

Perspective on the cost-effectiveness of transapical aortic valve implantation in high-risk patients: Outcomes of a decision-analytic model

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Background: The incremental cost-effectiveness of transapical transcatheter aortic valve implantation (TAVI) is ill-defined in high-risk patients where aortic valve replacement (AVR) is an option, and has not been ascertained outside a randomized controlled trial.

Methods: We developed a Markov model to examine the progression of patients between health states, defined as peri- and post-procedural, post-complication, and death. The mean and variance of risks, transition probabilities, utilities and cost of transapical TAVI, high-risk AVR, and medical management were derived from analysis of relevant registries. Outcome and cost were derived from 10,000 simulations. Sensitivity analyses further evaluated the impact of mortality, stroke, and other commonly observed outcomes.

Results: In the reference case, both transapical TAVI and high-risk AVR and TAVI were cost-effective when compared to medical management (\$44,384/QALY and \$42,637/QALY, respectively). Transapical TAVI failed to meet accepted criteria for incremental cost-effectiveness relative to AVR, which was the dominant strategy. In sensitivity analyses, the mortality rates related to the two strategies, the utilities post-AVR and post-transapical TAVI, and the cost of transapical TAVI, were the main drivers of model outcome.

Conclusion: Transapical TAVI did not satisfy current metrics of incremental cost-effectiveness relative to high-risk AVR in the reference case. However, it may provide net health benefits at acceptable cost in selected high-risk patients among whom AVR is the standard intervention.

Key Words: Aortic valve replacement; transcatheter valve; aortic stenosis; cost-effectiveness

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Introduction

Transcatheter approaches for management of aortic stenosis (AS) have revolutionized the treatment of AS in several patient populations. In patients of high, but not prohibitive, surgical risk, TAVI appears to provide similar outcomes to surgical aortic valve replacement (AVR), as demonstrated by the Placement of Aortic Transcatheter Valve (PARTNER) Cohort A (1). Analysis from this trial has determined that transfemoral, but not transapical, transcatheter aortic valve implantation (TAVI) is incrementally cost-effective relative to AVR.

The avoidance of bias in prospective randomized controlled trials have led these protocols to be considered the reference standard with respect to defining the effectiveness of therapies. However, concerns about external validity may arise if aspects of the trial differ from standard practice (2). As variations in the apparent effect of TAVI may be modulated by the prevalence and effect of comorbid disease, stricter inclusion/exclusion criteria in this circumstance may lead to potential inflation of relative benefit (3). Therefore, despite the risk of selection bias, prospective, registry data may provide insights additional

Table 1 Characteristics of underlying groups (95% confidence intervals in parentheses, where applicable)

	AVR (4-11)	Transapical TAVI (12-13)	P
N	1,544	2,786	
Age	81.95 (81.59-82.31)	81.20 (80.94-81.45)	0.101
Female	49.88% (43.13-56.64%)	53.90% (46.62-61.17%)	0.472
NYHA III-IV	87.39% (71.13-100%)	76.63% (70.44-82.83%)	0.092
EF	46.49% (44.47-48.52%)	52.88% (51.35-54.42%)	0.010
History of MI	25.04% (4.69-45.39%)	20.54% (8.36-32.71%)	0.620
History of stroke	19.17% (14.84-23.50%)	13.25% (8.57-17.93%)	0.110
History of PAD	27.42% (12.86-41.98%)	48.57% (39.52-57.62%)	0.016
Diabetes	22.30% (12.13-32.47%)	27.18% (24.31-30.04%)	0.335
Hypertension	78.89% (64.84-92.93%)	77.61% (74.21-81.01%)	0.652
Renal failure	23.84% (11.44-36.23%)	16.78% (9.08-24.49%)	0.514
Logistic EuroSCORE	30.77% (26.36-35.18%)	29.39% (26.59-31.83%)	0.696
STS score	13.26 (7.18-19.33)	12.51 (10.77-14.26)	0.843

to randomized studies. We sought to study the cost-effectiveness of transapical TAVI using registry data, in order to provide better perspective into real-world clinical practice employing this technology.

