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ORIGINAL RESEARCH ARTICLE

Cost-Effectiveness of Transcatheter Versus Surgical Aortic Valve Replacement in Patients With Severe Aortic Stenosis at Intermediate Risk

Results From the PARTNER 2 Trial

BACKGROUND: In patients with severe aortic stenosis (AS) at intermediate surgical risk, treatment with transcatheter aortic valve replacement (TAVR) or surgical aortic valve replacement (SAVR) results in similar rates of death or stroke at 2 years. Whether TAVR is cost-effective compared with SAVR for intermediate-risk patients remains uncertain.

METHODS: Between 2011 and 2014, 3110 intermediate-risk AS patients were treated with TAVR or SAVR in the PARTNER 2 trial (Placement of Aortic Transcatheter Valves 2). A total of 2032 patients were randomized to receive TAVR using the SAPIEN XT valve (XT-TAVR) or SAVR in the PARTNER 2A trial, whereas the PARTNER S3i registry included an additional 1078 patients treated with TAVR using the SAPIEN 3 valve (S3-TAVR), which offers a lower delivery profile and sealing skirt designed to reduce paravalvular regurgitation compared with XT-TAVR. Procedural costs were estimated using measured resource utilization. Other in-trial costs were assessed by linkage of trial data with Medicare claims (n=2333) or by linear regression models for unlinked patients (n=682). Health utilities were estimated using the EQ-5D at baseline and 1, 12, and 24 months. Using a Markov model informed by in-trial costs, utilities, and survival data, lifetime cost-effectiveness from the perspective of the US healthcare system was estimated in terms of cost per quality-adjusted life-year gained.

RESULTS: Although procedural costs were ≈$20 000 higher with TAVR than SAVR, total cost differences for the index hospitalization were only $2888 higher with XT-TAVR (*P*=0.014) and were $4155 lower with S3-TAVR (*P*<0.001) owing to reductions in length of stay with TAVR. Follow-up costs were significantly lower with XT-TAVR (Δ=−$9304; *P*<0.001) and S3-TAVR (Δ=−$11 377; *P*<0.001) than with SAVR. Over a lifetime horizon, TAVR was projected to lower total costs by $8000 to $10 000 and to increase quality-adjusted survival by 0.15 to 0.27 years. XT-TAVR and S3-TAVR were found to be economically dominant compared with SAVR in 84% and 97% of bootstrap replicates, respectively.

CONCLUSIONS: Among intermediate-risk AS patients, TAVR is projected to be economically dominant from the perspective of the US healthcare system by providing both greater quality-adjusted life expectancy and lower long-term costs than SAVR. If long-term data demonstrate comparable late mortality with TAVR and SAVR, these findings suggest that TAVR might be the preferred treatment strategy for intermediate-risk AS patients based on both clinical and economic considerations.

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Clinical Perspective

What Is New?

- Previous economic analyses have demonstrated that transcatheter aortic valve replacement (TAVR) is cost-effective, although not cost-saving, compared with surgical aortic valve replacement (SAVR) in patients with aortic stenosis at high surgical risk.
- Whether TAVR is cost-effective compared with SAVR for AS patients at intermediate surgical risk was uncertain.
- In this analysis, TAVR was projected to lower total costs by $8000 to $10 000 and to increase quality-adjusted survival by 0.15 to 0.27 years compared with SAVR over a lifetime horizon.
- Compared with SAVR, TAVR using either the SAPIEN XT valve or the SAPIEN 3 valve was found to be economically dominant in 84% and 97% of bootstrap replicates, respectively.

What Are the Clinical Implications?

- This is the first analysis to demonstrate that TAVR is an economically dominant strategy, by providing both greater quality-adjusted life expectancy and lower long-term costs, compared with SAVR in patients with severe aortic stenosis at intermediate surgical risk.
- If long-term data demonstrate comparable late mortality with TAVR and SAVR, these findings suggest that TAVR may be the preferred treatment strategy for this patient population based on both clinical and economic considerations.

Over the past 10 years, transcatheter aortic valve replacement (TAVR) has become the preferred treatment modality for the management of severe aortic stenosis (AS) in inoperable patients and in patients at high risk for surgical complications.[1–4] More recently, TAVR has been shown to provide comparable outcomes to surgical aortic valve replacement (SAVR), both in terms of survival[5,6] and quality of life,[7] for intermediate-risk patients as well.

Given the size of the intermediate-risk population and the cost of transcatheter valve technology, decisions regarding the appropriateness of this technology from a societal perspective should incorporate both clinical and economic considerations. Previous economic analyses have demonstrated that TAVR is cost-effective, although not cost-saving, compared with medical therapy in inoperable AS patients[8] and compared with SAVR in AS patients at high surgical risk.[9,10] However, it is likely that the cost-effectiveness of TAVR versus SAVR in patients at intermediate surgical risk differs from that observed in higher-risk populations, owing not only to differences in patient comorbidities and surgical risk but also to the evolution of TAVR technology, implantation technique, and postprocedure management over time. As such, we performed a formal economic analysis alongside the PARTNER 2 trial (Placement of Aortic Transcatheter Valves 2) to compare the costs of TAVR and SAVR in an intermediate-risk population and to evaluate the relative cost-effectiveness of the 2 treatment strategies.

METHODS

Patient Population and Study Design

As described previously, the PARTNER 2 Trial, which included both the PARTNER 2A randomized trial and the nested SAPIEN 3 intermediate-risk (S3i) registry, enrolled patients with severe, symptomatic AS at intermediate surgical risk (defined as a predicted risk of 30-day mortality between 4% and 8%, based on either the Society of Thoracic Surgeons [STS] mortality risk score or clinical assessment by a multidisciplinary heart team).[5,11] In the PARTNER 2A trial, patients were stratified according to access route (transfemoral versus transthoracic) and randomized 1:1 to undergo either TAVR using the second-generation balloon-expandable SAPIEN XT valve (XT-TAVR) or SAVR. In the PARTNER S3i registry, which used the same inclusion and exclusion criteria as the randomized PARTNER 2A trial, all patients underwent TAVR using the third-generation SAPIEN 3 valve (S3-TAVR) via either a transfemoral or transthoracic approach, as dictated by patient anatomy. Both the PARTNER 2A trial and S3i registry were approved by the institutional review board at each site, and written informed consent was obtained from all patients. The economic study was funded by Edwards Lifesciences, the manufacturer of the SAPIEN 3 and SAPIEN XT valves; however, study design, analyses, and manuscript creation were performed solely by the authors without involvement from the sponsor. The data, analytic methods, and study materials for this analysis will not be made available to other researchers.

