
- E8. Ferraris VA, Ferraris SP, Wehner PS, Setser ER. The dangers of gathering data: surgeon-specific outcomes revisited. *Int J Angiol.* 2011;20:223-8.
- E9. Iturra SA, Suri RM, Greason KL, Stulak JM, Burkhart HM, Dearani JA, et al. Outcomes of surgical aortic valve replacement in moderate risk patients: implications for determination of equipoise in the transcatheter era. *J Thorac Cardiovasc Surg.* 2014;147:127-32.
- E10. Arnold SV, Reynolds MR, Lei Y, Magnuson EA, Kirtane AJ, Kodali SK, et al. Predictors of poor outcomes after transcatheter aortic valve replacement: results from the PARTNER (Placement of Aortic Transcatheter Valve) trial. *Circulation.* 2014;129:2682-90.
- E11. Friedman JH. Greedy function approximation: a gradient boosting machine. *Annu Stat.* 2000;29:1189-232.
- E12. *The PARTNER Trial: Placement of AoRTic TraNscatheter Valves, Version 2.0.* Irvine, CA: Edwards Lifesciences; 2008.
- E13. Cox DR. Two further applications of a model for binary regression. *Biometrika.* 1958;45:562-5.
- E14. Miller ME, Langefeld CD, Tierney WM, Hui SL, McDonald CJ. Validation of probabilistic predictions. *Med Decis Making.* 1993;13:49-58.
- E15. Beach JM, Mihaljevic T, Svensson LG, Rajeswaran J, Marwick T, Griffin B, et al. Coronary artery disease and outcomes of aortic valve replacement for severe aortic stenosis. *J Am Coll Cardiol.* 2013;61:837-48.

FIGURE E1. CONSORT-style diagram of PARTNER-I trial. SAVR, Surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement.

FIGURE E2. Observed versus expected operative mortality over the spectrum of expected risk. Top smoothed curve depicts the density of patients along the scale of expected probability of operative mortality. Symbols represent observed mortality within deciles of expected mortality. Dashed line is line of identity. Note that observed risk was worse than expected at both lower and upper ends of the spectrum of expected mortality, and better or equivalent in the center of the distribution of risk values (~8%-11%). The refinement parameter^{E13,E14} estimate is 0.21, suggesting that observed responses varied more than the national average. However, the estimated standard error of this parameter is 0.37. This may be due to smaller sample size or few events.

FIGURE E3. Observed versus expected occurrence of stroke over the spectrum of expected risk. Format is as in Figure E2. Note that there was little correlation between observed and expected occurrence. The refinement parameter estimate is 0.24 ± 0.89 . Interpretation is similar to that of Figure E2.

FIGURE E4. Cumulative distribution of predicted probability of operative mortality using contemporary STS models (blue curve to left) versus the STS score used in the PARTNER-I trial. Predicted mortality calculated from contemporary STS models^{3,4} was lower than the PARTNER-I risk score, which was based on an older STS model.⁷ STS, Society of Thoracic Surgeons; PARTNER, Placement of Aortic Transcatheter Valves.

FIGURE E5. Observed versus expected renal failure over the spectrum of expected risk. Format is as in Figure E2. In general, renal failure occurred less often than expected, except for the lowest risk decile. The refinement parameter estimate is 0.87 ± 0.41 , a somewhat larger standard error for a point estimate of this magnitude.

FIGURE E6. Observed versus expected prolonged postoperative length of stay over the spectrum of expected risk. Format is as in [Figure E2](#). Patients had a prolonged postoperative length of stay more often than expected. The refinement parameter estimate is 0.60 ± 0.29 , a somewhat larger standard error for a point estimate of this magnitude.

FIGURE E7. Partial dependency plot of 1-year survival and age at surgical AVR. *Squares and solid line* represent risk-adjusted estimates, and *dashed lines* indicate the 68% confidence band. Older age was not a reliable risk factor in the parametric model; nevertheless, this risk-adjusted graph indicates that patients aged more than approximately 88 years are at progressively higher risk of 1-year mortality than younger patients.

