Predictors of Poor Outcomes After Transcatheter Aortic Valve Replacement

Results From the PARTNER (Placement of Aortic Transcatheter Valve) Trial

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Background—Transcatheter aortic valve replacement (TAVR) is a less invasive option for treatment of high-risk patients with severe aortic stenosis. We sought to identify patients at high risk for poor outcome after TAVR using a novel definition of outcome that integrates quality of life with mortality.

Methods and Results—Among 2137 patients who underwent TAVR in the PARTNER (Placement of Aortic Transcatheter Valve) trial or its associated continued access registry, quality of life was assessed with the Kansas City Cardiomyopathy Questionnaire–Overall Summary Scale (KCCQ-OS; range 0–100, where a higher score equates to a better quality of life) at baseline and at 1, 6, and 12 months after TAVR. A poor 6-month outcome (defined as death, KCCQ-OS score <45, or ≥10-point decrease in KCCQ-OS score compared with baseline) occurred in 704 patients (33%). Using a split-sample design, we developed a multivariable model to identify a parsimonious set of covariates to identify patients at high risk for poor outcome. The model demonstrated moderate discrimination (*c*-index=0.66) and good calibration with the observed data, performed similarly in the separate validation cohort (*c*-index=0.64), and identified 211 patients (10% of the population) with a ≥50% likelihood of a poor outcome after TAVR. A second model that explored predictors of poor outcome at 1 year identified 1102 patients (52%) with ≥50% likelihood and 178 (8%) with ≥70% likelihood of a poor 1-year outcome after TAVR.

Conclusions—Using a large, multicenter cohort, we have developed and validated predictive models that can identify patients at high risk for a poor outcome after TAVR. Although model discrimination was moderate, these models may help guide treatment choices and offer patients realistic expectations of outcomes based on their presenting characteristics.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00530894.

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Key Words: aortic valve stenosis ■ heart valves ■ outcomes assessment ■ quality of life

Among patients with severe aortic stenosis, transcatheter aortic valve replacement (TAVR) has emerged as a less invasive option for aortic valve replacement and offers substantial reductions in mortality and improvement in quality of life (QoL) compared with medical therapy[1,2] and long-term outcomes similar to those of surgical valve replacement.[3,4] With increasing experience, however, it has become evident that some patients do not improve functionally or live longer after TAVR. For example, in the Placement of Aortic Transcatheter Valve (PARTNER) Trial, ≈1 in 4 patients who were treated with TAVR were dead at 1 year.[1,3] Furthermore, there were a number of patients who received TAVR who, although alive at 1 year, continued to have very poor QoL after TAVR, with significant heart failure symptoms and functional limitation.[2,4]

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In light of these observations, there has been a recognition by practitioners,[5,6] regulators,[7] and third-party payers[8] that TAVR should not be offered to patients in whom valve

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replacement would not be expected to positively impact either their survival or quality of life. To date, however, there has been little guidance as to how best to identify these patients. To address this need, several efforts have focused on predicting mortality after TAVR, with the goal of trying to identify patients at high risk for poor outcomes.[9,10] However, in this elderly population of patients, often with extensive comorbidity and impaired health status, it is likely that prolonged survival alone (without improved QoL) would not be viewed as a desirable outcome. Therefore, any definition of a successful outcome of TAVR (and conversely, of a poor outcome) must consider both survival and QoL. In a previous study, we examined a range of alternative definitions of poor outcome after TAVR.[11] On the basis of both their conceptual underpinnings and empirical observations, we concluded that the most reasonable definition was the composite of death, very poor QOL, or an important decline in QOL compared with baseline. The goal of the present study was to build and validate a prediction model to prospectively identify patients at high risk of a poor outcome after TAVR.

Methods

Study Population and Protocol

The study population was derived from patients with severe symptomatic aortic stenosis who were enrolled in cohort A or cohort B of the PARTNER trial or in the associated nonrandomized, continued access PARTNER registry. Enrolled patients in both the trial and the registry had severe aortic stenosis (aortic valve area of <0.8 cm^2 with either a mean aortic valve gradient ≥40 mm Hg or a peak aortic jet velocity ≥4.0 m/s); New York Heart Association (NYHA) class II or greater heart failure symptoms; and high surgical risk based on the Society for Thoracic Surgeons mortality risk score and other factors.[1,3] Patients with severe (4+) mitral or aortic regurgitation were excluded. Eligible patients were classified into 2 cohorts: Cohort A patients were at high risk but suitable for surgical aortic valve replacement,[3] whereas cohort B patients were deemed ineligible for cardiac surgery because of coexisting medical or anatomic conditions associated with a predicted probability of perioperative death or permanent disability ≥50%.[1] In the randomized trial, cohort A patients were randomized to surgical AVR or TAVR, and cohort B patients were randomized to medical therapy or TAVR. For the present study, we included only patients who received TAVR. After enrollment in the PARTNER trial was complete but before commercial approval of the Edwards-Sapien valve, a limited number of patients who would have been eligible for the PARTNER randomized trial were allowed to receive TAVR via either the transfemoral or transapical route as clinically indicated, as part of a continued access registry. Inclusion and exclusion criteria, study protocols, and follow-up procedures were identical in the registry to those in the randomized trial.

Patients were assessed for clinical factors and QoL/health status at baseline and at 1, 6, and 12 months after randomization. Baseline QoL/health status questionnaires were administered before randomization (or study registration for the continued access registries), and follow-up questionnaires were administered during in-person visits to the enrolling centers or by mail. The study was approved by the institutional review board at each participating site, and all patients provided written informed consent for baseline and follow-up assessments.

Health Status Data

Disease-specific health status (ie, symptoms, functional status, and QoL) was assessed with the Kansas City Cardiomyopathy Questionnaire (KCCQ),[12] a 23-item self-administered questionnaire that assesses specific health domains pertaining to heart failure and yields an overall summary scale, which was the primary health status outcome for the present study. Values for the KCCQ overall summary score (KCCQ-OS) range from 0 to 100, with higher scores indicating less symptom burden and better QoL. Linguistically and culturally validated translations of the KCCQ were provided to non-English speakers. Previous studies have suggested that KCCQ-OS scores correlate roughly with NYHA functional class as follows: Class I, KCCQ-OS ≈75 to 100; class II, ≈60 to 74; class III, ≈45 to 59; and class IV, ≈0 to 44.[13] Among outpatients with heart failure, small, moderate, and large clinical improvements/deteriorations, as rated by treating physicians, correspond to changes in the KCCQ-OS of approximately 5, 10, and 20 points, respectively.[13] The KCCQ has undergone extensive reliability and validity testing in various heart failure populations,[12,14,15] as well as in patients with severe aortic stenosis.[16]

Functional status was assessed objectively by means of a 6-minute walk test (6MWT). If a patient could not perform the test, the value for the 6MWT distance was set to zero. Generic health status was assessed with the physical and mental summary scores of the Medical Outcomes Study 12-Item Short Form Health Survey (SF-12).[17] Because the physical summary score of this survey represents functional status, which was also assessed by means of the KCCQ and the 6MWT, we did not include this as a potential predictor for poor outcome.

Definition of a Poor Outcome

Although any single definition of a poor outcome after TAVR is a somewhat arbitrary construct, we have previously examined several potential definitions that combine mortality and QoL.[11] For the purposes of the present study, we used outcomes at 6 months after TAVR as the basis for our primary end point, because we believe that survival for at least 6 months with a reasonable QoL would be the minimum acceptable outcome for the procedure. Therefore, for our primary analysis, a poor outcome was defined as any of the following at 6 months after TAVR (definition No. 1): (1) death, (2) KCCQ-OS score <45, or (3) decrease of ≥10 points in the KCCQ-OS score from baseline to 6 months.[11,18]

From a conceptual standpoint, this definition means that if a patient had a very poor QoL before TAVR, his or her QoL would have to improve to a minimum threshold (approximately NYHA class III symptoms or better) to be considered an acceptable outcome. On the other hand, if a patient had a satisfactory QoL before TAVR, then survival for ≥6 months with a QoL that had not deteriorated substantially from baseline would be considered an acceptable result. This combined definition integrates the 2 potential benefits of TAVR, reduced mortality and improved QoL, and recognizes that patients who have good QoL at baseline may not improve symptomatically after TAVR but could still derive a mortality benefit (which would represent a clinically meaningful benefit of the procedure). In addition, we constructed an alternative, expanded definition of poor outcome (definition No. 2) that included any of the following at 1 year after TAVR: (1) death, (2) KCCQ-OS score <60, or (3) decrease of ≥10 points in the KCCQ-OS score from baseline to 1 year. This definition allows for a longer time frame of analysis and may be beneficial to patients and providers in conjunction with, or as an alternative to, definition No. 1 depending on the patient's goals of care.