Analytic Overview

The economic analyses were performed from the perspective of the US healthcare system. The XT-TAVR versus SAVR comparison was based on the randomized PARTNER 2A trial, whereas the S3-TAVR analysis was based on comparison of the S3i registry with the surgical arm from the PARTNER 2A randomized trial. Although we considered limiting our analysis to the randomized comparison of XT-TAVR versus SAVR, we believed that it was also important to assess the cost-effectiveness of S3-TAVR, because it is the device used currently in the United States and offers several modifications over the SAPIEN XT valve that could affect clinical and economic outcomes (ie, a lower delivery profile and an external sealing skirt to reduce paravalvular regurgitation). Additionally, an examination of the S3-TAVR versus SAVR analysis alongside the XT-TAVR versus SAVR analysis provides insight into the economic impact of device modification and changing clinical practice over time.

Consistent with previous trial-based economic analyses,[9,10] the analytic cohort for both comparisons was based on the as-treated population from each trial (ie, those patients who

underwent attempted valve replacement). Survival and health status data were available for all patients through 2-year follow-up, whereas cost data (which were derived from linked Medicare claims as described below) were available through 2 years for the XT-TAVR and SAVR groups but only 1 year for the S3-TAVR group (because it was enrolled ≈1 year later than the randomized trial).

Our general approach was to first perform within-trial comparisons of cost and quality-adjusted life expectancy based on observed data. These observed data were then used to project patient-level survival, quality-adjusted survival, and costs over a lifetime horizon. Lifetime cost-effectiveness was estimated in terms of cost per quality-adjusted life-year (QALY) gained. All costs are shown in 2016 US dollars, and all future costs and benefits were discounted at 3%, consistent with US guidelines.[12]

Assessment of Costs

To calculate in-trial costs, probabilistic matching was used to link trial patients with Medicare claims data. Linkage was successful for 78% of the XT-TAVR and SAVR patients and 77% of the S3-TAVR cohort. Costs for the initial TAVR and SAVR procedures and the associated index hospitalizations were calculated using a combination of resource-based accounting (for the index procedure) and Medicare claims data (for nonprocedural costs). For the index valve replacement procedure, study centers recorded procedure duration, contrast usage, and intraprocedural complications. For the SAVR procedure, the cost was calculated based on valve cost (assumed to be $5000) and ancillary costs for an operating room (including overhead, nonphysician personnel, and general supplies), adjusted for observed procedural time. For the TAVR procedure, the cost was calculated based on valve cost (assumed to be $32 500), ancillary costs for a cardiac catheterization laboratory (adjusted for observed procedural time), and the cost of resources used (eg, sheaths, support wires, temporary pacing catheters) for an uncomplicated procedure, as well as those used for the treatment of specific complications (ie, major vascular complication; permanent pacemaker insertion).

For patients with linked Medicare claims (XT-TAVR, n=786; S3-TAVR, n=823; SAVR, n=724), nonprocedural costs were estimated based on hospital charges, which were converted to costs based on hospital and cost center–specific cost-to-charge ratios. All other in-trial costs, including repeat hospitalizations, physician fees, outpatient testing, and rehabilitation/skilled nursing care, were based directly on Medicare payments derived from claims. For patients who could not be linked with Medicare claims (XT-TAVR, n=208; S3-TAVR, n=254; SAVR, n=220), costs were estimated using regression models based on those patients with linked data. For the index hospitalization, separate models were fit for each treatment group. For follow-up costs, models were fit according to time interval (discharge to 30 days, 30 days to 6 months, 6 to 12 months, and 12 to 24 months). In addition to baseline patient characteristics and treatment group, model covariates included intensive care unit and non–intensive care unit length of stay (for the index hospitalization) and postprocedure complications (for the index hospitalization and all subsequent time intervals; see the Methods in the online-only Data Supplement for list of variables included in models).

Future costs beyond the trial period for all patients were projected using the regression model based on the last follow-up observation period for each comparison (12–24 months for XT-TAVR versus SAVR and 6–12 months for S3-TAVR versus SAVR).

Life Expectancy Estimation

Projected survival was estimated separately for the SAVR and TAVR groups. For the SAVR group, observed mortality between 6 and 24 months was compared with expected age- and sex-specific mortality from US life tables[13] to calculate a calibration factor. The 6- to 24-month time period was chosen to minimize the impact of perioperative events. For each surviving patient, life expectancy beyond 24 months was then estimated using the recalibrated life tables.

Long-term survival for the TAVR groups was estimated in an analogous fashion, after application of an additional hazard ratio (HR) for the comparison of TAVR versus SAVR mortality derived from a landmark analysis of trial data from between 6 and 24 months. Because the empirically derived HR did not differ significantly from unity (XT-TAVR versus SAVR: HR, 1.07; 95% confidence interval [CI], 0.78–1.45; S3-TAVR versus SAVR: HR, 1.04; 95% CI, 0.76–1.42), an HR of 1.0 was used for the base-case analysis.

Quality-Adjusted Life Expectancy

Consistent with current guidelines, quality-adjusted life years (QALYs) were used as the measure of health benefit.[12] QALYs are calculated by multiplying the time in each health state by the utility weight for that health state, where utility is a measure of a patient's preference for that condition (on a scale where 1 represents perfect health and 0 represents death).[14,15] To assess utilities, the EQ-5D questionnaire was administered to all patients at baseline, 1 month, 12 months, and 24 months, and responses were converted to health-state utilities with an algorithm derived from a US population reference group.[15] Observed QALYs were then calculated for each patient as the time-weighted average of the patient's utility values, with the midpoint between assessments used as the transition between health states. On the basis of previous studies,[9,10] we assumed that utilities at 6 months were the same as those at 12 months to avoid overestimating the recovery time for SAVR (and thus underestimating QALYs). Beyond the trial, utilities were estimated by use of linear regression models based on available data at 24 months. Quality-adjusted life expectancy beyond 24 months was calculated by multiplying estimated survival in 1-year intervals by predicted utilities.

