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EXPEDITED PUBLICATION

Cost-Effectiveness of Transcatheter Aortic Valve Replacement Compared With Surgical Aortic Valve Replacement in High-Risk Patients With Severe Aortic Stenosis

Results of the PARTNER (Placement of Aortic Transcatheter Valves) Trial (Cohort A)

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Objectives The aim of this study was to evaluate the cost-effectiveness of transcatheter aortic valve replacement (TAVR) compared with surgical aortic valve replacement (AVR) for patients with severe aortic stenosis and high surgical risk.

Background TAVR is an alternative to AVR for patients with severe aortic stenosis and high surgical risk.

Methods We performed a formal economic analysis based on cost, quality of life, and survival data collected in the PARTNER A (Placement of Aortic Transcatheter Valves) trial in which patients with severe aortic stenosis and high surgical risk were randomized to TAVR or AVR. Cumulative 12-month costs (assessed from a U.S. societal perspective) and quality-adjusted life-years (QALYs) were compared separately for the transfemoral (TF) and transapical (TA) cohorts.

Results Although 12-month costs and QALYs were similar for TAVR and AVR in the overall population, there were important differences when results were stratified by access site. In the TF cohort, total 12-month costs were slightly lower with TAVR and QALYs were slightly higher such that TF-TAVR was economically dominant compared with AVR in the base case and economically attractive (incremental cost-effectiveness ratio <$50,000/QALY) in 70.9% of bootstrap replicates. In the TA cohort, 12-month costs remained substantially higher with TAVR, whereas QALYs tended to be lower such that TA-TAVR was economically dominated by AVR in the base case and economically attractive in only 7.1% of replicates.

Conclusions In the PARTNER trial, TAVR was an economically attractive strategy compared with AVR for patients suitable for TF access. Future studies are necessary to determine whether improved experience and outcomes with TA-TAVR can improve its cost-effectiveness relative to AVR. (THE PARTNER TRIAL: Placement of AoRTic TraNscathetER Valve Trial; NCT00530894) (J Am Coll Cardiol 2012;60:2683–92) © 2012 by the American College of Cardiology Foundation

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Abbreviations and Acronyms

AS = aortic stenosis
AVR = aortic valve replacement
EQ-5D = EuroQol
ICER = incremental cost-effectiveness ratio
mITT = modified intention-to-treat
QOL = quality of life
TA = transapical
TAVR = transcatheter aortic valve replacement
TF = transfemoral

Transcatheter aortic valve replacement (TAVR) was recently developed as an effective treatment for severe aortic stenosis (AS) that is less invasive than traditional surgical aortic valve replacement (AVR). In the PARTNER (Placement of Aortic Transcatheter Valves) B trial, TAVR was shown to lead to substantial gains in both survival and quality of life (QOL) compared with standard nonsurgical therapy in patients with severe AS who were unsuitable for AVR based on anatomic factors or surgical risk (1,2). Although the short-term costs of TAVR were high in that study, formal economic evaluation demonstrated that the benefits of TAVR in such inoperable patients were achieved at an acceptable incremental cost to society, at least in the context of the U.S. health system (3).

In patients with severe, symptomatic AS who are at high but not prohibitive surgical risk, the PARTNER A trial recently demonstrated that TAVR using the Edwards SAPIEN valve results in similar 1- and 2-year survival compared with standard surgical AVR (4,5). Although rates of periprocedural complications differed between the treatments, at 2 years, the overall rates of major adverse events, including stroke, were similar as well. On the other hand, TAVR did result in significant early benefits in terms of health-related QOL, but these benefits were no longer present 6 to 12 months post-procedure and were observed only when TAVR was performed via the transfemoral (TF) but not the transapical (TA) route (6).

Given the similar 1- and 2-year clinical outcomes of TAVR and AVR in the PARTNER A trial, secondary considerations such as cost may affect the adoption of TAVR. For high-risk surgical candidates, however, a direct comparison of the costs and cost-effectiveness of TAVR and AVR has not yet been reported. To address these questions, we performed a prospective health economic study in conjunction with the PARTNER A trial.

Methods

Study design and patient population. As previously reported, Cohort A of the PARTNER trial enrolled 699 patients with severe, symptomatic AS, defined as an aortic valve area <0.8 cm^2 with either a mean valve gradient >40 mm Hg or a peak jet velocity >4.0 m/s and New York Heart Association functional class II or higher (4). All patients were required to have a predicted risk of operative mortality rate of $\geq$15% or a Society of Thoracic Surgery risk score of $\geq$10.

After enrollment in the trial, but before randomization, patients were evaluated for anatomic suitability for TAVR via the TF approach based on imaging of the aorta and iliofemoral arterial system. Those patients found to be suitable for TF access were then randomized to TF-TAVR versus AVR (TF cohort, n = 492), whereas those patients who were not suitable for a TF approach (due to angiographic findings precluding safe placement of a 22- or 24-F introducer sheath such as severe obstructive calcification, tortuosity, or vessel diameter <7 mm) were randomized to TA-TAVR versus AVR (TA cohort, n = 207).