ACD

FIGURE E8. Observed survival after surgical AVR compared with that predicted for comparable PARTNER-IB standard therapy patients (based on [Table E2](#)). A, Survival comparisons. For surgical AVR, each symbol represents a death by the Kaplan-Meier estimator, *vertical bars* represent 68% confidence limits of these nonparametric estimates, and *smooth solid curve* and 68% confidence band represent parametric estimates. Standard therapy curve and its confidence limits represent the ensemble average of individual survival curves generated for each AVR patient based on their characteristics and the multivariable equation for survival of patients receiving standard therapy. B, Time-related area between survival curves shown in A, expressed as time-related lifetime gained by AVR compared with standard therapy. By 3 years of follow-up, surgical AVR, on average, added 0.75 years to patients' lives. AVR, Aortic valve replacement.

FIGURE E9. Nomograms of survival after surgical AVR based on 3 different risk profiles noted in the table and the multivariable model for death (Table 4). AVR, Aortic valve replacement; BMI, body mass index; CABG, coronary artery bypass grafting.

FIGURE E10. Cumulative distribution of difference in survival between surgical AVR and standard therapy. Note that because of prolonged early risk, more surgical patients have worse survival than standard therapy patients at 1 year (red line going to the left of 0), but few have worse survival at 2 (brown line) and 3 (blue line) years.

FIGURE E11. Paradoxical apparent increasing survival benefit of AVR in older patients, referenced to the US population. A, Survival after AVR stratified by age groups in a 9-institution study of 13,258 patients.⁵ Of these, 1700 were aged 50 years or less (*circles*), 8562 were aged 50 to 75 years (*squares*), and 2996 were aged 75 years or more (*triangles*). Each symbol represents a death. Vertical bars are confidence limits equivalent to ± 1 standard error, and the solid lines represent parametric estimates. Numbers below horizontal axis are patients remaining at risk. Dash-dot-dash lines represent age-, sex-, and race-matched expected survival in the US population. B, Instantaneous risk of death (hazard function) stratified by age groups in the 9-institution study.⁵ Solid lines are point estimates, and dash-dot-dash lines are risk of death in the US population. C, Survival after AVR at a single institution.^{E15} Survival of younger patients was worse than that of the general population, but in elderly patients it was commensurate. Format is as in Figure E11, A. D, Instantaneous risk of death after AVR at a single institution.^{E15} Format is as in Figure E11, B. AVR, Aortic valve replacement.

TABLE E1. Placement of Aortic Transcatheter Valves database variables used as contemporaneous Society of Thoracic Surgeons risk model variables^{3,4}

STS risk model variable	PARTNER variable assumptions	No. (%) or mean $\pm$ SD
Age (y)	—	84.5 $\pm$ 6.33
Female	—	134 (43)
Height (cm)	—	166 $\pm$ 10.3
Weight (kg)	—	74.2 $\pm$ 17.1
LV ejection fraction (%)	—	53.3 $\pm$ 12.4
Race/ethnicity		
Black	—	7 (2.2)
Hispanic	—	9 (2.9)
Asian	—	0 (0)
History of dialysis	—	5 (1.7)
Creatinine (mg/dL)	—	1.32 $\pm$ 0.46
Unstable angina	No	0 (0)
Myocardial infarction	>21 d	0 (0)
Atrial fibrillation	—	69 (22)
Chronic pulmonary disease	Graded chronic pulmonary disease (no FEV1[%] available)	
	None	166 (53)
	Mild: chronic pulmonary disease only	112 (36)
	Moderate: chronic pulmonary disease with steroid, no home oxygen	8 (2.6)
	Severe: chronic pulmonary disease with home oxygen	27 (8.6)
Stroke	—	54 (17)
Cerebrovascular disease	—	112 (36)
Peripheral arterial disease	—	210 (67)
Diabetes	—	128 (41)
Insulin-treated diabetes	PARTNER database: Cardiovascular risk factors	104 (33)
	Currently taking insulin	
	Type of insulin (injection)	
	With end-organ damage	
	PARTNER database: Medication used	
	Insulin	
Hypertension	—	294 (94)
Immunosuppressants	—	14 (4.5)
Active endocarditis	No active endocarditis	0 (0)
No. of coronary systems diseased $\geq$ 50%	—	
0		144 (46)
1		47 (15)
2		59 (19)
3		63 (20)
LMT stenosis $\geq$ 50%	—	37 (12)
Urgency	Elective surgery	313 (100)
Cardiogenic shock	No	0 (0)
Heart failure	—	308 (99)
NYHA functional class	—	
II		16 (5.1)
III		134 (43)
IV		163 (52)
IABP or inotropes	No	0 (0)
PCI	None within 6 h of surgery	0 (0)
MV stenosis	No	0 (0)
AV stenosis	Yes	313 (100)
MV regurgitation grade	—	
0		78 (26)
1+		162 (54)
2+		53 (18)
3+		6 (2)