Statistical Analysis

Continuous data are reported as mean±SD and compared with 2-sample Student *t* tests or Wilcoxon rank-sum tests as appropriate. Categorical data are reported as frequencies and compared with Fisher exact test. Group means and between-group differences (with associated 95% CIs) for projected life expectancy, quality-adjusted life expectancy, and costs were generated by bootstrap resampling with 1000 replicates. Incremental cost-effectiveness ratios (ICERs) were calculated as the difference in mean discounted

lifetime costs divided by the difference in mean discounted quality-adjusted life expectancy. Consistent with current recommendations, we considered an ICER <$50 000 per QALY gained to represent high economic value, an ICER between $50 000 and $150 000 per QALY to represent intermediate value, and an ICER >$150 000 per QALY gained to represent low value within the US healthcare system.[16] Because the S3-TAVR versus SAVR comparison was nonrandomized, all comparisons of S3-TAVR versus SAVR were adjusted for baseline differences by use of propensity score stratification for clinical outcomes and propensity bin bootstrapping for costs.[17] The propensity score methodology for these analyses was identical to that used to compare clinical outcomes between S3-TAVR and SAVR and to support US Food and Drug Administration approval of the SAPIEN 3 valve.[11]

Subgroup and Sensitivity Analyses

Because previous studies have demonstrated that patient-reported outcomes and economic outcomes associated with TAVR differ by access site,[2,6,7,9,10,17–19] in addition to the overall cost-effectiveness analysis, separate analyses, stratified by access site (transfemoral versus transthoracic using either a transapical approach or direct aortic approach), were performed for the randomized XT-TAVR versus SAVR comparison. We did not perform stratified analyses for the S3-TAVR versus SAVR comparisons because the definition of transfemoral eligibility was different for the PARTNER 2A trial (from which the SAVR patients were derived) than for the PARTNER S3i registry (from which S3-TAVR patients were derived) owing to differences in the diameter of the SAPIEN XT and SAPIEN 3 device delivery systems.

In addition to evaluating the effects of access site, lifetime cost-effectiveness results were estimated separately for subgroups according to sex, age (dichotomized at 85 years), STS risk score (dichotomized at 5%), and previous coronary artery bypass graft surgery for both the XT-TAVR versus SAVR and S3-TAVR versus SAVR comparisons. Sensitivity analyses were also performed to evaluate the effect of variation in the following parameters: discount rate, TAVR device cost, long-term mortality HR for TAVR versus SAVR, and follow-up costs associated with TAVR. In addition, we performed a sensitivity analysis that incorporated excess long-term mortality for patients with moderate or severe paravalvular regurgitation (HR estimated at 1.59 based on the trial data).

RESULTS

Patient Population

Of the 3110 patients enrolled in the PARTNER 2A trial and S3i registry, 944 underwent SAVR, 994 underwent XT-TAVR, and 1077 underwent S3-TAVR. Baseline characteristics of the analytic (as treated) cohorts are summarized in Table 1. Patients had a mean age of 81 years, and more than half were male. Patients in all groups were considered to be at intermediate surgical risk as demonstrated by a mean STS risk score of 5% to 6%. Patients treated with XT-TAVR were less likely to have peripheral arterial disease (28% versus 32%; *P*=0.029) and atrial fibrillation (31% versus 35%; *P*=0.050) than SAVR patients. S3-TAVR patients were more likely to be male (62% versus 55%; *P*=0.002), to have a lower STS risk score (5.3% versus 5.8%; *P*<0.001), and to have undergone previous PCI (32% versus 27%; *P*=0.013) than SAVR patients. Transfemoral access was used in 77% of the XT-TAVR group and 88% of the S3-TAVR group.

Table 1. Baseline Characteristics of Analytic Population

	XT-TAVR* (n=994)	S3-TAVR* (n=1077)	SAVR* (n=944)	*P* Value XT-TAVR Versus SAVR	*P* Value S3-TAVR Versus SAVR
Age, y	81.5±6.7	81.9±6.6	81.6±6.8	0.925	0.226
Male	537 (54)	665 (62)	519 (55)	0.673	0.002
STS risk score, %	5.8±2.1	5.3±1.3	5.8±1.9	0.669	<0.001
Coronary artery disease	685 (69)	750 (70)	628 (67)	0.260	0.133
Previous PCI	265 (27)	344 (32)	254 (27)	0.902	0.013
Previous CABG	233 (23)	301 (28)	243 (26)	0.239	0.264
Cerebrovascular disease	102 (10)	97 (19)	97 (10)	0.991	0.333
Peripheral artery disease	275 (28)	304 (28)	304 (32)	0.029	0.051
COPD	313 (32)	322 (30)	283 (30)	0.492	0.915
Atrial fibrillation	305 (31)	388 (36)	329 (35)	0.050	0.581
Diabetes mellitus	375 (38)	367 (34)	328 (35)	0.172	0.751
LV ejection fraction, %	56.5±10.6	58.6±13.4	55.4±11.8	0.093	<0.001
Transfemoral access	749 (77)	942 (88)	719 (77)	0.965	<0.001

Values are n (%) or mean±SD. CABG indicates coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; LV, left ventricular; PCI, percutaneous coronary intervention; S3, SAPIEN 3 valve; SAVR, surgical aortic valve replacement; STS, Society of Thoracic Surgery; TAVR, transcatheter aortic valve replacement; and XT, SAPIEN XT valve.

*As-treated population.

Table 2. Index Admission Resource Use and Costs for XT-TAVR Versus SAVR

Resource Category	XT-TAVR	SAVR	Difference (95% CI)*	*P* Value
Procedure duration, min	102±46 [94]	236±83 [219]	−134 (−140 to −128)	<0.001
Length of stay, d				
ICU	2.4±3.4 [1]	4.6±6.1 [3]	−2.2 (−2.6 to −1.8)	<0.001
Non-ICU	4.0±4.0 [3]	6.2±4.7 [5]	−2.3 (−2.7 to −1.9)	<0.001
Postprocedure	5.2±5.7 [4]	9.7±6.9 [8]	−4.6 (−5.1 to −4.0)	<0.001
Total	6.4±5.5 [5]	10.9±7.6 [8]	−4.5 (−5.1 to −3.9)	<0.001
Permanent pacemaker placement	72 (7.2)	66 (7.0)	0.3 (−2.0 to 2.5)	0.829
Major bleeding	95 (9.6)	438 (46.4)	−36.8 (−40.5 to −33.2)	<0.001
Major vascular complication	75 (7.5)	51 (5.4)	2.1 (-2.7 to 0.5)	0.055
Costs, $				
Index procedure costs	38 548±2874 [37 353]	16 465±3336 [15 654]	22 083 (21 805 to 22 346)	<0.001
Nonprocedural costs	19 417±17 390 [14 176]	37 409±33 958 [27 383]	−17 992 (−20 478 to −15 692)	<0.001
Physician fees	3827±1985 [3306]	5421±2558 [4759]	−1594 (−1802 to −1391)	<0.001
Total index admission costs†	61 433±17 532 [55 928]	58 545±32 023 [48 749]	2888 (562 to 5110)	0.014

Values are mean±SD [median] or n (%). CI indicates confidence interval; ICU, intensive care unit; SAVR, surgical aortic valve replacement; and TAVR, transcatheter aortic valve replacement.