Analytic overview. Our economic analysis was performed from the perspective of the U.S. health care system (i.e., a modified societal perspective). All costs are reported in 2010 U.S. dollars. We performed our primary analyses on a modified intention-to-treat (mITT) population, which was defined by excluding 42 subjects from the intention-to-treat population who received neither study treatment (mainly due to refusal, early withdrawal, or clinical deterioration [4]) and 10 additional subjects who did not have complete follow-up information through either death or 12 months (see Figure 1 for details). Additionally, for the purpose of describing index admission resource use and costs among only those patients who actually underwent a true attempt at valve implantation, we defined a secondary "treated as randomized" population, which excluded the 42 patients who did not receive either treatment and a different set of 10 patients whose procedures were abandoned at preliminary stages due to transesophageal echocardiographic findings or failed vascular access (9 TAVR, 1 AVR). All analyses followed the principle of intention to treat by grouping patients according to their randomized treatment assignment.

Although the primary clinical analysis of the PARTNER A trial pooled all patients treated in either the TA or TF cohort, for the economic analysis, we made the a priori decision to stratify the analysis according to access site (TF or TA) for several reasons. First, study randomization was stratified by access site, and the TF cohort was independently powered to demonstrate the noninferiority of TAVR compared with AVR for the trial's primary endpoint of 12-month mortality (4). In addition, although TAVR procedures done via both TF and TA routes functionally replace the aortic valve in a similar manner, TF and TA procedures have fundamental differences in terms of anatomic site, risk, and, potentially, recovery. Finally, in a previous analysis from this trial (6), we found a significant

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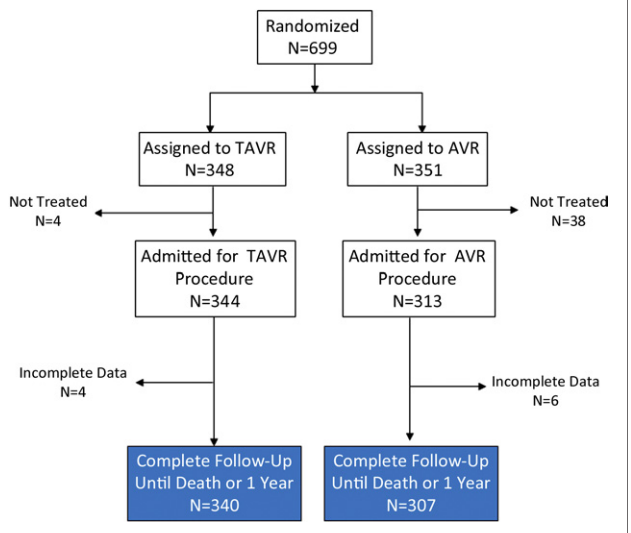

Figure 1 **Analysis Populations**

Of the 699 patients randomized in PARTNER, 42 were not treated with either procedure and were excluded from this analysis. After excluding an additional 10 patients with incomplete 12-month clinical or cost data, mainly due to withdrawal after the index admission, the primary analytic population consisted of 647 patients (blue boxes) who were analyzed according to the intention-to-treat principle. This population is referred to as the modified intention-to-treat population for the purpose of this economic study. AVR = aortic valve replacement; TAVR = transcatheter aortic valve replacement.

interaction between treatment assignment (TAVR or AVR) and access site (TF or TA) on QOL outcomes. For all of these reasons, we thought that independent health economic analyses of TF-TAVR and TA-TAVR, each compared with their separate AVR control groups, would be most relevant and informative.

Index procedure and admission costs. Costs were determined using a combination of hospital billing data and resource-based accounting methods, as described previously (7,8). For the initial TAVR and AVR procedures, study centers recorded procedure duration and counts of major items used, such as valve prostheses, support wires, guiding catheters, valvuloplasty balloons, temporary pacing catheters, and vascular closure devices (3). Procedural costs were calculated by multiplying item counts by their respective unit prices, determined by the average acquisition costs at a sample of U.S. hospitals. An acquisition cost of $30,000 was used for the Edwards SAPIEN valve system, and a cost of $5,277 was used for a standard bioprosthetic aortic valve. Ancillary costs for the catheterization laboratory or operating room included overhead and depreciation, nonphysician personnel, and general supplies required for each procedure and were estimated based on a survey of study hospitals and adjusted for observed procedure duration. We assumed that TF-TAVR procedures would be performed in a catheterization laboratory setting, whereas TA-TAVR procedures and AVR procedures would be performed in an operating room setting, based on a survey of PARTNER trial sites at the completion of the study.

Costs of the remainder of each index admission were calculated from hospital bills, which were available for 525 subjects in the primary mITT population (80%), by multiplying all nonprocedural charges by cost center–specific cost-to-charge ratios from each hospital's Medicare cost report (9). For admissions without available billing data (n = 132), the remainder of costs were estimated using linear regression models derived from the subjects with complete billing data. Covariates in these models, which were derived separately for the TAVR and AVR groups (R^2 = 0.83 and 0.78, respectively), included intensive care unit and non–intensive care unit length of stay, in-hospital bleeding, and in-hospital death.

Follow-up hospitalization costs. Information on follow-up hospital admissions for any cause was collected by the study sites at scheduled follow-up visits (1, 6, and 12 months) and on learning of adverse events. Costs for subsequent hospital admissions were calculated from billing data using hospital and cost center–specific cost-to-charge ratios when bills were available (65% of admissions). When bills were not available (mainly because of admission to non-U.S. or nonstudy hospitals), diagnosis, procedure, and adverse event information from the study database were used to assign each admission to a unique Medicare Severity-Adjusted Diagnosis-Related Group. Mean reimbursements for each respective Medicare Severity-Adjusted Diagnosis-Related Group, based on 2008 Medicare Provider Analysis and Review data (10), were used as the proxy for admission costs in these cases.