Statistical Analysis

Demographics, cardiac and noncardiac comorbidities, and echocardiographic variables were compared between patients who had a poor outcome and patients who had an acceptable outcome after TAVR by use of *t* tests for continuous variables and χ^2 tests for categorical variables. We then randomly split the cohort of TAVR patients into 2 groups, two thirds for model derivation and one third for validation. In the derivation cohort, we developed a multivariable logistic regression model to predict a poor 6-month outcome (using definition No. 1 as described above). Variables for the prediction model were selected from 25 candidate variables (Table 1). Baseline data had a high rate of completion, with an average of 0.55 missing data items per patient, which were imputed with a single imputation data set by use of IVEware (Institute for Social Research, University of Michigan, Ann Arbor, MI).

Table 1. Baseline Characteristics of Patients With Acceptable Versus Poor Outcomes According to Definition No. 1

	All Patients (n=2137)	Acceptable Outcome (n=1433)	Poor Outcome (n=704)	*P* Value
Age, y	84.4 (7.2)	84.3 (7.2)	84.6 (7.0)	0.357
Male, %	52.8	51.3	56.0	0.042
Coronary artery disease, %	78.2	78.1	78.6	0.807
Cerebrovascular disease, %	26.6	26.5	26.8	0.872
Carotid disease, %	27.0	27.6	25.7	0.364
Peripheral vascular disease, %	42.2	42.0	42.6	0.791
Diabetes mellitus, %	36.6	38.4	33.1	0.017
Major arrhythmia, %*	50.9	47.5	57.8	<0.001
Creatinine, mg/dL	1.31 (0.48)	1.29 (0.46)	1.36 (0.51)	0.002
Hemoglobin, g/dL	11.7 (1.5)	11.8 (1.5)	11.6 (1.5)	0.033
Mean arterial pressure, mm Hg	87.1 (13.1)	87.2 (12.8)	87.0 (13.4)	0.656
Body mass index, kg/m^2	26.9 (6.3)	27.1 (6.1)	26.6 (6.8)	0.093
Oxygen-dependent lung disease, %	10.9	9.3	14.3	<0.001
Pulmonary hypertension, %	40.0	39.2	41.5	0.316
Mitral regurgitation (>1+), %	25.3	24.8	26.3	0.473
Aortic regurgitation (>1+), %	10.5	10.8	9.9	0.536
Mean aortic gradient, mm Hg	43.8 (14.3)	45.1 (14.3)	41.2 (14.0)	<0.001
Ejection fraction, %	52.0 (13.1)	52.4 (13.0)	51.2 (13.4)	0.053
Stroke volume, mL/beat	64.5 (21.1)	65.1 (20.0)	63.2 (23.1)	0.053
Mini-Mental Status Examination score	27.4 (3.0)	27.5 (2.9)	27.1 (3.0)	0.008
6-Min Walk Test, % able to perform	65.0	70.1	54.8	<0.001
6-Min Walk Test distance, m	110.8 (118.1)	123.9 (122.2)	84.0 (104.3)	<0.001
KCCQ Overall Summary score	42.0 (21.7)	43.8 (20.8)	38.4 (23.0)	<0.001
SF-12 Mental Summary score	47.6 (11.2)	48.3 (11.0)	46.2 (11.5)	<0.001
STS mortality risk score	11.5 (4.4)	11.4 (4.5)	11.9 (4.1)	0.005

Values in parentheses are standard deviations. KCCQ indicates Kansas City Cardiomyopathy Questionnaire; SF-12, 12-Item Short Form Health Survey; and STS, Society of Thoracic Surgeons.

*Defined as a history of atrial fibrillation or flutter, supraventricular tachycardia, ventricular arrhythmias, or high-degree atrioventricular block.

Harrell's backward selection strategy was used to select a parsimonious set of variables for the final model.[19] The contribution of each covariate in the multivariable model was ranked by *F* value, and variables with the smallest contribution to the model were sequentially eliminated. This iterative process continued until further variable elimination led to a >5% loss in model prediction compared with the initial model. The remaining covariates constituted the final parsimonious model and explained >95% of the variance of the full model. This selection strategy supports inclusion of only variables that provide incremental prognostic value, minimizes overfitting, and maximizes the potential clinical usefulness of the model.[19] Nonlinear spline terms were considered for all continuous variables. Model discrimination was assessed with the *c*-index, and model calibration was assessed by plotting deciles of predicted risk against the observed event rate and comparing the regression line to the line of unity. These analyses were performed in both the derivation and validation cohorts and were repeated using definition No. 2 of a poor outcome.

As sensitivity analyses, to further explore the associations of the covariates with the outcome, we applied the model to each of the component end points to explore its ability to predict (1) death or (2) poor QoL or QoL decline (among survivors). Second, to ensure that our results were not heavily influenced by the consequences of early complications (which might be considered outliers), we conducted a sensitivity analysis that excluded patients who had a major periprocedural complication (ie, major stroke, bleeding complication, vascular complication, or surgical aortic valve replacement within 7 days of the TAVR procedure). Third, we applied the model separately to patients according to access site (transfemoral or transapical) to ensure that model performance did not vary markedly by site of valve delivery. Finally, we constructed an alternative model for ease of implementation in a clinical setting. For this model, we included the 12-item KCCQ,[20] excluded the 6MWT and SF-12 Mental summary score as potential predictors, and used 10% loss of information as the cut point for variable selection (to create a more parsimonious model). All statistical analyses were performed with the use of SAS software, version 9.2 (SAS Institute, Inc, Cary, NC).

Results

Patient Population

Of the 1057 patients with severe aortic stenosis who were enrolled in the PARTNER randomized trial, 527 underwent TAVR (Figure 1; 348 in cohort A, 179 in cohort B), and an additional 2068 patients underwent TAVR in the nonrandomized continued access registry via the transfemoral (n=1503) or transapical (n=1092) route. Of these, 400 died within 6 months of TAVR. Among the 2195 who survived 6 months, KCCQ data were available for 1737 (79%). Thus, our analytic population included 2137 patients who underwent TAVR and were either dead or were assessed with the KCCQ at 6 months after their procedure. Most baseline characteristics were

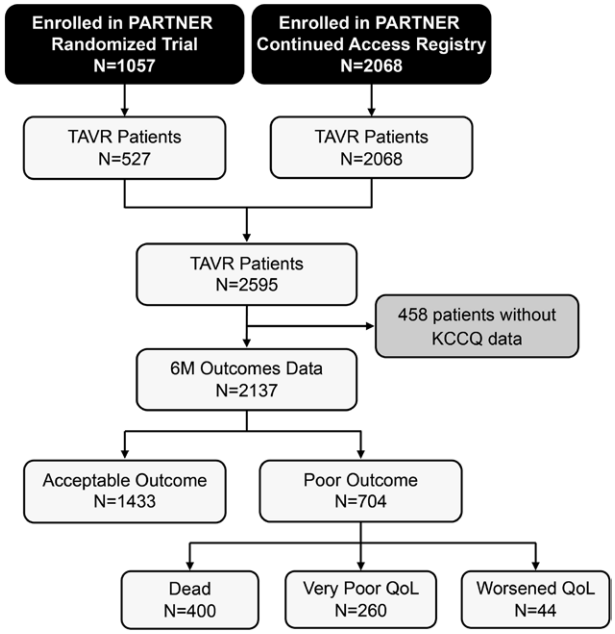

Figure 1. Patient flow. KCCQ indicates Kansas City Cardiomyopathy Questionnaire; PARTNER, Placement of Aortic Transcatheter Valve trial; QoL, quality of life; and TAVR, transcatheter aortic valve replacement.

similar for patients with versus without complete KCCQ data; however, patients with missing KCCQ data had lower baseline 6-minute walk distances (85 versus 119 m, $P<0.001$), lower body mass indexes (26.3 versus 27.2 kg/m^2, $P=0.008$), and lower hemoglobin levels (11.6 versus 11.8 g/dL, $P=0.026$).