Methods

Model development

Outcomes and costs attributed to transapical TAVI with the Edwards SAPIEN valve (Edwards Lifesciences, Irvine, CA) and tissue AVR for the management of high-risk patients with severe AS were evaluated in a decision-analytic model. This model was informed from registries of high-risk patients undergoing transapical TAVI and AVR, defined as a logistic EuroSCORE $>15\%$ and/or STS score $>10\%$ (Table 1) (4-23).

The passage of a hypothetical cohort of 10,000 patients through a number of health states that arose as consequence of transapical TAVI, AVR, or medical management (Figure 1) was assessed by Monte Carlo simulation using a Markov model (TreeAge Pro 2008, TreeAge, Williamstown, MA) (24). This approach allows estimation of quality-adjusted life years (QALY) and lifetime cost, and therefore calculation of the incremental cost-effectiveness ratio (ICER) of the technique with the most favorable outcome. Costs were estimated in 2012 US dollars; an adjustment to allow calculation of present value was performed using a discount rate of 5% per year in order to permit comparisons.

Health states, transitions and assumptions

The cycle length of the model (i.e. the interval at which patients changed health states) was set at 1 year, and the rest of life was simulated. Candidates for AVR (mean initial age of 80 years) entered the model with severe AS. The frequency of outcomes as well as transitions between health states, were obtained from the literature, using pooled estimates (Table 2). Transitions in operable patients who are medically managed were obtained from a registry that compared outcomes of patients offered intervention with AVR or transapical TAVI versus medical management (25). We assumed that only a proportion of patients that underwent work-up would proceed to transapical TAVI. The proportion of patients evaluated for transapical TAVI and then found unsuitable for implantation would include those converted to AVR after failed transapical TAVI implantation, based on the premise that the transapical implantation is being used as an alternative to standard AVR, rather than being in response to inoperability.

Overlapping health states were attributed the outcomes, utilities and costs of the worst state. For example, all patients have a substantial mortality, so this was not increased further in those with heart failure or stroke. Because of the high-risk status of patients in the medical management group, they were assumed to have heart failure. Likewise, the impact of stroke with regards to both cost and quality of life in the medical management group