Physician fees. We assumed that physician fees for the index AVR and TAVR procedures would be identical and assigned these costs using current reimbursement rates for surgical AVR from the Medicare fee schedule including both a primary operator and a surgical assistant. In addition, for the index procedure, we included physician fees for cardiac anesthesia (based on measured procedure duration) and intraoperative transesophageal echocardiography. Physician fees for the initial consultation and daily care during the remainder of the initial hospital stay were also derived from the Medicare fee schedule. For follow-up hospitalizations, we estimated total physician fees based on the diagnosis-related group for each admission, as described previously (11). In sensitivity analyses, we assigned physician costs to subsequent hospitalizations based on a fixed percentage of hospital costs for each admission (ranging from 10% to 30%).

Other costs. At each follow-up visit through 12 months, enrolling sites collected data on rehabilitation facility stays, nursing home stays, and outpatient resource use (emergency department visits, physician office visits, outpatient cardiac testing). We estimated costs for services using national average per-diem rates for residential care and Medicare reimbursement rates for outpatient care based on the Medicare fee schedule. Outpatient medication costs were as-

sumed to be similar and therefore excluded from our analysis.

Quality-adjusted life expectancy. Patients completed the EuroQol (EQ-5D) health status questionnaire at baseline and 1, 6, and 12 months. EQ-5D responses were converted to utility weights using a published algorithm derived from a U.S. population reference group (12). Quality-adjusted life-years (QALYs) were calculated for each patient by multiplying observed survival duration by the time-weighted average of his or her utility values, with the midpoint between assessments used as the transition between health states (13). Missing utility values were estimated by multiple imputation techniques, taking into account baseline patient characteristics, clinical events, number of hospitalizations, and previous utility values.

Statistical methods. Categorical data are reported as frequencies, and continuous data are reported as mean ± SD. Discrete variables were compared using the Fisher exact test. Normally distributed continuous variables were compared using the 2-sample *t* test, and non-normally distributed data were compared by the Wilcoxon rank sum test. Cost data are reported as both mean and median values and compared using *t* tests, which are appropriate given our focus on comparing mean costs between groups (rather than the underlying distributions) (14).

We evaluated the cost-effectiveness of TAVR relative to AVR, expressed as the incremental cost per QALY gained over the initial 12-month follow-up period, with separate analyses for the TF and TA cohorts. This analytic time horizon is comparable to a lifetime analysis under the assumption that all major clinical and economic outcomes between the TAVR and AVR groups would be equivalent after 1 year. On the basis of the empirical data from the PARTNER A trial, we believe that this is a reasonable assumption because there were no differences in either survival or functional status between TAVR and AVR at 1 or 2 years (4–6), and preliminary data have shown no divergence in the survival curves to 3 years (15).

Incremental cost-effectiveness ratios (ICERs) were calculated as the difference in mean cumulative 12-month costs divided by the difference in mean 12-month quality-adjusted life expectancy. Bootstrap resampling (16,17) was used to assess the joint distribution of lifetime cost and survival differences.

In the TA cohort, baseline EQ-5D utility scores were slightly lower in the TAVR group compared with the AVR group (0.67 vs. 0.72, p = 0.07) (6), and our primary analysis was based on the observed data for the mITT population. To account for this unexpected imbalance in baseline utility scores, we performed a secondary analysis for the TA cohort in which all utility scores (both baseline and follow-up) were increased in TAVR patients and decreased in AVR patients by half of the between-group baseline difference, such that baseline utility scores between groups were equal (18).

Results

Of the 699 patients enrolled in Cohort A of the PARTNER trial, 657 underwent an attempted TAVR or AVR procedure (Fig. 1). Among this "treated" population, 10 subjects had incomplete clinical or health economic data within the 12 months after randomization and were excluded from our primary analysis. The remaining 647 subjects constituted our primary mITT analysis population.

The baseline characteristics of the primary mITT population were well balanced in both the TF and TA cohorts (Table 1). Patients enrolled in the TA cohort (who were, by definition, unsuitable for the TF approach) more frequently had a history of peripheral arterial and cerebrovascular disease than patients in the TF cohort. No differences were observed in the baseline characteristics of the 52 subjects excluded from the mITT population, compared with those included (Online Table).

Index procedural and admission resource use and costs. Major items of resource use and calculated costs for the index procedures and hospital stays for the "treated as

Table 1 Baseline Characteristics (Modified ITT Population)

	TF Cohort			TA Cohort		
	TAVR (n = 239)	AVR (n = 217)	p Value	TAVR (n = 101)	AVR (n = 90)	p Value
Age, yrs	83.9 ± 6.8	84.8 ± 6.5	0.14	83.1 ± 6.9	83.4 ± 5.5	0.76
Male	60.7	56.2	0.34	50.5	58.9	0.25
STS risk score	11.8 ± 3.2	11.6 ± 3.3	0.42	11.8 ± 3.7	12.0 ± 3.5	0.69
Previous MI	26.8	25.8	0.81	26.7	36.7	0.14
Previous CABG	39.3	40.1	0.87	50.5	55.6	0.48
Cerebrovascular disease	23.8	24.0	0.98	36.6	27.8	0.19
Peripheral artery disease	34.6	35.0	0.92	62.4	62.5	0.99
COPD (oxygen dependent)	8.8	7.4	0.58	10.9	7.8	0.46
LV ejection fraction	52.2 ± 14.1	53.6 ± 13.1	0.25	53.4 ± 12.3	53.5 ± 10.9	0.98
Frailty	16.1	19.0	0.48	15.8	18.0	0.70

Values are mean ± SD or %.