*95% CIs of cost differences and the associated *P* values were derived via bootstrap resampling.

†Mean costs trimmed at 99th percentile.

Index Hospitalization Resource Use and Costs

Resource utilization and costs associated with the index hospitalization are shown in Tables 2 (XT-TAVR versus SAVR) and 3 (S3-TAVR versus SAVR). Although procedure duration was significantly shorter for both XT-TAVR and S3-TAVR than for SAVR, index procedure costs were more than $20 000 higher with both XT-TAVR and S3-TAVR, driven by the higher cost of the TAVR valve implant compared with a surgical bioprosthesis. However, the higher procedure costs associated with TAVR were offset by significant reductions in other costs, driven primarily by reductions in total length of stay (differences of 4.5 days and 6.3 days with XT-TAVR and S3-TAVR, respectively [*P*<0.001 compared with SAVR for both comparisons]) and days spent in the intensive care unit (differences of 2.2 days and 2.8 days with XT-TAVR and S3-TAVR, respectively [*P*<0.001 versus SAVR for both comparisons]). As a result, nonprocedural costs associated with the index hospitalization were ≈$18 000 lower with XT-TAVR than SAVR and ≈$23 000 lower with S3-TAVR than with SAVR (*P*<0.001 for both comparisons). Physician costs were also significantly lower with both XT-TAVR and S3-TAVR than with SAVR, driven mainly by reductions in anesthesia services. In aggregate, total index hospitalization costs were ≈$3000 higher per patient with XT-TAVR ($61 433 versus $58 545; *P*=0.014) and ≈$4000 lower per patient with S3-TAVR ($54 256 versus $58 410; *P*<0.001) than with SAVR.

Cumulative Resource Use and Costs

Follow-up resource utilization and costs derived from Medicare claims are summarized in Tables 4 and 5. Between discharge and 2-year follow-up, XT-TAVR led to significant reductions in hospital days and rehabilitation/skilled nursing facility days compared with SAVR. As a result, follow-up medical care costs were reduced by ≈$9000 per patient with XT-TAVR versus SAVR, which led to significantly lower cumulative 2-year costs with XT-TAVR ($107 716 versus $114 132; Δ=−$6414 [95% CI, −$11 571 to −$1616]; *P*=0.014). Larger differences in follow-up resource utilization were observed between S3-TAVR and SAVR, including significant reductions in the number of hospitalizations and a >50% reduction in total rehabilitation/skilled nursing days. As a result, 1-year follow-up costs with S3-TAVR were more than $11 000 lower per patient than with SAVR, which led to even greater cumulative cost savings ($80 977 versus $96 489; Δ=−$15 511 [95% CI, −$19 579 to −$11 487]; *P*<0.001). Most follow-up cost savings with both XT-TAVR and S3-TAVR compared with SAVR occurred within the first 6 months after the index hospitalization, with little to no difference in cost in later follow-up (Figures I and II in the online-only Data Supplement).

QALY and Cost Lifetime Projections

As reported previously, 2-year mortality was nonsignificantly lower in the XT-TAVR group than in the SAVR group (16.1% versus 17.5%, respectively).[5] Health-state utility scores, as measured by the EQ-5D, were significantly higher with XT-TAVR at 1 month.[7] At later time points, both XT-TAVR and SAVR patients reported improved health status compared with baseline, but there was no significant difference

between the groups.[7] As a result, in-trial QALYs were 1.39 years (95% CI, 1.36–1.42 years) and 1.32 years (95% CI, 1.28–1.35 years) for XT-TAVR and SAVR, respectively (mean difference 0.07 years; 95% CI, 0.02–0.12; *P*<0.001).

Using observed 2-year survival and predicted survival rates from the calibrated life table approach, life expectancy was estimated at 7.80 years for the XT-TAVR group and 7.64 years for the SAVR group (6.49 and 6.35 years after discounting, respectively; Figure III in the online-only Data Supplement). Projected quality-adjusted survival was slightly lower in both groups (5.16 versus 5.01 QALYs; mean difference 0.15 QALYs; 95% CI, −0.08 to 0.39). After incorporating costs in future years of life, total discounted lifetime costs were projected to be $7949 lower per patient with XT-TAVR than with SAVR (95% CI for difference, −$17 429 to $809) (Figure IV in the online-only Data Supplement).

Similar findings were seen when S3-TAVR was compared with SAVR. Two-year mortality was significantly lower with S3-TAVR than with SAVR (13.1% versus 17.1%, respectively; *P*=0.012). EQ-5D scores were also substantially better with S3-TAVR at 1 month (adjusted difference 0.078; 95% CI, 0.062–0.094; *P*<0.001) but did not differ thereafter. In-trial QALYs through 2-year follow-up were 1.44 years (95% CI, 1.41–1.46 years) and 1.33 years (95% CI, 1.30–1.37 years) for S3-TAVR and SAVR, respectively, with an estimated difference of 0.11 years (95% CI, 0.06–0.15 years; *P*<0.001). Life expectancy was projected to be 7.95 years with S3-TAVR and 7.61 years with SAVR (6.63 and 6.34 years after discounting; Figure V in the online-only Data Supplement), and discounted quality-adjusted life expectancy was projected to be 5.29 and 5.01 years with S3-TAVR and SAVR, respectively (mean difference 0.27 QALYs; 95% CI for difference, 0.06–0.51). Total discounted lifetime costs were projected to be $9692 per patient lower in the S3-TAVR group (95% CI for difference: -$18 886 to -$416; Figure IV in the online-only Data Supplement).

Cost-Effectiveness

Plots of the joint distributions of the projected differences in lifetime costs and QALYs between XT-TAVR and SAVR and between S3-TAVR and SAVR are shown in the Figure (A and B, respectively). On the basis of these lifetime estimates, XT-TAVR was projected to be economically dominant in 84% of bootstrap replicates and to provide high economic value compared with SAVR in 100% of replicates. Similarly, the probability that S3-TAVR would be economically dominant compared with SAVR was 97%, and the probability that it would provide high economic value was 100%.