The mean age of the analytic population was 84 years, and 53% were male (Table 1). The mean aortic valve gradient was 44 mm Hg, and 93% of patients were classified as NYHA class III to IV. At 6-month follow-up, among the 2137 study patients, 400 (19%) had died, 260 (12%) had a very poor QoL (ie, KCCQ-OS <45), and an additional 44 (2%) had worsened QoL (ie, decrease in KCCQ-OS of ≥10 points; Figure 1). Thus, a total of 704 patients (33%) had a poor 6-month outcome. The baseline characteristics of patients with an acceptable versus poor outcome after TAVR are summarized in Table 1.

Model Development

After backward stepwise elimination, the final predictive model consisted of 10 covariates, which are summarized in Table 2. According to F values, the distance walked on the 6MWT had the strongest association with poor outcome after TAVR, with each additional 10 m walked being associated with a 3% lower risk of poor outcome (adjusted odds ratio, 0.97; 95% confidence interval, 0.96–0.98). Higher mean aortic valve gradients were also strongly associated with a lower risk of poor outcome; each 10-mm Hg increase in mean gradient was associated with 18% lower odds of a poor outcome (adjusted odds ratio, 0.82; 95% confidence interval, 0.75–0.89). Other baseline factors associated with a poor outcome after TAVR included oxygen-dependent chronic lung disease, renal dysfunction, decreased cognition, and cardiac arrhythmias (defined as a history of atrial fibrillation or flutter, supraventricular tachycardia, ventricular arrhythmia, or high-degree atrioventricular block). Nonlinear spline terms were considered for all continuous variables but were not significant. The c-index of the model was 0.66, which indicates moderate discriminatory capacity.

The observed versus predicted risk of poor outcome after TAVR within risk deciles is shown in Figure 2A. In general, the model demonstrated good calibration with the observed outcomes, with an intercept of −0.01 (P value for difference from 0=0.806), a slope of 1.03 (P value for difference from 1=0.793), and an R^2 of 93%.

Model Validation

The baseline characteristics of the derivation versus validation cohort are presented in Table I in the online-only Data Supplement. Patients were similar in terms of baseline demographic and clinical characteristics, except that patients in the validation cohort had somewhat worse QoL at baseline (KCCQ-OS 40 versus 43, $P=0.007$). The model performed similarly in the validation cohort, with moderate discrimination (c-index=0.64) and reasonable calibration (Figure 2B), with an intercept of 0.07 (P value for difference from 0=0.277), a slope of 0.75 (P value for difference from 1=0.203), and an R^2 of 69%.

Table 2. Association of Preprocedure Factors With Poor Outcomes After TAVR

	Poor Outcome at 6 mo (Definition No. 1)		Poor Outcome at 1 y (Definition No. 2)	
Predictor	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Male sex	1.23 (0.96–1.57)	0.097	1.22 (0.97–1.53)	0.097
Diabetes mellitus	0.82 (0.63–1.06)	0.130	N/A	N/A
Major arrhythmia	1.29 (1.02–1.63)	0.036	1.13 (0.91–1.40)	0.280
Serum creatinine (per 1 mg/dL)	1.32 (1.03–1.70)	0.028	1.41 (1.11–1.79)	0.005
Mean arterial pressure (per 1 mm Hg)	1.01 (1.00–1.02)	0.209	N/A	N/A
Body mass index (per 1 kg/m^2)	0.98 (0.96–1.00)	0.104	1.00 (0.98–1.02)	0.791
Oxygen-dependent lung disease	1.77 (1.23–2.54)	0.002	1.80 (1.25–2.61)	0.002
Mean aortic valve gradient (per 10 mm Hg)	0.82 (0.75–0.89)	<0.001	0.84 (0.77–0.90)	<0.001
Mini-Mental Status Examination (per 1 point)	0.96 (0.92–1.00)	0.036	0.94 (0.90–0.97)	0.001
6-Min Walk Test distance (per 10 m)	0.97 (0.96–0.98)	<0.001	0.97 (0.96–0.98)	<0.001

CI indicates confidence interval; OR, odds ratio; and TAVR, transcatheter aortic valve replacement.

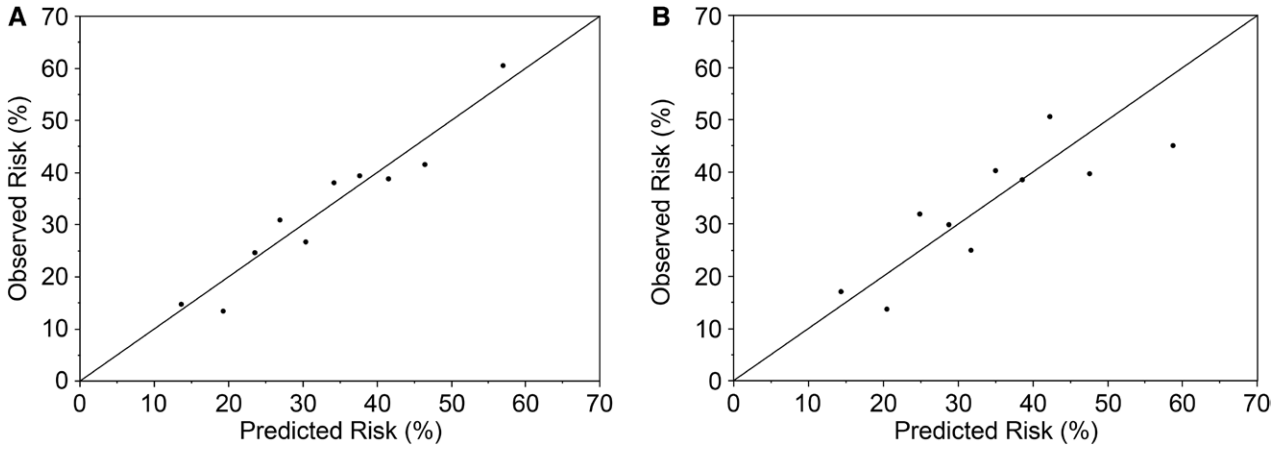

Figure 2. Calibration plots for prediction of poor outcome at 6 months after transcatheter aortic valve replacement (definition No. 1) in the derivation cohort (**A**) and validation cohort (**B**). **A**, Intercept of −0.01 (standard error, 0.04; *P* value [for difference from 0]=0.806), a slope of 1.03 (standard error, 0.10; *P* value [for difference from 1]=0.793), and R^2 of 93%. **B**, Intercept of 0.07 (standard error, 0.06; *P* value [for difference from 0]=0.277), a slope of 0.75 (standard error, 0.18; *P* value [for difference from 1]=0.203), and R^2 of 69%.

Sensitivity Analyses

When the same covariates were applied to the individual components of the composite end point (ie, mortality and poor QoL), there was general concordance of the 2 models such that the direction of association of each covariate with the 2 end-point components was similar (although the magnitude of the association varied; Table II in the online-only Data Supplement). When patients with major periprocedural complications (n=194) were excluded from the analytic population, the model *c*-index was unchanged at 0.66 and the calibration remained good (Figure I in the online-only Data Supplement). When the transfemoral and transapical cohorts were analyzed separately (baseline characteristics of the 2 groups are shown in Table III in the online-only Data Supplement), the model demonstrated similar discrimination within each access site group (*c*-index 0.65 versus 0.66, respectively), although the calibration was worse within the transapical group, with somewhat higher rates of poor outcomes than predicted (Figure II in the online-only Data Supplement). Finally, when we excluded the 6MWT distance and the SF-12 as potential predictors and included the 12-item KCCQ (for ease of implementation), the discrimination decreased slightly (*c*-index 0.64; Table IV in the online-only Data Supplement).