AVR = aortic valve replacement; CABG = coronary artery bypass graft; COPD = chronic obstructive pulmonary disease; LV = left ventricular; MI = myocardial infarction; STS = Society of Thoracic Surgeons; TA = transapical; TAVR = transcatheter aortic valve replacement; TF = transfemoral.

Table 2 Index Admission Resource Use and Costs, Transfemoral Cohort (Treated as Randomized Population)

Resource Category	TF-TAVR (n = 234)	AVR (n = 221)	Difference (95% CI)	p Value
Procedure duration, min	244 ± 78 [231]	330 ± 102 [315]	−87 (−69 to −104)	<0.001
Total hospital LOS, days	10.2 ± 11.1 [7]	16.4 ± 13.9 [12]	−6.2 (−3.8 to −8.2)	<0.001
ICU	3.3 ± 6.0 [2]	5.6 ± 6.7 [3]	−2.3 (−0.9 to −3.3)	<0.001
Non-ICU	6.9 ± 7.8 [4]	10.8 ± 10.2 [8]	−4.0 (−2.2 to −5.5)	<0.001
Post-procedure	7.4 ± 10.0 [5]	13.5 ± 12.1 [10]	−6.1 (−3.7 to −8.0)	<0.001
Major vascular complication	13.2%	3.2%	10.1% (5.1 to 15.1)	<0.001
Major bleeding	9.4%	22.6%	−13.2% (−6.6 to −19.9)	<0.001
Costs, $				
Procedural	36,652 ± 4,703 [35,609]	14,475 ± 2,612 [14,081]	22,177 (21,496 to 22,884)	<0.001
Nonprocedural	31,705 ± 38,308 [20,745]	53,834 ± 45,572 [40,439]	−22,129 (−29,880 to −14,469)	<0.001
Physician fees	4,861 ± 1,549 [4,433]	5,758 ± 1,810 [5,179]	−896 (−1209 to −594)	<0.001
Total admission costs	73,219 ± 40,596 [61,162]	74,067 ± 47,422 [59,687]	−849 (−8,977 to 7,014)	0.84

Values are mean ± SD [median] or %.
CI = confidence interval; ICU = intensive care unit; LOS = length of stay; other abbreviations as in Table 1.

randomized" population are shown in Table 2 (for the TF cohort) and Table 3 (for the TA cohort). In the TF cohort, TAVR procedures were ~90 min shorter than AVR procedures, but given the higher acquisition cost of the transcatheter valve system, TAVR procedural costs were significantly higher ($36,652 ± $4,703 vs. $14,475 ± $2,612). Mean length of stay for TF-TAVR admissions was ~6 days shorter than for AVR admissions including a mean difference of >2 intensive care unit days. This reduced length of stay was associated with substantially lower nonprocedural hospital costs after TF-TAVR compared with AVR, such that overall admission costs were not significantly different between groups ($73,219 vs. $74,067, mean difference, −$849; 95% CI: −$8,977 to $7,014).

In the TA cohort, index procedure duration was shorter for TAVR than for AVR, and total procedure costs were higher ($40,368 ± $12,651 vs. $15,076 ± $2,665). Although mean overall (14.7 ± 10.1 days vs. 16.1 ± 12.5 days) and post-procedure (12.4 ± 9.9 vs. 14.4 ± 12.2) lengths of stay were 1 to 2 days shorter with TA-TAVR compared with AVR, the resulting cost savings were insufficient to offset the higher procedural costs. Consequently, total admission costs remained higher with TA-TAVR compared with AVR ($90,919 vs. $79,024; mean difference, $11,896; 95% CI: −$1,012 to $24,304).

Follow-up resource use and costs. Resource use and costs from hospital discharge through 12 months for the TF and TA cohorts (mITT population) are summarized in Tables 4 and 5, respectively. In the TF cohort, there were no differences between TAVR and AVR patients in terms of repeat hospital admissions, follow-up hospital days, or measures of major outpatient resource use, although TAVR patients tended to require slightly less rehabilitative care and slightly more skilled nursing care. Follow-up costs through 12 months were similar for the TF-TAVR and AVR groups (mean difference, $1,247; 95% CI: −$12,426 to $14,074). Likewise, in the TA cohort, there were no significant differences in major categories of resource use between the TAVR and AVR groups, although there was a tendency toward fewer rehabilitative care days and more skilled nursing days in the TA-TAVR group. Total follow-up costs through 12 months were slightly, but not significantly,

Table 3 Index Admission Resource Use and Costs, Transapical Cohort (Treated as Randomized Population)