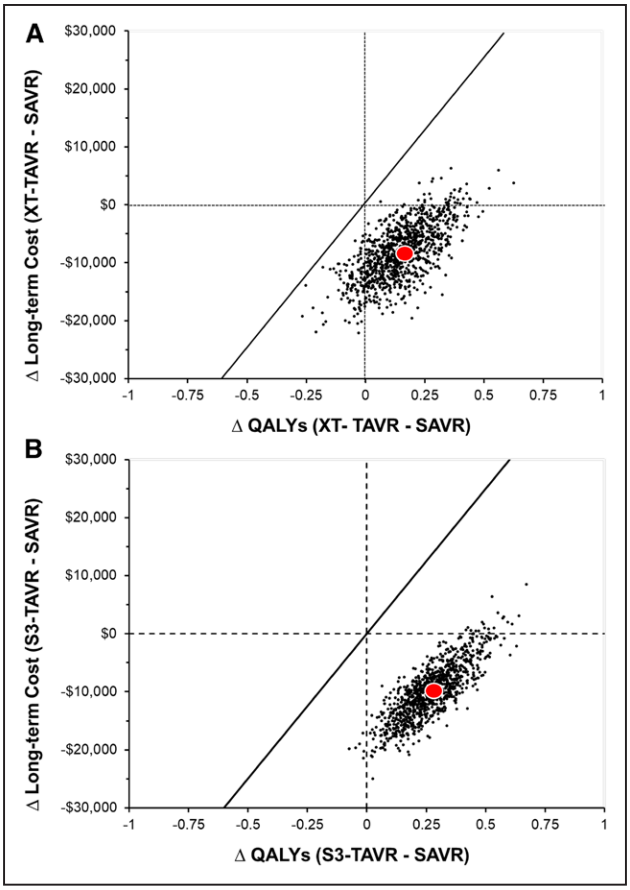

Figure. Mean incremental lifetime costs and quality-adjusted life-years (QALYs) for transcatheter aortic valve replacement (TAVR) vs surgical aortic valve replacement (SAVR).
A, SAPIEN XT transcatheter heart valve (XT-TAVR) vs SAVR comparison; **B,** SAPIEN S3 transcatheter heart valve (S3-TAVR) vs SAVR comparison. The solid red circle represents base-case estimates, the surrounding small circles represent individual results for 1000 replicates of the study using bootstrap resampling, and the solid line represents a willingness-to-pay threshold of $50 000 per QALY gained. For the XT-TAVR vs SAVR comparison, the base-case results demonstrated a gain of 0.15 QALYs and cost savings of $7949 per patient (after discounting). For the S3-TAVR vs SAVR comparison, the base-case results demonstrated a gain of 0.27 QALYs and cost savings of $9692 per patient (after discounting).

XT-TAVR Versus SAVR Analyses Stratified by Access Site

Resource utilization and costs associated with the index hospitalization are shown in Table I in the online-only Data Supplement for transfemoral XT-TAVR versus SAVR and in Table II in the online-only Data Supplement for transthoracic XT-TAVR versus SAVR. As expected, index procedure costs were significantly higher with both transfemoral and transthoracic XT-TAVR than with SAVR (*P*<0.001 for both comparisons). Although nonprocedural costs were significantly lower with both transfemoral and transthoracic XT-TAVR than with SAVR, the magnitude of difference was substantially larger for transfemoral XT-TAVR (Δ versus SAVR, −$21 614; 95% CI, −$24 440 to −$18 828; *P*<0.001) than for transthoracic XT-TAVR (Δ versus SAVR, −$6135; 95% CI,

−$10 268 to −$1669; *P*=0.002). As a result, index hospitalization costs associated with transthoracic XT-TAVR were significantly higher than for SAVR ($72 368 versus $55 216, respectively; *P*<0.001), whereas there was no significant difference in index hospitalization cost between transfemoral XT-TAVR and SAVR ($58 103 versus $59 568, respectively; *P*=0.264).

Follow-up resource utilization and costs derived from Medicare claims for the stratified analyses are summarized in Tables III and IV in the online-only Data Supplement. Between discharge and 2-year follow-up, transfemoral XT-TAVR was associated with fewer repeat hospitalizations and less use of rehabilitation and skilled nursing facilities than SAVR. As a result, follow-up medical care costs were reduced by ≈$12 000 per patient with transfemoral XT-TAVR versus SAVR, which led to significantly lower cumulative 2-year costs with transfemoral XT-TAVR ($102 496 versus $115 802; Δ=−$13 307 [95% CI, −$19 340 to −$7643]; *P*<0.001). Conversely, there was no significant difference in follow-up costs with transthoracic XT-TAVR compared with SAVR (Δ=−$792 [95% CI, −$8814 to $7645]; *P*=0.826). Thus, owing mainly to the higher costs associated with the index procedure, cumulative 2-year costs with transthoracic XT-TAVR were significantly higher than with SAVR ($124 471 versus $108 110; Δ=$16 316 [95% CI, $6460–$26 088]; *P*=0.002).

When these cost data were combined with in-trial survival and quality of life results and projected over a lifetime horizon, the cost-effectiveness of XT-TAVR versus SAVR differed substantially by access site. Among patients treated via the transfemoral approach, XT-TAVR was economically dominant in 96% of bootstrap replicates and provided high economic value in 100% of bootstrap replicates (Figure VI in the online-only Data Supplement). In contrast, patients treated with a transthoracic approach had higher lifetime costs and lower quality-adjusted life expectancy than those treated with SAVR. As a result, bootstrap replication demonstrated that XT-TAVR was economically dominated by SAVR in 57% of replicates, and the probability that XT-TAVR would provide high economic value was only 1% in those patients eligible only for transthoracic access (Figure VII in the online-only Data Supplement).

Subgroup and Sensitivity Analyses

Lifetime costs, effectiveness, and cost-effectiveness within other key subgroups are shown in Table V in the online-only Data Supplement (XT-TAVR versus SAVR) and Table VI in the online-only Data Supplement (S3-TAVR versus SAVR). In general, results were consistent with the primary analysis, because both XT-TAVR and S3-TAVR remained economically dominant compared with SAVR across subgroups based on age, sex, STS risk score, and previous coronary artery bypass graft surgery status.

The cost-effectiveness of both XT-TAVR and S3-TAVR compared with SAVR was relatively insensitive to modest variations in discount rate, TAVR valve cost, late mortality with TAVR, or inclusion of excess mortality associated with moderate or severe paravalvular regurgitation after TAVR (Tables 6 and 7; Tables VII and VIII in the online-only Data Supplement). When annual follow-up cost after TAVR was increased by 10% (≈$2000/year) compared with observed values, TAVR with either the XT or S3 valve was no longer economically dominant. If follow-up cost after TAVR was increased by 20% (≈$4000/year), neither XT-TAVR nor S3-TAVR was projected to provide high economic value compared with SAVR.