Outcomes According to Predicted Risk

To better understand the ability of the model to inform clinical decisions, we stratified patients into 3 groups according to their predicted risk of a poor outcome: Low risk (<25%; n=612), intermediate risk (25% to <50%; n=1314), and high risk (≥50%; n=211). The baseline characteristics of the 3 groups are shown in Table 3. Compared with patients at low risk of a poor outcome, high-risk patients less often had diabetes mellitus and had lower body mass indexes, worse kidney function, more frequent oxygen-dependent lung disease, lower mean aortic valve gradients, worse cognitive function, worse functional status, and worse QoL at baseline. In the 6 months after TAVR, 31% of high-risk patients died, and an additional 24% had very poor QoL or a decline in QoL. In contrast, among intermediate-risk patients, 17% had died, and an additional 20% had a very poor QoL or a decline in QoL, whereas among low-risk patients, only 8% had died and 10% had a very poor QoL or a decline in QoL (*P*<0.001; Figure 3A).

Definition No. 2 for Poor Outcome

For definition No. 2, the analytic population consisted of 2130 patients who had available QOL data or had died by 1-year follow-up. Of these, 1073 (50%) had a poor 1-year outcome based on either death (n=558), poor QoL (n=503), or QoL decline (n=12). After backward stepwise elimination, the final predictive model consisted of 8 covariates, which are summarized in Table 2. In general, the predictors were similar to those for definition No. 1, both in the variables that were included and their magnitude of association, except that the alternative model did not include mean arterial pressure or diabetes mellitus.

The *c*-index of the model was again 0.66, but the calibration of the model was better than the 6-month model (Figure IIIa in the online-only Data Supplement), with an intercept of −0.01 (*P* value for difference from 0=0.875), a slope of 1.01 (*P* value for difference from 1=0.871), and an R^2 of 97%. The model also performed reasonably well in the validation cohort, with good calibration (Figure IIIb in the online-only Data Supplement) although discrimination did decrease to a *c*-index of 0.62. We then divided the patients into 4 groups based on their predicted risk of poor outcome at 1 year: Low risk (<25%; n=65), intermediate risk (25% to <50%; n=963), high risk (50% to <70%; n=924), and very high risk (≥70%, n=178; Table V in the online-only Data Supplement). At 1 year after TAVR, 50% of very high-risk patients had died, and an additional 23% had poor QoL or a decline in QoL. In contrast, among low-risk patients, only 17% had died, and 12% had a poor QoL or a decline in QoL (*P*<0.001; Figure 3B).

Discussion

Among patients with severe aortic stenosis, TAVR is highly effective at relieving the hemodynamic obstruction and can lead to excellent outcomes in many patients; however, there are some patients who do not achieve either a survival or functional benefit from the intervention. In the present study, we have identified a set of covariates and 2 associated prediction models that can prospectively identify patients at high risk for

Table 3. Patient Characteristics According to Predicted Risk of Poor Outcome (Definition No. 1)

	Predicted Risk*		
	Low (n=612)	Intermediate (n=1314)	High (n=211)
Age, y	83.4 (8.2)	85.0 (6.6)	84.0 (7.0)
Male, %	43.0	53.3	78.2
Coronary artery disease, %	77.6	78.4	79.1
Cerebrovascular disease, %	25.3	27.1	27.5
Carotid disease, %	30.1	25.8	25.1
Peripheral vascular disease, %	42.5	42.8	37.9
Diabetes mellitus, %	45.1	34.2	27.5
Major arrhythmia, %	29.1	57.3	74.4
Creatinine, mg/dL	1.17 (0.41)	1.32 (0.46)	1.60 (0.60)
Hemoglobin, g/dL	11.9 (1.5)	11.7 (1.5)	11.5 (1.6)
Mean arterial pressure, mm Hg	86.6 (12.2)	87.4 (13.2)	86.9 (13.7)
Body mass index, kg/m^2	28.0 (7.4)	26.6 (5.9)	25.6 (5.2)
Oxygen-dependent lung disease, %	2.5	9.5	44.5
Pulmonary hypertension, %	35.8	41.6	42.2
Mitral regurgitation (>1+), %	20.9	26.6	30.3
Aortic regurgitation (>1+), %	9.2	11.5	8.5
Mean aortic gradient, mm Hg, %	53.0 (15.2)	41.3 (12.0)	32.7 (9.7)
Ejection fraction, %	55.5 (11.2)	51.2 (13.3)	46.6 (15.0)
Stroke volume, mL/beat	68.9 (24.0)	62.9 (19.4)	61.1 (20.1)
Mini-Mental Status Examination score	28.1 (2.1)	27.3 (2.9)	25.3 (4.3)
6-Min Walk Test, % able to perform	89.2	61.2	19.0
6-Min Walk Test distance, m	208.9 (128.9)	80.7 (88.6)	13.2 (33.1)
KCCQ-OS score	50.2 (21.6)	40.3 (20.8)	29.4 (18.5)
SF-12 Mental Summary score	49.6 (10.9)	47.3 (11.2)	43.9 (11.1)
STS mortality risk score	10.7 (4.3)	11.8 (4.3)	12.6 (4.6)
Outcomes at 6 mo, %			
Dead	8.8	20.3	37.4
Poor outcome	17.8	36.5	55.0

KCCQ-OS indicates Kansas City Cardiomyopathy Questionnaire Overall Summary; SF-12, 12-Item Short Form Health Survey; and STS, Society of Thoracic Surgeons.

*Low risk: <25%; intermediate risk: 25% to <50%; high risk: ≥50%.

poor outcomes after TAVR. The most important predictors of poor outcomes, using either definition, were poor functional capacity (as assessed by the distance walked on the 6MWT) and lower mean aortic valve gradients. Other important predictors were oxygen-dependent lung disease, renal dysfunction, and poorer baseline cognitive function. Of note, the Society for Thoracic Surgeons mortality risk score was not a predictor in either model. Taken together in a validated statistical model, these factors allowed us to predict each patient's probability of a poor outcome after TAVR.

Within the PARTNER trial, one third of all patients treated had a poor outcome at 6 months according to definition No. 1 (conservative definition), and one half of the patients had a poor outcome at 1 year using definition No. 2 (expanded definition). By applying these predictive models, however, we were able to refine these predictions. Using model No. 1, we were able to prospectively identify a cohort of patients with >50% probability of a poor 6-month outcome. Using model No. 2, we were able to prospectively identify a small but important group of patients with >70% probability of a poor 1-year outcome. Such information could help inform clinical decision making for patients and their physicians when TAVR is considered and could also help patients and their families set realistic expectations when they choose to undergo TAVR.

Importance of a Composite End Point

Although our definitions for poor outcome after TAVR are unique among prior studies, we believe that the optimal definition for a poor outcome after TAVR should reflect a failure to achieve the goals of the intervention and therefore must include both a mortality and a QoL component. Combining these 2 end points into a single definition can be challenging, however.[11] Nonetheless, in this elderly population of patients with multiple comorbidities, inclusion of QoL as a component of the determination of a poor (or acceptable) outcome is critical, because improved QoL can be the primary treatment goal of many patients considering TAVR. We believe that the definitions of poor outcome that we considered reflect