Resource Category	TA-TAVR (n = 101)	AVR (n = 91)	Difference (95% CI)	p Value
Procedure duration, min	224 ± 76 [210]	354 ± 104 [335]	−130 (−104 to −155)	<0.001
Total hospital LOS, days	14.7 ± 10.1 [10]	16.1 ± 12.5 [12]	−1.4 (1.7 to −4.7)	0.39
ICU	6.6 ± 8.9 [3]	8.0 ± 11.0 [4]	−1.4 (1.3 to −4.4)	0.33
Non-ICU	8.1 ± 7.0 [6]	8.1 ± 6.2 [7]	0.0 (1.9 to −1.8)	1.0
Post-procedure	12.4 ± 9.9 [9]	14.4 ± 12.2 [9]	−2.0 (1.1 to −5.3)	0.22
Major vascular complication	4.0%	4.4%	−0.4% (6.2% to −5.3%)	1.0
Major bleeding	5.9%	20.9%	−14.9% (−5.5% to −24.3%)	0.002
Costs, $				
Procedural costs	40,368 ± 12,651 [37,853]	15,076 ± 2,665 [14,592]	25,292 (23,091 to 28,145)	<0.001
Nonprocedural costs	44,909 ± 34,603 [30,091]	57,827 ± 44,815 [39,103]	−12,918 (−24,763 to −1,805)	0.03
Physician fees	5,642.22 ± 1,890.62 [4,929]	6,121 ± 2,418 [5,302]	−479 (−1,145 to 103)	0.13
Total admission costs	90,919 ± 39,397 [74,721]	79,024 ± 47,343 [61,395]	11,896 (−1,013 to 24,304)	0.06

Values are mean ± SD [median] or %.
Abbreviations as in Tables 1 and 2.

JACC Vol. 60, No. 25, 2012
December 25, 2012:2683–92

Table 4 Cumulative 1-Year Resource Use and Costs, Transfemoral Cohort (mITT Population)

	TF-TAVR (n = 239)	AVR (n = 217)	Difference (TAVR-AVR) (95% CI)	p Value
Follow-up hospitalizations	0.9 ± 1.3	0.6 ± 1.0	0.3 (0.1 to 0.5)	0.02
Cardiovascular	0.3 ± 0.7	0.2 ± 0.6	0.0 (−0.1 to 0.2)	0.51
Noncardiovascular	0.6 ± 1.0	0.4 ± 0.7	0.2 (0.1 to 0.4)	0.01
Rehabilitation days	2.3 ± 9.0	4.5 ± 21.9	−2.3 (−5.3 to 0.7)	0.14
Skilled nursing days	11.2 ± 45.9	8.4 ± 38.3	2.9 (−5.0 to 10.7)	0.47
Costs, $				
Index admission*	71,955 ± 37,747 [61,297]	74,452 ± 47,725 [60,159]	−2,496 (−10,312 to 5,428)	0.53
Follow-up hospitalizations	18,122 ± 58,142	15,645 ± 77,412	2,477 (−11,156 to 14,382)	0.70
Rehabilitation	2,316 ± 9,213	4,666 ± 22,492	−2,350 (−5,948 to 200)	0.14
Skilled nursing	3,223 ± 13,182	2,397 ± 11,002	827 (−1452 to 3,164)	0.47
Other outpatient services	1,126 ± 2,584	833 ± 1,510	293 (−47 to 701)	0.14
Total follow-up costs	24,787 ± 64,348 [5,580]	23,540 ± 82,003 [5,535]	1247 (−12,426 to 14,074)	0.86
Total 12-month costs	96,743 ± 76,185 [71,975]	97,992 ± 94,873 [74,361]	−1,250 (−18,132 to 13,867)	0.88

Values mean ± SD or mean ± SD [median]. *Note that index admission costs for the mITT population differ slightly from the treated as randomized population as shown in Table 2.
mITT = modified intention-to-treat; other abbreviations as in Table 2.

lower for TA-TAVR compared with AVR (mean difference, −$1,102; 95% CI: −$10,590 to $8,661).

Over the full study period, cumulative 12-month costs in the mITT population were marginally lower for TF-TAVR compared with AVR (mean difference, −$1,250; 95% CI: −$18,132 to $13,867). In the TA cohort, cumulative 12-month costs were higher for TAVR compared with AVR (mean difference, $9,906; 95% CI: −$5,263 to $24,814). Pooled results for the full mITT population demonstrated slightly higher costs with TAVR than AVR ($100,504 vs. $98,434; mean difference, $2,070; 95% CI: −$9,960 to $13,499).

Life-years and QALYs. Life expectancy and quality-adjusted life expectancy for the mITT population are summarized in Table 6. As previously described, for the TF cohort, both early survival and QOL tended to favor the TAVR group (4,6), resulting in small but significant differences in life expectancy and quality-adjusted life expectancy. In the TA cohort, no difference in mortality was observed at any time point, and early QOL tended to be better in the AVR group (4,6). Thus, for the TA cohort, life-years were similar for the TAVR and AVR groups, whereas quality-adjusted life expectancy tended to be less with TAVR. When results were pooled across both access sites, there were nonsignificant trends toward greater life expectancy and quality-adjusted life expectancy with TAVR compared with AVR.

Cost-effectiveness analysis. The results of the trial-based cost-effectiveness analysis are summarized in Table 7. For the overall mITT population, TAVR resulted in slightly higher 12-month costs and a small gain in QALYs with a resulting ICER of $76,877/QALY gained. This result was highly uncertain, however, because TAVR was found to be dominant in 34.5% of bootstrap replicates but either dominated or economically unattractive (ICER >$100,000/QALY) in 48.5%.