DISCUSSION

This is the first economic analysis to evaluate the cost-effectiveness of TAVR versus SAVR from the perspective of the US healthcare system in patients with severe AS at intermediate surgical risk. On the basis of the results of the PARTNER 2A trial and S3i Registry, TAVR using the SAPIEN XT valve or the SAPIEN 3 valve was projected to be an economically dominant strategy over a lifetime horizon, by providing both greater quality-adjusted life expectancy and lower long-term costs than SAVR. Cost savings in the TAVR cohorts were driven by both shorter length of stay during the index hospitalization and less resource utilization during follow-up in the form of fewer hospital days and fewer rehabilitation and skilled nursing facility days. Although TAVR with either valve implant was economically dominant compared with SAVR, results using the SAPIEN 3 valve demonstrated outcomes that were more favorable than those with the earlier generation SAPIEN XT valve, with significant gains in quality-adjusted life expectancy and lifetime cost savings of >$9000 per patient. These results were generally consistent across most patient subgroups and stable over a broad range of sensitivity analyses, although stratified analyses by access site did demonstrate that SAVR was projected to be a dominant strategy in the subset of patients who were ineligible for transfemoral access.

Although several previous studies have examined the cost-effectiveness of TAVR versus SAVR, these studies either have been restricted to patients at high surgical risk,[9,10] have involved only 1-year cost analysis,[20] or have been performed from a non-US perspective.[20,21] Using data from the PARTNER A trial (which enrolled high-risk patients), Reynolds and colleagues[10] found that TAVR using a first-generation balloon-expandable valve was of intermediate economic value compared with SAVR (ICER $76 877 per QALY gained), although economic value was higher for patients who were suitable for

Table 3. Index Admission Resource Use and Costs for S3-TAVR Versus SAVR

Resource Category	S3-TAVR	SAVR	Difference (95% CI)	*P* Value
Procedure duration min	84±38 [77]	236±83 [219]	−152 (−158 to −146)	<0.001
Length of stay, d				
ICU	1.8±2.9 [1]	4.6±6.1 [3]	−2.8 (−3.2 to −2.4)	<0.001
Non-ICU	2.7±4.8 [2]	6.2±4.7 [5]	−3.5 (−3.9 to −3.1)	<0.001
Postprocedure	4.1±5.4 [3]	9.7±6.9 [8]	−5.6 (−6.2 to −5.1)	<0.001
Total	4.6±5.7 [3]	10.9±7.6 [8]	−6.3 (−6.2 to −5.1)	<0.001
Permanent pacemaker placement	90 (8.4)	66 (7.0)	1.4 (−1.0 to 3.7%)	0.251
Major bleeding	46 (4.3)	438 (46.4)	−42.1 (−45.5 to −38.7)	<0.001
Major vascular complication	62 (5.8)	51 (5.4)	0.4 (−1.6 to 2.4)	0.729
Adjusted costs, $*				
Index procedure costs	37 776 (37 598 to 37 954)	16 502 (16 311 to 16 692)	21 275 (21 012 to 21 538)	<0.001
Nonprocedural costs	14 259 (12 582 to 15 935)	37 294 (33 501 to 39 086)	−23 035 (−25 511 to −20 559)	<0.001
Physician fees	2998 (2876 to 3120)	5403 (5272 to 5533)	−1760 (−4311 to 791)	<0.001
Total index admission costs†	54 256 (52 783 to 55 729)	58 410 (56 836 to 59 985)	−4155 (−6330 to −1979)	<0.001

Values are n (%) or mean (95% CI) for costs and mean±SD [median] for all other resources. CI indicates confidence interval; ICU, intensive care unit; S3, SAPIEN 3 valve; SAVR, surgical aortic valve replacement; and TAVR, transcatheter aortic valve replacement.

*Risk-adjusted costs and cost differences based on propensity bin bootstrapping (S3-TAVR=1068; SAVR=936).

†Mean costs trimmed at 99th percentile.

transfemoral access. Subsequent economic analyses of TAVR using a self-expanding valve versus SAVR in a similar population demonstrated an ICER of $55 090 per QALY gained for the overall population and $52 897 per QALY among patients eligible for transfemoral access, again demonstrating that for high-risk patients, TAVR using first-generation devices provides intermediate to high economic value compared with SAVR.

Previous economic analyses of TAVR versus SAVR in the intermediate-risk population are limited. Osnabrugge and colleagues[20] reported a 1-year cost analysis of 42 propensity-matched TAVR and SAVR patients who were treated at a single Dutch hospital and found higher 1-year costs with TAVR; however, longer-term costs were not considered. More recently, Tam and colleagues[21] published an analysis modeling the cost-effectiveness of TAVR in an intermediate-risk population from a Canadian perspective based on aggregate clinical data from the PARTNER 2A trial, utility data from the PARTNER A trial, and cost data from the Canadian healthcare system. In their base-case analysis, although long-term costs remained higher with TAVR than SAVR,

Table 4. Follow-Up Resource Use and Costs for XT-TAVR Versus SAVR at 2 Years

Resource Category	XT-TAVR	SAVR	Difference (95% CI)	*P* Value
Rehospitalizations*†	137.2±117.1 [1]	133.4±115.5 [1]	3.7 (−8.0 to 15.5)	0.534
Cardiovascular	45.7±67.6 [0]	42.1±64.9 [0]	3.6 (−3.1 to 10.2)	0.298
Noncardiovascular	91.5±95.6 [0]	91.3±95.6 [0]	0.2 (−9.5 to 9.8)	0.971
Hospital days*†	735.5±271.2 [2]	842.0±290.2 [3]	−106.5 (−134.9 to −78.1)	<0.001
SNF/rehab days*†	1350.8±367.5 [0]	2121.1±460.6 [7]	−770.4 (−812.6 to −728.1)	<0.001
Costs, $				
Follow-up hospitalizations*	16 785±29 460 [5876]	19 220±33 937 [6650]	−2435(−5784 to 939)	0.138
Rehab/SNF costs*	7082±15,377 [0]	11 999±17 564 [3955]	−4917 (−6571 to −3189)	<0.001
Outpatient services*	5353±7301 [3249]	6816±19 562 [3594]	−1463 (−3215 to −115)	0.024
Physician fees*	10 075±10 532 [7669]	10 027±9787 [7121]	48 (−1031 to 1025)	0.942
Total follow-up costs‡	46 284±42 728 [38 412]	55 587±49 348 [43 905]	−9304 (−13 653 to −5375)	<0.001
Cumulative 2-y costs‡	107 716±48 277 [100 830]	114 132±64 498 [98 460]	−6416 (−11 571 to −1616)	0.014

Values are mean±SD [median]. CI indicates confidence interval; Rehab, rehabilitation facility; SAVR, surgical aortic valve replacement; SNF, skilled nursing facility; and XT-TAVR, transcatheter aortic valve replacement with SAPIEN XT valve.