(Continued)

TABLE E1. Continued

STS risk model variable	PARTNER variable assumptions	No. (%) or mean $\pm$ SD
TV regurgitation	No	0 (0)
AV regurgitation	—	
0		129 (43)
1+		130 (43)
2+		38 (13)
3+		5 (1.7)
Prior cardiac surgery	No. of cardiac surgeries, based on history and No. of previous CABGs	
	0	173 (55)
	1	113 (36)
	2	24 (7.7)
	3	3 (0.96)

AV, Aortic valve; CABG, coronary artery bypass grafting; FEV1 (%), forced expiratory volume in 1 second (percent of predicted); IABP, intra-aortic balloon pump; LMT, left main trunk; LV, left ventricle; MV, mitral valve; NYHA, New York Heart Association; PARTNER, Placement of Aortic Transcatheter Valves; PCI, percutaneous coronary intervention; SD, standard deviation; STS, Society of Thoracic Surgeons; TV, tricuspid valve.

TABLE E2. Incremental risk factors for death in Placement of Aortic Transcatheter Valves IB: Standard therapy group

Risk factor	Coefficient $\pm$ SE	P value
Early peaking hazard		
Lower hematocrit*	-0.53 ± 0.23	.05
Lower stroke volume index†	1.2 ± 0.63	.05
Higher aortic valve regurgitation grade	1.1 ± 0.60	.06
Previous CABG (less risk)	-0.036 ± 0.77	>.9
Lower albumin‡	1.6 ± 1.9	.4
Intermediate-term constant hazard		
Higher NYHA functional class§	-5.6 ± 1.7	.0009
Pacemaker	0.55 ± 0.24	.02
Balloon aortic valvotomy	0.47 ± 0.24	.05
Higher white blood cell count	0.076 ± 0.028	.007
Higher LV mass index	-0.59 ± 0.32	.06
Smaller body mass index¶	0.30 ± 0.26	.2
Cancer	-0.037 ± 0.23	.9

C-statistic = 0.66. CABG, Coronary artery bypass grafting; LV, left ventricle; NYHA, New York Heart Association; SE, standard error. *Log (hematocrit), logarithmic transformation. †(30/stroke volume index), inverse transformation. ‡(1/albumin), inverse transformation. §(1/NYHA), inverse transformation. ||(150/LV mass index), inverse transformation. ¶(25/body mass index)², inverse squared transformation.

TABLE E3. Postoperative outcomes not included in Society of Thoracic Surgeons Benchmarks

Outcome	n*	No. (%)
Discharge location	139	
Home		109 (78)
Extended care facility		29 (21)
Another hospital		1 (0.72)
NYHA functional class		
Discharge	269	
I		10 (3.8)
II		104 (40)
III		112 (43)
IV		35 (13)
30 d	264	
I		55 (21)
II		117 (44)
III		70 (27)
IV		22 (8.3)
6 mo	217	
I		93 (43)
II		93 (43)
III		28 (13)
IV		3 (1.4)

NYHA, New York Heart Association. *Patients with data available.