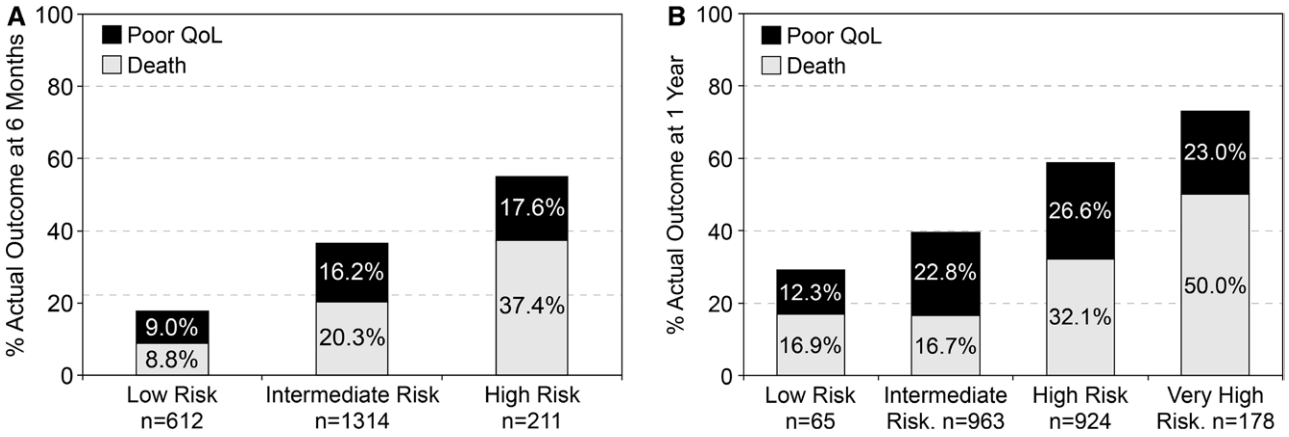

Figure 3. Outcomes of patients by their predicted risk of poor outcome at baseline at (**A**) 6 months (definition No. 1) and (**B**) 1 year (definition No. 2). QoL indicates quality of life.

the treatment goals of patients considering TAVR, because patients who have minimal symptoms choose TAVR primarily to achieve an expected improvement in survival, whereas patients with substantial symptom burden most likely undergo TAVR for an expected improvement in symptoms.

Prior Studies

There have been a number of previous efforts to determine the predictors of poor outcome after TAVR. To date, all of these analyses have been restricted to identifying predictors of mortality or specific short-term complications, such as stroke or kidney dysfunction.[9,21–23] Despite differences in the study populations and settings, some factors have been consistently found to be prognostically important among patients undergoing TAVR. In a single-center German study, older age, lower body mass index, NYHA class IV symptoms, depressed left ventricular function, and higher estimated surgical risk score were independently predictive of 1-year mortality.[21] In a large, multicenter French registry, higher estimated surgical risk score, NYHA class III to IV symptoms, transapical approach, and postimplantation aortic regurgitation were associated with reduced survival.[9] In a multicenter Canadian study, chronic lung disease, chronic kidney disease, atrial fibrillation, and a subjective assessment of frailty were all associated with long-term mortality after TAVR.[23] Finally, in a single-center Canadian study, male sex, chronic lung disease, and the 6MWT distance were associated with 1-year mortality after TAVR.[24]

Although our models also included many of these same factors (body mass index, lung disease, kidney disease, arrhythmias, functional and cognitive decline [components of frailty]), the present study offers advantages compared with these previous studies. Most important, our models were based on preprocedural factors alone and therefore can be used prospectively to inform clinical decision making. It is also one of the few studies that performed model validation, which provides greater assurance of reliability.

Implications for Clinical Practice

One of the main goals of developing a prediction model is to inform clinical practice and to counsel patients and their families as to the expected outcomes of care. In the case of our models, however, their discriminative ability (as measured by the *c*-index) was only moderate, at best, which limits our ability to reliably identify individuals who are certain not to benefit from TAVR (ie, medical futility). Although some prediction models are highly discriminative (eg, those that predict short-term mortality after angioplasty),[25] *c*-indices of 0.62 to 0.66, as obtained for the models in the present study, are similar to those of other cardiovascular prediction models (eg, those for predicting restenosis after angioplasty[26] or readmission after acute myocardial infarction).[27]

We believe that the limited discrimination of our initial models reflects several factors. First, QoL outcomes, although exceedingly important to patients, can be quite challenging to predict.[28] Nonetheless, we believe that the inclusion of QoL in our combined end point is a key strength of the present study. By integrating QoL into our definition of a poor outcome, we believe that our model is better aligned with the goals of many patients who are considering TAVR. Second, some potentially important risk factors for poor outcomes (such as frailty scales and disability) were not routinely collected in these early studies of TAVR. When data relating to additional markers of frailty (such as grip strength and gait speed) are available, it will be important to determine the incremental prognostic information gained from their addition to the models, because such measures have been demonstrated to predict poor outcomes with other therapies.[29,30] Because TAVR is evolving rapidly, novel predictors of poor outcomes will certainly continue to be discovered. When such factors are identified in the future, their incremental predictive value can be tested with our models, thereby leading to further refinement and improvement of the models over time.

Notwithstanding these challenges and limitations, we believe our models can be useful in clinical practice. The models were well calibrated, a key factor in determination of the clinical usefulness of a model when perfect discrimination is not achievable,[31] which indicates that our ability to inform patients about their probability of a poor outcome is quite reasonable. For example, we were able to identify a group of patients with a nearly 70% risk of poor outcome at 1 year. Although we cannot state with certainty which patients will or will not have that poor outcome, this assessment of risk could be quite valuable to patients as they decide whether or not to

choose TAVR, particularly given the virtual absence of reliable information that is currently available. Finally, these models (or future iterations) could eventually be applied in routine clinical care to improve decisional quality, reduce anxiety associated with the treatment decision, and provide patients and their families with realistic expectations of recovery.

Study Limitations

The present study had several important limitations. First, the study population was derived from the PARTNER trial, which included patients with a mean Society for Thoracic Surgeons mortality risk score of ≈12%, much higher than most previous studies. Consequently, it is uncertain whether our models apply to patients at moderate risk. Nonetheless, because many of the factors that were included in our final models had been identified previously as being associated with poor outcomes even in moderate-risk TAVR patients, there is reason to believe such extrapolation may be reasonable until future studies evaluating the performance of our models in lower-risk patients are performed. Second, given the reduced discrimination and calibration in the validation cohort compared with the derivation cohort, external validation of these models will be particularly important to ensure that the predictive ability of our models remains consistent outside of the PARTNER trial and registry populations.

Conclusions

Using a large, multicenter cohort of patients with severe, symptomatic aortic stenosis who underwent TAVR, we have created and validated 2 related prediction models for poor outcome after TAVR based on readily available preprocedure patient characteristics. Although model discrimination was only moderate, with these models it is possible to identify subsets of patients who are relatively unlikely to derive meaningful survival or QoL benefit from TAVR. In the future, providing this information to patients prospectively could offer valuable guidance as patients and their families decide whether or not to undergo TAVR. Further studies are necessary to understand the incremental contribution of additional risk factors to the discrimination of the models and to understand how the models perform in lower-risk TAVR populations.

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Disclosures

Dr Reynolds reports receipt of research support from Edwards Lifesciences and Medtronic and consulting income from Medtronic. Dr Kodali has received consulting income from Edwards Lifesciences and Medtronic and has served as an advisory board member for Thubrikar Aortic Valve, Inc, Paieon Medical, and St. Jude Medical. Dr Thourani reports receiving research support from Edwards Lifesciences and Sorin Medical; consulting income from DirectFlow, St. Jude Medical, and Sorin Medical; and royalties/intellectual property rights from Apica. Dr Rodés-Cabau reports receipt of consulting income from Edwards Lifesciences and St. Jude Medical. Drs Leon and Mack received travel reimbursements from Edwards Lifesciences for activities related to their positions on the Executive Committee of the PARTNER Trial. Dr Cohen has received research support from Edwards Lifesciences, Medtronic, Boston Scientific, Abbott Vascular, MedRad, Merck/Schering-Plow, and Eli Lilly-Daiichi Sankyo; consulting income from Schering-Plow, Eli Lilly, Medtronic, and Cordis; and speaking honoraria from Eli Lilly, The Medicines Company, and St. Jude Medical. The other authors report no conflicts.