The cost-effectiveness results differed substantially according to access site. Among patients suitable for a TF

Table 5 Cumulative 1-Year Resource Use and Costs, Transapical Cohort (mITT Population)

	TA-TAVR (n = 101)	AVR (n = 90)	Difference (TAVR-AVR) (95% CI)	p Value
Follow-up hospitalizations	0.7 ± 1.1	0.8 ± 1.1	0.1 (−0.4 to 0.2)	0.68
Cardiovascular	0.3 ± 0.6	0.3 ± 0.7	0.0 (−0.2 to 0.2)	0.81
Noncardiovascular	0.4 ± 0.8	0.5 ± 0.9	0.0 (−0.3 to 0.2)	0.72
Rehabilitation days	3.2 ± 16.9	4.8 ± 17.5	−1.6 (−6.5 to 3.3)	0.38
Skilled nursing days	10.4 ± 36.3	7.6 ± 38.5	2.8 (−7.8 to 13.5)	0.60
Costs, $				
Index admission*	90,548 ± 39,909 [74,721]	79,540 ± 47,429 [61,784]	11,008 (−2,053 to 22,485)	0.08
Follow-up hospitalizations	11,733 ± 31,924 [0]	11,692 ± 20,414 [0]	41.37 (−6,675 to 8,090)	0.99
Rehabilitation	3,254 ± 17,303 [0]	4,930 ± 17,951 [0]	−1,676 (−6,734 to 3,108)	0.51
Skilled nursing	2,995 ± 10,415 [0]	2,181 ± 11,053 [0]	814 (−2,296 to 3,665)	0.60
Other outpatient services	874 ± 1,468 [0]	1,156 ± 1,961 [0]	−282 (−771 to 199)	0.27
Total follow-up costs	18,856 ± 41,604 [3,731]	19,959 ± 29,618 [8,666]	−1,102 (−10,590 to 8,661)	0.84
Total 12-month costs	109,405 ± 56,874 [92,819]	99,499 ± 54,541 [86,747]	9,906 (−5,263 to 24,814)	0.22

Values mean ± SD or mean ± SD [median]. *Note that index admission costs for the mITT population differ slightly from the treated as randomized population as shown in Table 2.
Abbreviations as in Tables 3 and 4.

Table 6 Life-Years and QALYs Over the 12-Month Follow-Up Period (mITT Population)

	TAVR	AVR	TAVR-AVR	95% CI*
All patients				
Life-years	0.858	0.817	0.041	−0.010 to 0.088
QALYs	0.633	0.606	0.027	−0.018 to 0.071
Transfemoral cohort				
Life-years	0.878	0.813	0.065	0.011 to 0.125
QALYs	0.659	0.591	0.068	0.017 to 0.123
Transapical cohort				
Life-years	0.811	0.826	−0.015	−0.103 to 0.080
QALYs	0.570	0.641	−0.070	−0.151 to 0.012

*95% confidence intervals calculated from bootstrap resampling.
QALYs = quality-adjusted life-years; other abbreviations as in Table 3.

approach, TAVR resulted in cost savings of ~$1,250 per patient and a modest gain in QALYs compared with AVR. Bootstrap simulation demonstrated that TF-TAVR was economically dominant compared with AVR in 55.7% of replicates and economically attractive at an ICER of $50,000/QALY gained in 70.9% (Fig. 2A). On the other hand, among patients who were unsuitable for TF access, TA-TAVR resulted in higher 12-month costs and lower quality-adjusted life expectancy than AVR in our primary analysis and was economically dominated by AVR in 86.6% of bootstrap replicates (Fig. 2B). At an ICER threshold of $50,000/QALY, TA-TAVR was economically attractive relative to AVR in just 7.1% of replicates.

Threshold analysis demonstrated that the ICER for TF-TAVR would remain <$50,000/QALY as long as the difference in acquisition cost between the TAVR device and a standard bioprosthetic valve remained <$29,390. On the other hand, assuming no change in other clinical or economic outcomes, TA-TAVR would be economically attractive at this ICER threshold only if the difference in valve acquisition costs was <$11,324.

Sensitivity analyses. When the analysis was expanded to include the full "treated" population (N = 657), TAVR marginally increased costs in the TF cohort by $396/patient, and TAVR was economically dominant in 46.0% of bootstrap replicates and economically attractive at an ICER of $50,000/QALY in 61.9%. For the TA cohort, the incremental cost associated with TAVR increased slightly to $10,227/patient, and TAVR remained economically dominated by AVR in 87.7% of replicates. Finally, when the analysis for the TA cohort was repeated after adjusting for the baseline imbalance in EQ-5D utility scores, the difference in quality-adjusted life expectancy between TA-TAVR and AVR was smaller (mean difference, −0.036 QALYs, 95% CI: −0.117 to 0.046). Nonetheless, TA-TAVR re-