*Data derived from Medicare-linked population only (XT-TAVR=786; SAVR=724).

†Counts per 100 patients.

‡Index hospitalization costs, total follow-up costs, and cumulative 2-year costs are based on the as-treated population (XT-TAVR=994; SAVR=944) and trimmed at 99th percentile.

Table 5. Follow-Up Resource Use and Costs for S3-TAVR Versus SAVR at 1 Year

Resource Category	S3-TAVR	SAVR	Difference (95% CI)	*P* Value
Rehospitalizations*†	69.1±83.2	87.2±93.4	−18.0 (−26.9 to −9.2)	<0.001
Cardiovascular	22.1±47.0	30.0±54.8	−7.9 (−13.0 to −2.7)	0.003
Noncardiovascular	47.0±68.6	57.2±75.6	−10.2 (−17.4 to −2.9)	0.006
Hospital days*†	380.2±195.0	583.6±241.6	−203.4 (−225.4 to −181.3)	<0.001
SNF/rehab days*†	750.9±274.0	1600.3±400.0	−849.4 (−884.0 to −814.7)	<0.001
Risk-adjusted costs, $				
Follow-up hospitalizations*	9301±21 167 [0]	13 659±28 625 [0]	−4358 (−6897 to −1850)	0.002
Rehab/SNF costs*	4588±11 799 [0]	9757±14,046 [2341]	−5169 (−6376 to −3850)	<0.001
Outpatient services*	3894±6593 [1882]	3838±9830 [2309]	56 (−911 to 845)	0.702
Physician fees*	5087±5567 [3598]	5956±6142 [4129]	−869 (−1460 to −272)	0.010
Total follow-up costs‡	26 861 (25 082–28 748)	38 238 (35 980–40 589)	−11 377 (−14 257 to −8435)	<0.001
Cumulative 1-y costs‡	80 977 (78 898 to 83 134)	96 489 (92 988 to 99 944)	−15 511 (−19 579 to −11 487)	<0.001

Values are mean±SD [median]. Rehab indicates rehabilitation facility; S3-TAVR, transcatheter aortic valve replacement with SAPIEN 3 valve; SAVR, surgical aortic valve replacement; and SNF, skilled nursing facility.

*Data derived from Medicare-linked population only (S3-TAVR=823; SAVR=724).

†Counts per 100 patients.

‡Index hospitalization costs, total follow-up costs, and cumulative 1-year costs are based on the valve implant population (S3-TAVR=1068; SAVR=936) and adjusted using propensity bin bootstrapping; mean costs trimmed at 99th percentile.

TAVR was projected to provide high economic value, with an ICER of $46 083 per QALY gained (in Canadian dollars); however, probabilistic sensitivity analyses showed that TAVR met the threshold for high economic value of $50 000 per QALY gained in only 52.7% of the simulations.

In contrast to these previous studies, our study of intermediate-risk patients is the first to demonstrate that TAVR is an economically dominant strategy compared with SAVR. In addition to differences in the patient population and analytic perspective, several factors likely contributed to these findings. First, nonprocedural costs for the index hospitalization were substantially lower with TAVR than SAVR, with associated savings of ≈$18 000 per patient in the randomized PARTNER 2A trial and ≈$23 000 per patient in the SAPIEN-3 intermediate-risk

Table 6. Sensitivity Analyses for XT-TAVR Versus SAVR

	Lifetime Costs			QALYs			ICER ($/QALY)	% Dominant	Probability <$50 000 per QALY, %
	XT-TAVR	SAVR	Δ	XT-TAVR	SAVR	Δ			
Base case	$227 363	$235 312	−$7949	5.16	5.01	0.15	Dominant	84	100
Discount rate									
0%	$259 892	$268 041	−$8148	6.20	6.02	0.18	Dominant	76	100
5%	$210 984	$218 843	−$7860	4.64	4.50	0.14	Dominant	88	100
TAVR valve cost									
$25 000	$219 863	$235 312	−$15 449	5.16	5.01	0.15	Dominant	88	100
$35 000	$229 863	$235 312	−$5449	5.16	5.01	0.15	Dominant	76	100
Long-term HR (TAVR vs SAVR)									
1.05	$224 535	$235 312	−$10 777	5.07	5.01	0.06	Dominant	66	100
1.10	$221 855	$235 312	−$13 457	4.98	5.01	−0.03	40 778	38	100
1.20	$216 889	$235 312	−$18 423	4.81	5.01	−0.20	93 995	5	97
Increased annual follow-up cost with TAVR									
+5%	$233 373	$235 312	−$1939	5.16	5.01	0.15	Dominant	54	98
+10%	$239 382	$235 312	$4070	5.16	5.01	0.15	27 315	15	78
+20%	$251 402	$235 312	$16 090	5.16	5.01	0.15	107 987	0	3
Excess mortality with postprocedure PVL (HR=1.585)	$225 130	$234 978	−$9848	5.09	5.00	0.09	Dominant	74	100

Δ indicates difference; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; PVL, paravalvular leak; QALY, quality-adjusted life-year; SAVR, surgical aortic valve replacement; and XT-TAVR, transcatheter aortic valve replacement with SAPIEN XT valve.