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CLINICAL PERSPECTIVE

In patients with severe aortic stenosis at high surgical risk, transcatheter aortic valve replacement (TAVR) offers substantial reductions in mortality and improvement in quality of life compared with medical therapy and similar long-term outcomes to surgical valve replacement; however, a substantial proportion of patients do not improve functionally or live longer after TAVR. Using data from 2137 TAVR patients from the PARTNER (Placement of Aortic Transcatheter Valve) study, we sought to identify patients at high risk for poor outcome after TAVR using a novel approach that integrates both quality of life and mortality outcomes. We used these data to develop and validate a multivariable model to identify patients at high risk for poor outcome. Although model discrimination was moderate, we were able to identify a group of patients with a nearly 70% risk of poor outcome at 1 year. Although one cannot predict with certainty whether a particular patient will or will not have that poor outcome, this assessment of risk could be quite valuable to patients to improve decisional quality, reduce anxiety associated with the TAVR treatment decision, and provide patients and their families with realistic expectations of recovery. These models can also serve as the basis by which to test the incremental value of novel predictive markers of poor outcomes after TAVR, such as markers of frailty, thereby leading to further refinement of the models over time.

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Predictors of Poor Outcomes After Transcatheter Aortic Valve Replacement: Results From the PARTNER (Placement of Aortic Transcatheter Valve) Trial

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SUPPLEMENTAL MATERIAL

Supplemental Table 1. Characteristics of patients in the development cohort vs. validation cohort

	Development Cohort n=1420	Validation Cohort n=717
Age (y)	84.4 (7.1)	84.3 (7.3)
Male (%)	51.5	55.4
Coronary artery disease (%)	77.7	79.2
Cerebrovascular disease (%)	26.0	27.9
Carotid disease (%)	26.5	27.8
Peripheral vascular disease (%)	41.8	43.0
Diabetes mellitus (%)	37.2	35.6
Major arrhythmia (%)	50.2	52.3
Creatinine (mg/dL)	1.32 (0.48)	1.29 (0.48)
Hemoglobin (g/dL)	11.7 (1.6)	11.8 (1.5)
Mean arterial pressure (mmHg)	87.1 (12.7)	87.2 (13.5)
Body mass index (kg/m²)	26.7 (6.3)	27.2 (6.5)
Oxygen-dependent lung disease (%)	10.6	11.7
Pulmonary hypertension (%)	40.7	38.5
Mitral regurgitation (>1+) (%)	25.0	25.9
Aortic regurgitation (>1+) (%)	10.0	11.6
Mean aortic gradient (mmHg)	43.9 (14.2)	43.6 (14.4)
Ejection fraction (%)	52.1 (13.1)	51.7 (13.3)
Stroke volume (mL/beat)	64.5 (21.5)	64.5 (20.2)
Mini-Mental Status Exam score	27.4 (2.8)	27.2 (3.3)
6-Min Walk Test (% able to perform)	65.7	63.7
6-Min Walk Test distance (m)	112.8 (118.9)	106.7 (116.6)
KCCQ Overall Summary score	42.9 (21.9)	40.3 (21.3)
SF-12 Mental Summary score	47.6 (11.1)	47.7 (11.4)
STS mortality risk score	11.6 (4.6)	11.4 (3.9)
Outcomes at 6 Months		
Dead (%)	18.7	20.5
Poor Outcome (%)	32.9	33.1

KCCQ, Kansas City Cardiomyopathy Questionnaire; STS, Society of Thoracic Surgeons

Supplemental Table 2. Association of pre-procedure factors with individual components of poor outcome after TAVR (Definition #1)

	Death			Poor QoL		
	OR	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**
Male sex	1.06	(0.84-1.34)	0.613	1.28	(0.98-1.67)	0.073
Diabetes mellitus	0.80	(0.62-1.02)	0.069	0.75	(0.57-0.99)	0.043
Major arrhythmia	1.34	(1.07-1.68)	0.010	1.31	(1.02-1.70)	0.035
Creatinine (per 1 mg/dL)	1.60	(1.28-2.00)	<0.001	0.90	(0.67-1.19)	0.453
Mean arterial pressure (per 1 mmHg)	1.00	(1.00-1.01)	0.425	1.00	(0.99-1.01)	0.679
Body mass index (per 1 kg/m2)	0.96	(0.94-0.98)	<0.001	1.02	(1.00-1.04)	0.074
Oxygen-dependent lung disease	1.49	(1.07-2.06)	0.017	1.41	(0.97-2.07)	0.076
Mean aortic valve gradient (per 10 mmHg)	0.83	(0.76-0.90)	<0.001	0.84	(0.76-0.92)	<0.001
Mini-Mental Status Exam (per 1 point)	0.96	(0.93-1.00)	0.041	0.99	(0.95-1.04)	0.790
6-Min Walk Test distance (per 10m)	0.97	(0.96-0.98)	<0.001	0.98	(0.97-0.99)	<0.001
		c-index	0.67		**c-index**	0.63

Supplemental Table 3. Characteristics of patients in the transfemoral vs. transapical cohorts

	Transfemoral n=1261	Transapical n=876	P-Value
Age (y)	84.4 (7.7)	84.4 (6.2)	0.864
Male (%)	55.8%	48.5%	<0.001
Coronary artery disease (%)	75.4%	82.3%	<0.001
Cerebrovascular disease (%)	23.2%	31.5%	<0.001
Carotid disease (%)	22.8%	32.9%	<0.001
Peripheral vascular disease (%)	28.6%	61.8%	<0.001
Diabetes mellitus (%)	37.4%	35.5%	0.363
Major arrhythmia (%)	52.7%	48.3%	0.043
Creatinine (mg/dL)	1.31 (0.48)	1.31 (0.47)	0.915
Hemoglobin (g/dL)	11.7 (1.6)	11.8 (1.5)	0.752
Mean arterial pressure (mmHg)	86.4 (12.9)	88.2 (13.0)	0.002
Body mass index (kg/m²)	27.4 (6.7)	26.2 (5.8)	<0.001
Oxygen-dependent lung disease (%)	12.3%	9.0%	0.017
Pulmonary hypertension (%)	41.2%	38.1%	0.149
Mitral regurgitation (>1+) (%)	25.3%	25.3%	0.981
Aortic regurgitation (>1+) (%)	11.2%	9.6%	0.238
Mean aortic gradient (mmHg)	44.3 (14.6)	43.1 (13.9)	0.066
Ejection fraction (%)	52.0 (13.4)	51.9 (12.8)	0.793
Stroke volume (mL/beat)	64.7 (22.4)	64.1 (19.0)	0.487
Mini-Mental Status Exam score	27.3 (3.2)	27.5 (2.6)	0.072
6-Min Walk Test (% able to perform)	61.4%	70.3%	<0.001
6-Min Walk Test distance (m)	103.8 (116.2)	120.8 (120.1)	0.001
KCCQ Overall Summary score	40.9 (21.6)	43.6 (21.7)	0.005
SF-12 Mental Summary score	47.4 (11.2)	47.9 (11.2)	0.335
STS mortality risk score	11.2 (4.1)	12.1 (4.7)	<0.001

KCCQ, Kansas City Cardiomyopathy Questionnaire; STS, Society of Thoracic Surgeons

Supplemental Table 4. Association of pre-procedure factors with poor outcome after TAVR using the alternative model (Definition #1; excluding 6MWT as a predictor and using 90% as the cut-point for variable selection)

	Poor Outcome at 6 Months	
	OR (95% CI)	**P-Value**
Diabetes mellitus	0.76 (0.62-0.93)	0.008
Major arrhythmia	1.41 (1.17-1.71)	<0.001
Creatinine (per 1 mg/dL)	1.23 (1.01-1.50)	0.038
Oxygen-dependent lung disease	1.62 (1.22-2.17)	0.001
Mean aortic valve gradient (per 10 mmHg)	0.81 (0.75-0.87)	<0.001
Mini-Mental Status Exam (per 1 point)	0.97 (0.94-1.00)	0.056
KCCQ-12 Score (per 10 points)	0.91 (0.87-0.96)	<0.001

KCCQ-12, 12-item Kansas City Cardiomyopathy Questionnaire
c-index=0.64

Supplemental Table 5. Patient characteristics according to predicted risk of poor outcome (Definition #2)