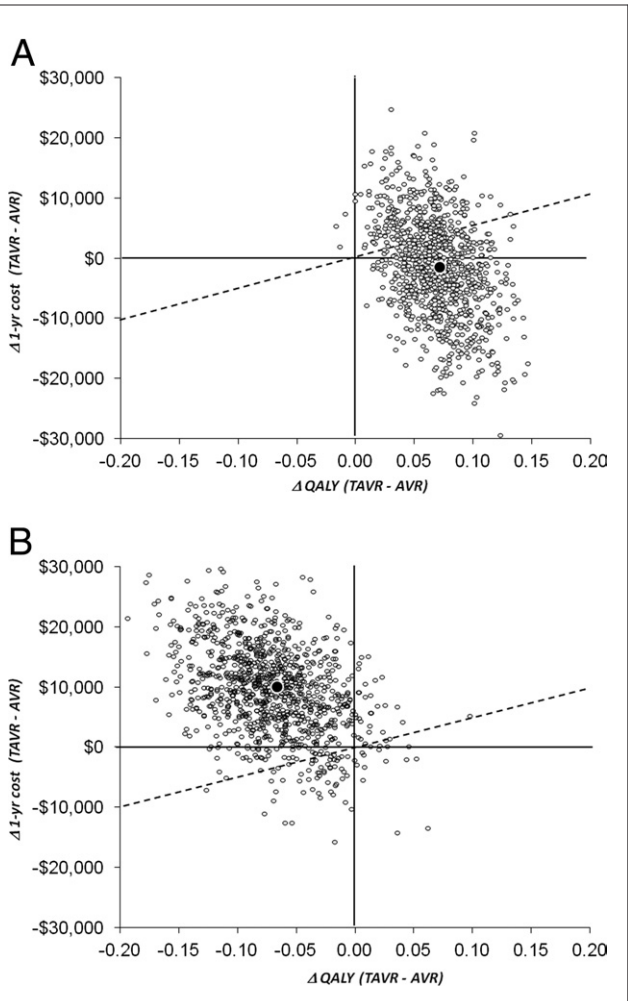

Figure 2 Cost-Effectiveness Results

Mean incremental 12-month costs and QALYs (TAVR–AVR) are plotted on the cost-effectiveness plane for the transfemoral (TF) **(A)** and transapical (TA) **(B)** cohorts. The **solid circles** represent base-case estimates, the surrounding **open circles** represent individual results for 1,000 replications of the study using bootstrap resampling, and the **dashed lines** represent a willingness to pay a threshold of $50,000/QALY gained. For the TF cohort, the base-case results are a gain of 0.068 QALYs and cost savings of $1,250 per patient. For the TA cohort, the base-case results are a "loss" of 0.070 QALYs and a net increase in costs of $9,906. QALYs = quality-adjusted life-years; other abbreviations as in Figure 1.

Table 7 Primary Cost-Effectiveness Results (mITT Population)

Population	Cost, $	QALYs	ICER ($/QALY)	Probability TAVR Dominant, %	Probability TAVR Dominated, %	Probability ICER <$50,000/QALY, %
Overall	2,070	0.027	76,877	34.5	10.5	43.8
TF cohort	−1,250	0.068	TAVR dominant	55.7	0.5	70.9
TA cohort	9,906	−0.07	TAVR dominated	1.1	86.6	7.1

Results based on mITT population; probabilities derived from bootstrap simulation.
ICER = incremental cost-effectiveness ratio; other abbreviations as in Tables 1, 4, and 6.

mained economically dominated by AVR in 74.7% of bootstrap replications. Using a fixed ratio of physician costs to hospitalization costs (ranging from 10% to 30%) or estimating the costs of all readmissions based on diagnosis-related groups had only a slight effect on our findings (results not shown).

Discussion

Although the PARTNER trial previously examined the cost-effectiveness of TAVR compared with standard therapy for patients who are not candidates for surgical valve replacement (3), this study represents the first attempt to directly evaluate the incremental cost-effectiveness of TAVR relative to AVR among patients who are acceptable candidates for high-risk surgical AVR. In this prospectively designed analysis of 12-month economic outcomes in the PARTNER A trial, we found that TAVR and AVR resulted in 12-month costs and QALYs that were sufficiently similar that neither therapy would be clearly preferred over the other on health economic grounds.

Economic outcomes differed substantially, however, when the analysis was stratified by TAVR access site. Among the >70% of trial patients who were eligible for a TF approach, TAVR provided a modest benefit in quality-adjusted life expectancy and slightly reduced costs compared with AVR. As a result, TF-TAVR was found to be economically attractive by generally accepted standards and possibly an economically dominant strategy compared with AVR in these patients. In contrast, for the minority of patients who were suitable for TAVR only via the TA approach, we observed higher 12-month costs and a trend toward reduced quality-adjusted life expectancy compared with AVR in the PARTNER A population.

These differences in cost-effectiveness are explained by differences in both hospital resource use and short-term clinical outcomes of TAVR according to access site. Procedural costs for both TF-TAVR and TA-TAVR were substantially greater than those for surgical AVR, driven almost entirely by the higher valve acquisition costs. In the TF cohort, however, TAVR resulted in substantial reductions in length of stay compared with AVR with associated cost savings sufficient to fully offset the higher procedural costs. In addition, formal QOL and utility assessment demonstrated significant early benefits with TF-TAVR. As a result, TF-TAVR compared favorably with AVR on both clinical and economic grounds. In contrast, among patients who were ineligible for a TF approach, TA-TAVR resulted in only a 1- to 2-day reduction in length of hospital stay, which was insufficient to offset the higher procedural costs, and early QOL was not improved compared with AVR.