Table 7. Sensitivity Analyses for S3-TAVR Versus SAVR

	Lifetime Costs			QALYs			ICER ($/QALY)	% Dominant	Probability <$50 000 per QALY, %
	S3-TAVR	SAVR	Δ	S3-TAVR	SAVR	Δ			
Base case	$231 179	$240 871	−$9692	5.29	5.01	0.27	Dominant	97	100
Discount rate									
0%	$264 572	$273 027	−$8454	6.33	6.02	0.32	Dominant	90	100
5%	$214 282	$224 569	−$10 287	4.76	4.51	0.25	Dominant	99	100
TAVR valve cost									
$25 000	$223 679	$240 871	−$17 192	5.29	5.01	0.27	Dominant	99	100
$35 000	$233 679	$240 871	−$7192	5.29	5.01	0.27	Dominant	93	100
Long-term HR (TAVR vs SAVR)									
1.05	$228 437	$240 871	−$12 434	5.19	5.01	0.18	Dominant	93	100
1.10	$225 829	$240 871	−$15 042	5.10	5.01	0.09	Dominant	75	100
1.20	$220 978	$240 871	−$19 893	4.93	5.01	−0.08	246 343	21	97
Increased annual follow-up cost with TAVR									
+5%	$237 500	$240 871	−$3371	5.29	5.01	0.27	Dominant	80	100
+10%	$243 821	$240 871	$2950	5.29	5.01	0.27	10 785	28	100
+20%	$256 463	$240 871	$15 592	5.29	5.01	0.27	57 000	0	29
Excess mortality with postprocedure PVL (HR=1.585)	$230 436	$240 543	−$10 107	5.26	5.00	0.26	Dominant	98	100

Δ indicates difference; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; PVL, paravalvular leak; QALY, quality-adjusted life-year; S3-TAVR, transcatheter aortic valve replacement with SAPIEN 3 valve; and SAVR, surgical aortic valve replacement.

registry. The reduction in nonprocedural costs was driven largely by a significant reduction in length of stay, both in the intensive care unit and on the general hospital floor, which could be attributed to a combination of factors. Iterative improvements in the TAVR device and delivery system, as well as improved procedural planning and operator experience, have led to lower rates of periprocedural complications (ie, major bleeding, disabling stroke, vascular complications) that have been associated with increased length of stay and costs.[22] Furthermore, recent modifications to both intraprocedural and post-TAVR care have been directed at decreasing the resources used during the procedure and facilitating early hospital discharge. This minimalistic approach includes the use of conscious sedation, transthoracic echocardiography, percutaneous femoral artery closure, and reductions in procedural staff (physician and nonphysician personnel alike). Variations of this approach have been studied on a small scale and have been shown to be associated with a shorter length of stay and lower cost of index hospitalization without evidence of compromise in either procedural safety or efficacy.[23,24] Hence, it is likely that streamlining of the TAVR procedure itself and advances in postprocedural care have contributed to the substantial reductions in both length of stay and hospital cost for TAVR observed in this study.

Finally, it is important to recognize that the methodology used to assess follow-up costs differed between the PARTNER 2 and SAPIEN 3 intermediate-risk trials and previous studies. In particular, whereas previous studies have relied on medical records and patient recall to assess follow-up medical resource utilization, the current study assessed follow-up costs based on Medicare claims and the associated payments. With this approach, it is likely that follow-up costs (particularly costs associated with rehabilitation facility/skilled nursing facility stays and outpatient services) were captured more completely; as a result, the current study was able to demonstrate substantial follow-up cost-savings with TAVR compared with SAVR, a finding that was not seen in previous studies.[9,10]

Although both the PARTNER 2A randomized trial and the SAPIEN 3 intermediate-risk registry demonstrated that TAVR is an economically dominant strategy compared with SAVR, the results with S3-TAVR were particularly striking, with significant reductions in long-term costs and gains in quality-adjusted life expectancy. Given the nonrandomized nature of the S3-TAVR versus SAVR comparison, however, it may be tempting to discount these results. Nevertheless, there are several reasons to believe the economic benefits observed with S3-TAVR are real. As noted above, secular advances in both procedural efficiency and postprocedural TAVR care have likely impacted the economic results associated with S3-TAVR. Moreover, the high rate of transfemoral access (≈88%) used in the S3-TAVR cohort might have also contributed to the economic dominance of S3-TAVR over SAVR.

Previous studies in the high-risk population have demonstrated the critical impact of access site on the economic outcomes of TAVR. In the PARTNER A trial, trans-

femoral TAVR was economically dominant in 55.7% of bootstrap replicates, whereas transapical TAVR was dominated by SAVR in 86.6% of replicates.[10] Similarly, stratified analyses of the randomized XT-TAVR versus SAVR comparison described herein demonstrated that among patients suitable for transfemoral access, XT-TAVR was economically dominant compared with SAVR with a high degree of confidence, whereas transthoracic TAVR was dominated by SAVR. In fact, the projected lifetime cost-savings of $11 738 per patient and the 0.30-year gain in QALYs with transfemoral XT-TAVR are remarkably similar to those observed in the overall S3-TAVR versus SAVR comparison. Taken together, these observations are reassuring with regard to the validity of the S3-TAVR economic results and suggest that the principal mechanism of benefit of the SAPIEN 3 valve over the SAPIEN XT valve is its lower delivery profile, which allows the vast majority of patients to be treated via a transfemoral approach.

Study Limitations

This study should be interpreted in the context of several important limitations. First, the S3-TAVR versus SAVR comparison was derived from a nonrandomized study. Although the PARTNER 2A trial and S3i registry did use identical inclusion and exclusion criteria, and a prespecified propensity score was used to adjust for differences between the groups, it is still possible that observed differences in health status and costs were affected by confounding factors. Second, these results were based on a single clinical trial program that studied 2 balloon-expandable TAVR devices, and costs were derived from Medicare claims. As such, these results cannot necessarily be generalized to patients of different surgical risk, other TAVR devices, other healthcare systems outside the US, or payment models other than Medicare within the United States. Third, extrapolation of both clinical outcomes and costs beyond the trial period was based on assumptions and hence might not be accurate. Nonetheless, the methods used to project cost, health status, and survival were similar to ones used in previous economic analyses[9,25] and were supported by data from other TAVR versus SAVR trials, and wherever possible, our assumptions were intentionally conservative. Finally, the long-term durability of both the SAPIEN XT and SAPIEN 3 valves is unknown. As such, lifetime costs associated with TAVR could be higher than we have assumed owing to the need for more frequent repeat valve procedures. Nonetheless, sensitivity analyses demonstrated that TAVR would remain economically dominant unless follow-up costs increased substantially from our base-case assumptions.

Conclusions

In conclusion, for patients with severe AS at intermediate surgical risk, TAVR with either the SAPIEN XT valve or SAPIEN 3 valve is projected to be an economically dominant strategy from the perspective of the US healthcare system by providing both greater quality-adjusted life expectancy and lower long-term costs than SAVR. If long-term data demonstrate comparable late mortality with TAVR and SAVR, these findings suggest that TAVR might be the preferred treatment strategy for intermediate-risk AS patients on the basis of both clinical and economic considerations.

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