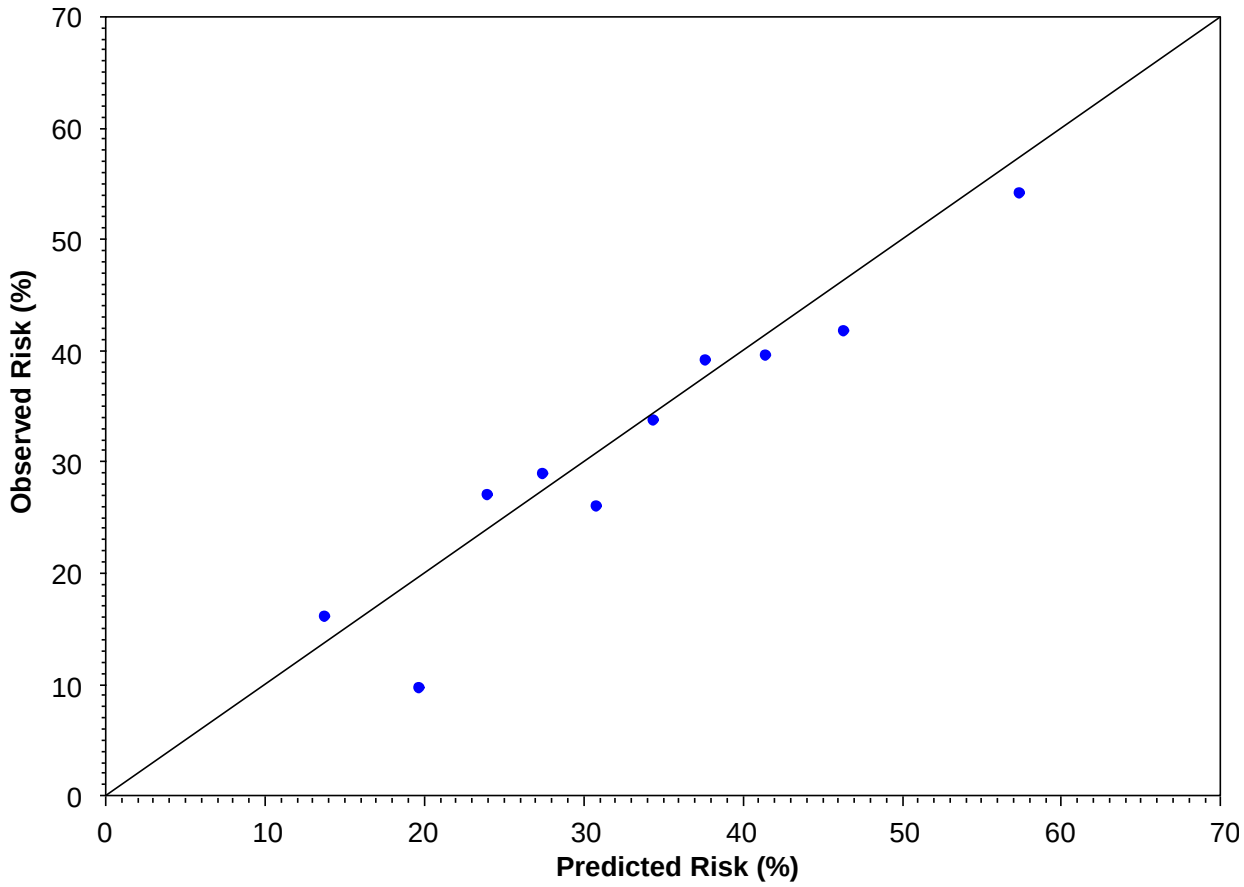
	Predicted Risk*			
	Low	**Intermediate**	**High**	**Very High**
	n=65	**n=963**	**n=924**	**n=178**
Age (y)	83.1 (8.7)	84.5 (7.5)	84.7 (6.7)	83.3 (7.4)
Male (%)	41.5	43.4	59.7	78.1
Coronary artery disease (%)	80.0	75.9	79.8	79.8
Cerebrovascular disease (%)	30.8	26.6	27.3	28.7
Carotid disease (%)	33.8	28.8	24.9	28.1
Peripheral vascular disease (%)	38.5	45.1	40.6	40.4
Diabetes mellitus (%)	30.8	35.4	38.2	42.1
Major arrhythmia (%)	35.4	42.4	58.9	62.4
Creatinine (mg/dL)	1.03 (0.33)	1.18 (0.40)	1.40 (0.48)	1.66 (0.61)
Hemoglobin (g/dL)	11.9 (1.5)	11.8 (1.5)	11.7 (1.6)	11.3 (1.6)
Mean arterial pressure (mmHg)	88.9 (11.3)	88.1 (12.9)	86.3 (13.2)	84.5 (14.1)
Body mass index (kg/m^2)	25.4 (5.0)	26.7 (6.2)	27.29 (6.6)	26.8 (6.0)
Oxygen-dependent lung disease (%)	1.5	2.7	12.6	50.0
Pulmonary hypertension (%)	35.4	38.8	43.4	42.7
Mitral regurgitation (>1+) (%)	21.5	24.1	26.7	30.9
Aortic regurgitation (>1+) (%)	13.8	9.8	11.6	9.6
Mean aortic gradient (mmHg)	59.4 (17.8)	48.7 (14.4)	39.8 (11.0)	33.1 (10.4)
Ejection fraction (%)	58.5 (8.8)	54.5 (12.1)	50.6 (13.5)	45.7 (14.9)
Stroke volume (mL/beat)	76.1 (44.5)	65.5 (19.7)	64.2 (20.3)	59.8 (19.8)
Mini-Mental Status Exam score	29.1 (1.3)	28.1 (2.1)	27.0 (2.8)	24.0 (4.9)
6-Min Walk Test (% able to perform)	100.0	82.7	51.0	19.1
6-Min Walk Test distance (m)	356.8 (114.9)	160.2 (115.3)	56.7 (72.8)	11.7 (33.5)
KCCQ Overall Summary score	55.4 (19.8)	47.6 (21.2)	37.9 (20.1)	28.9 (18.6)

SF-12 Mental Summary score	50.6 (11.4)	49.4 (10.7)	46.6 (11.1)	44.1 (11.2)
STS mortality risk score	9.6 (3.6)	11.0 (4.0)	11.9 (4.6)	13.2 (4.7)
Outcomes at 1 Year				
Dead (%)	29.2	39.6	58.8	73.0
Poor Outcome (%)	16.9	16.7	32.1	50.0

MAP, mean arterial pressure; MMSE, mini-mental status exam; 6MWT, 6-minute walk test; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire-Overall Summary; MCS, mental components summary; STS, Society of Thoracic Surgeons

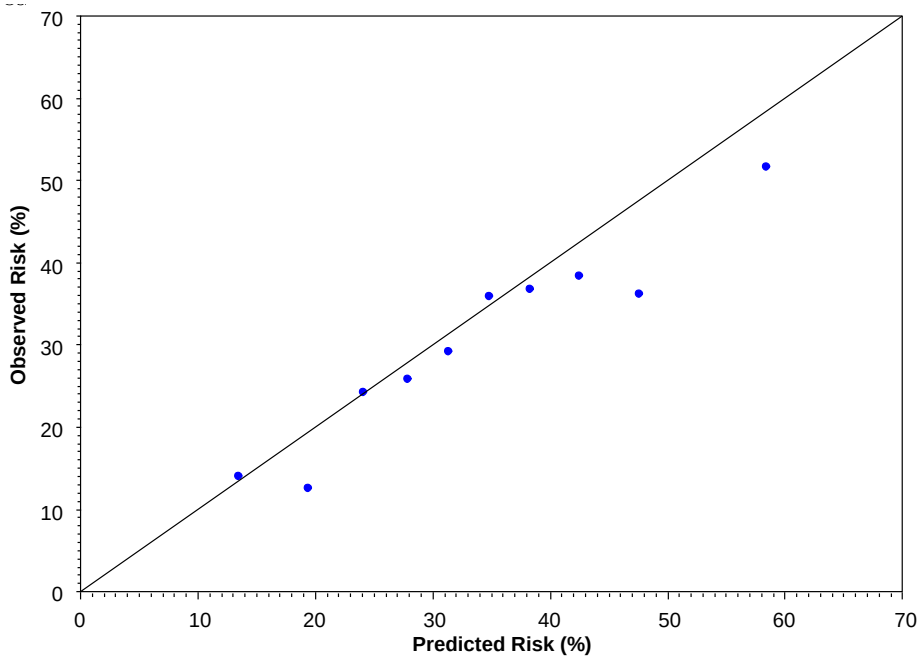
[*] Low Risk: <25%, Intermediate Risk: 25 to <50%, High Risk: 50 to <70%, Very High Risk: ≥70%

Supplemental Figure 1. Calibration plot for prediction of poor outcome (Definition #1) after TAVR after excluding patients who experienced major peri-procedural complications ; Intercept of -0.0001 (SE 0.04; p-value [for difference from 0]=0.998), a slope of 0.95 (SE 0.11; p-value [for difference from 1]=0.640), and R^2 of 90%.