We are aware of only 1 previously published study (19) assessing the cost-effectiveness of TAVR relative to AVR in high-risk surgical candidates in a U.S. practice setting. Gada et al. (19) used a Markov model to estimate lifetime costs and QALYs for high-risk patients treated with TAVR, AVR, or medical therapy, informed by a number of separate TAVR and AVR registries. The investigators' base-case analysis used a "provider perspective" under which the costs of index admissions for TAVR and AVR were assumed to be equal. This model predicted a lifetime gain of 0.06 QALYs comparing TAVR with AVR, with slightly higher lifetime costs, resulting in an ICER of ~$53,000/QALY gained. Although the main results of the previous study are consistent with our findings, the fundamentally different methodologies make comparisons between the 2 studies difficult. Although our study was limited to a 12-month time horizon, our approach had several advantages including a direct comparison of outcomes based on data from a randomized clinical trial, use of empirically derived costs from detailed analysis of hospital billing and resource use data, and separately evaluating TF and TA access for TAVR.

Although the economic outcomes of TAVR observed in the TF cohort of the PARTNER trial are remarkably positive for a relatively new technology in the early phase of clinical use, the results in the TA cohort were less favorable. Compared with AVR, TA-TAVR in the PARTNER trial increased costs and did not appear to provide any measurable survival or QOL benefit. Potential reasons underlying the lack of QOL benefit in the TA cohort have been discussed previously (6) and could include postoperative pain, early procedural complications, and limited experience with the TA procedure and post-procedure management.

In addition, it is important to recognize the context in which our study was conducted. As noted previously (4,6), the TA cohort of PARTNER A was small and not independently powered for major clinical endpoints such as survival. More importantly, site- and operator-level experience with TA-TAVR procedures in the PARTNER trial was very limited, with a median of 4 procedures per participating center. It is thus evident that most PARTNER sites did not perform enough TA-TAVR procedures to move beyond the point of learning curve effects (20). It seems likely that length of stay will shorten with greater experience, and it is conceivable that clinical and QOL outcomes after TA-TAVR may improve as well. Indeed, preliminary results from the continued access phase of the PARTNER trial suggest that substantial improvements in clinical outcomes of TA-TAVR have already been achieved at the PARTNER centers (21,22). Future studies are necessary to precisely quantify the nature of these developments and their overall impact on the cost-effectiveness of TA-TAVR.

One additional factor contributing to the higher incremental costs associated with the TA approach is the application of operating room overhead to the TA-TAVR procedures as opposed to the somewhat lower cardiac catheterization laboratory overhead, which was applied to the TF procedures. This methodological decision was based on a survey of PARTNER trial site practices at the end of the study and is similar to current practice in Europe, where

TAVR is a more established procedure. Sensitivity analyses demonstrate that even had we applied catheterization lab overhead rates to the TA-TAVR procedures, 12-month costs would have remained ~$7,000 higher with TAVR than with AVR. Thus, it is unlikely that changes in the procedural setting alone would be sufficient to render TA-TAVR an economically attractive procedure.

Although higher acquisition costs for the Edwards SAPIEN valve compared with current bioprosthetic valves are a key determinant of the cost-effectiveness of TAVR, sensitivity analyses based on the PARTNER A results demonstrate that substantial reductions in valve pricing (on the order of $15,000 less than current levels) would be required for TA-TAVR to be an economically attractive alternative to surgical AVR if clinical and QOL outcomes of TA-TAVR remain unchanged. For TA-TAVR to become a cost-effective alternative to AVR at current valve acquisition costs, it will be necessary to demonstrate substantial reductions in postoperative length of stay compared with the PARTNER A results as well as early QOL outcomes that are at least as good as (or better than) those achieved with surgical AVR.

Study limitations. Our analysis should to be interpreted in light of several important limitations. First, our study was based a 12-month time horizon. This approach offered the advantage of using only directly observed data, but does not address any potential differences between TAVR and AVR in long-term outcomes. Thus far, the durability of results with TAVR appears good (23,24), and no differences in survival or other major clinical outcomes between TAVR and AVR have been observed in the PARTNER trial population at 2 years (5), but truly long-term outcomes comparing TAVR with AVR must await further study. In addition, it is important to recognize that the PARTNER A trial enrolled patients within a narrow range of surgical risk. The results of this analysis thus cannot readily be extrapolated to patient groups with lower surgical risk or to patients with extensive comorbidities who would not generally be considered candidates for AVR. Our analysis was based on U.S. patients, hospitals, and cost structures; results in other health systems may differ. Finally, based on its sample size, the PARTNER trial had limited statistical power to identify small differences in outcomes, particularly within subgroups. This fact, coupled with unavoidable imprecision in some cost estimates, limits the certainty of our findings.

Conclusions

Based on the PARTNER trial, for patients with severe AS and high surgical risk, TAVR using the Edwards SAPIEN valve appears to be an economically attractive strategy compared with AVR, provided that patients are suitable for a TF approach. On the other hand, results for TA-TAVR compared with AVR were economically unfavorable in this small, early U.S. experience. Additional study is needed to establish whether clinical, QOL, and efficiency of care outcomes improve sufficiently to render TA-TAVR an economically attractive strategy as well.

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Key Words: aortic valve replacement ■ cost-effectiveness ■ TAVR.

APPENDIX

For a supplemental table, please see the online version of this article.