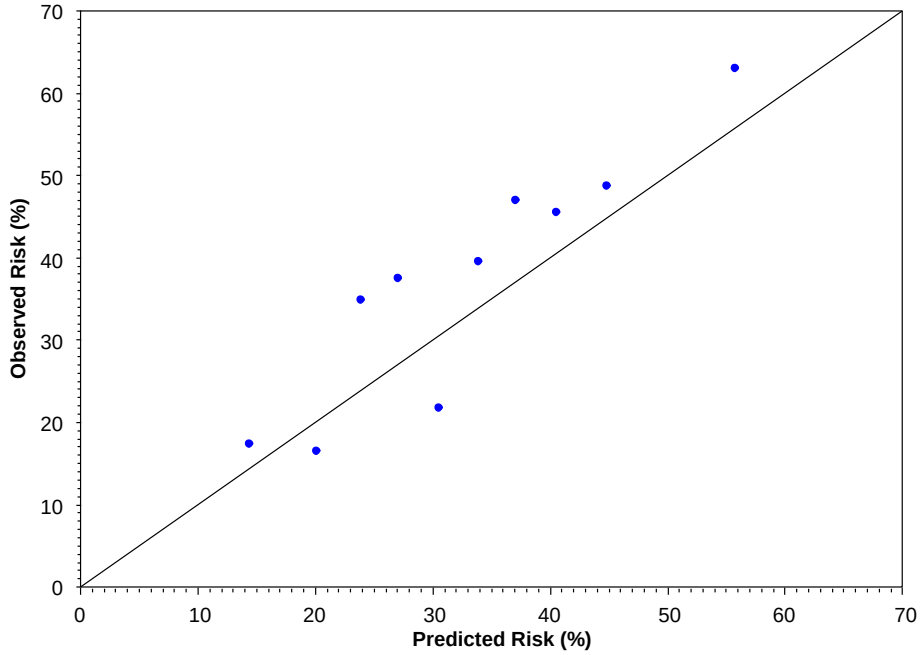


Supplemental Figure 2. Calibration plot for prediction of poor outcome (Definition #1) after TAVR via transfemoral route (a) and transapical route (b). (a) Intercept of 0.02 (SE 0.03; p-value [for difference from 0]=0.538), a slope of 0.84 (SE 0.09; p-value [for difference from 1]=0.105), and R^2 of 92%. (b) Intercept of 0.01 (SE 0.06; p-value [for difference from 0]=0.917), a slope of 1.11 (SE 0.18; p-value [for difference from 1]=0.543), and R^2 of 83%.

a.

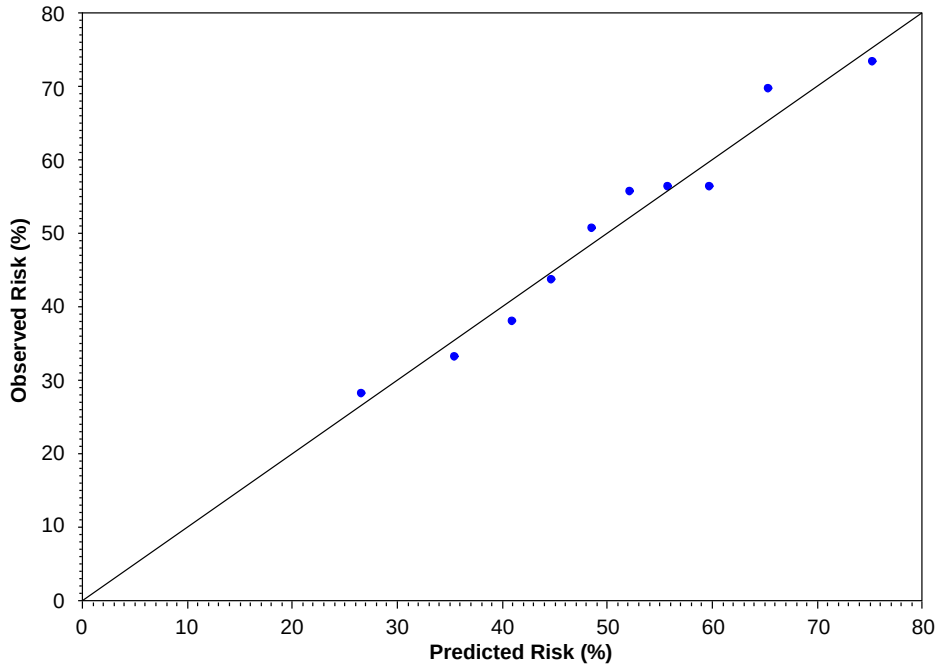


b.



Supplemental Figure 3. Calibration plots for prediction of poor outcome at 1 year after TAVR (Definition #2) in the derivation cohort (a) and validation cohort (b). (a) Intercept of -0.01 (SE 0.04; p-value [for difference from 0]=0.806), a slope of 1.01 (SE 0.07; p-value [for difference from 1]=0.871), and R^2 of 97%. (b) Intercept of 0.11 (SE 0.06; p-value [for difference from 0]=0.108), a slope of 0.79 (SE 0.11; p-value [for difference from 1]=0.093), and R^2 of 86%.

a.



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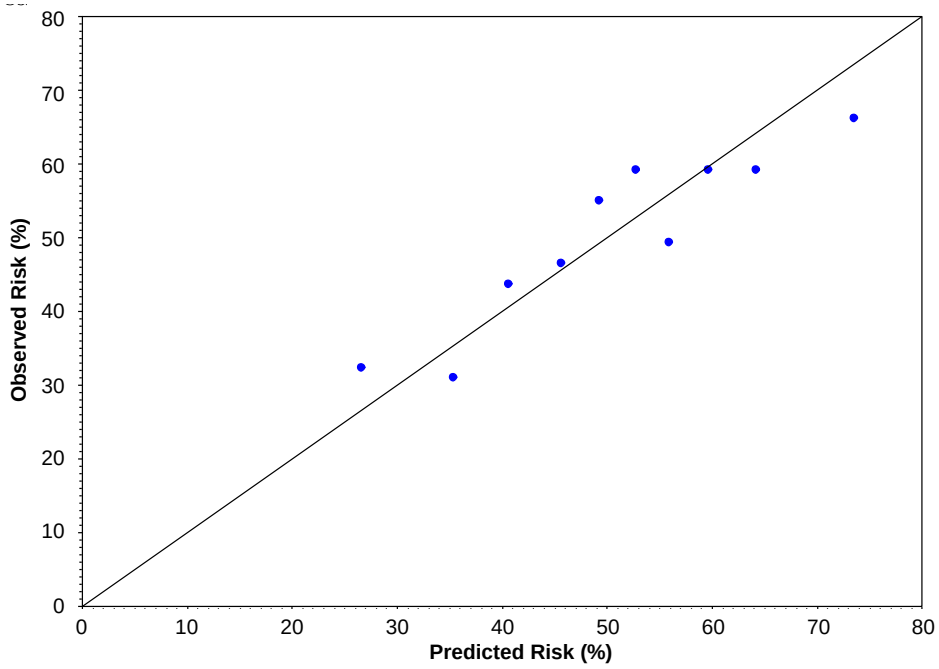

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