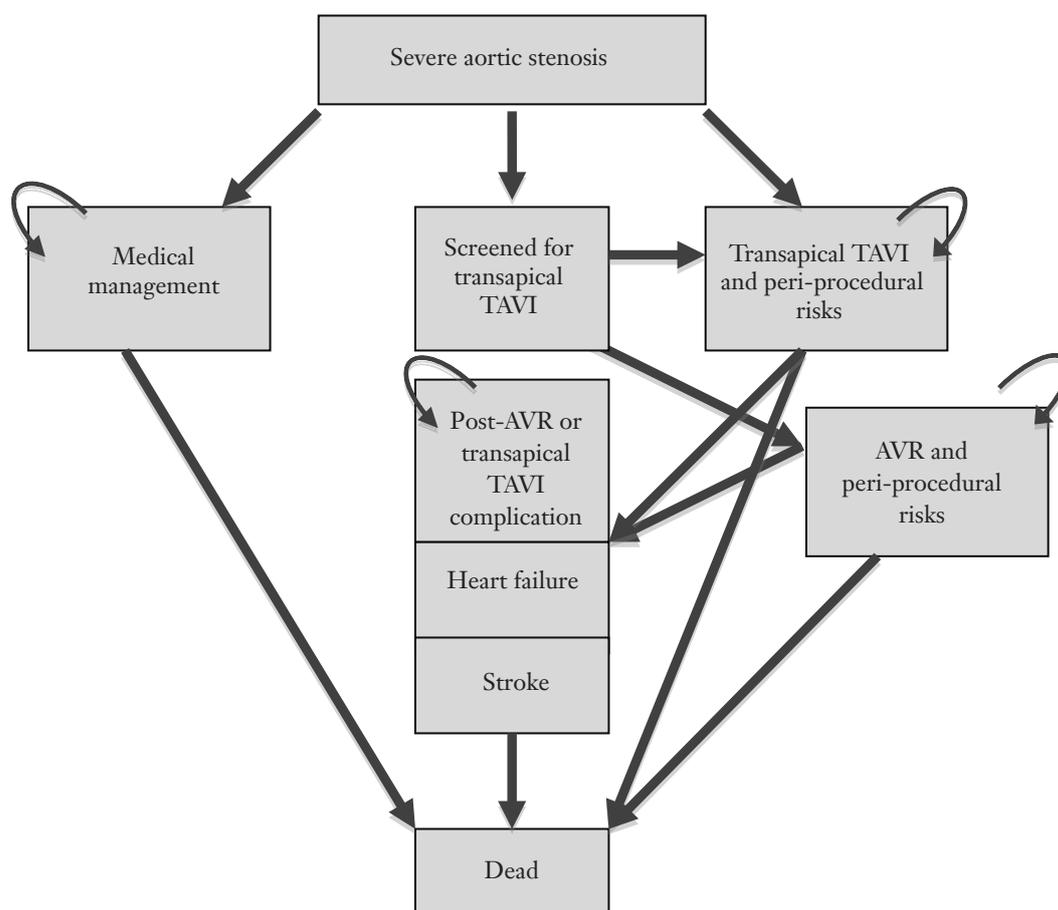


Figure 1 Markov model for comparing medical management, transcatheter aortic valve implantation (TAVI), and AVR in high-risk patients with severe aortic stenosis. The model allows for variable rates of progression to AVR from transcatheter aortic valve implantation (TAVI) screening. Patients undergoing transcatheter aortic valve implantation (TAVI) or AVR enter a Markov model whereby they may progress to five health states (heart failure, access site complications, other complications, stroke or death). AVR = Aortic valve replacement; TAVI = Transcatheter aortic valve implantation

would be minor, so stroke was not assessed in the medical management group. Patients with stroke did not proceed to reoperation.

The risk of other post-AVR complications, including endocarditis, hemorrhage, valve thrombosis, and non-cerebral thromboembolism, have not been adequately assessed in the transcatheter aortic valve implantation (TAVI) population, so we estimated them from linearized event rates in AVR recipients (27). Mortality related to post-AVR complications was derived from weighted averages from a meta-analysis of outcomes post-bioprosthetic AVR (28), and we assumed that as TAVI is a tissue valve, it would have a similar post-procedure complication rates.

Bleeding and vascular complications overlap, and were assessed as a single complication (12-14,17-20,22,23), with

a mortality derived from the one-year outcomes of the SOURCE Registry (17). Access site complications were assumed to occur only in the first cycle post-transcatheter aortic valve implantation (TAVI). Transcatheter aortic valve implantation (TAVI) patients undergoing valve replacement underwent only repeat TAVI (i.e. valve-in-valve). The reoperation rate for tissue valves has previously been described to follow a Weibull distribution (30).

Health outcomes

This information is summarized in *Table 3*. Age-specific data were obtained from the Medical Expenditure Panel Survey (31), and utility was age-adjusted, declining by 0.3% per year of age. QALYs were calculated from utility weights, multiplied by the duration in each health state. Heart failure

Table 2 Transition probabilities and mortality rates (95% confidence intervals in parentheses, where applicable)

	AVR	Transapical TAVI	Medical management
Peri-operative events			
Death*	9.76% (6.75-12.76%) (4-11)	9.73% (7.51-11.95%) (12-23)	15.40% (25)
TAVI access site Complications	-	2.53% (0.99-4.07%) (12-14,17-20,22,23)	-
Stroke – Peri-operative	3.78% (2.70-4.86%) (4-9,11)	2.00 (1.37-2.62%) (12-15,17-23)	-
Follow-up events			
Death	24.21% (18.87-29.55%) (7-11)	25.28 (21.06-29.51%) (12-18,20,21,23)	55.10% (25)
Heart failure		11.30% (26)	100%
Stroke – Post-operative	2.10% (2.70-3.70%) (27)	3.55% (3.42-3.68%) (12,14,17)	-
Post-AVR/TAVI Complications**		4.80% (4.10-5.60%) (27)	-
Reoperation	0.24% (27)	3.28% (3.19-3.37%) (12,14,17-19)	-
Complication mortality***			
TAVI access site complications	-	25.80% (17)	-
Post-AVR/TAVI complications		25.89% (28)	-
Stroke - Peri-operative		11.00 (8.00-14.00%) (29)	-

*: Assumed to be 30-day mortality in medical management group; **, Complications include endocarditis, hemorrhage, valve thrombosis, and non-cerebral thromboembolism; ***, Annual mortality related to stroke and heart failure was assumed the same as that after AVR or TAVI

Table 3 Utility values for each health state (\pm standard deviation)

Heart failure	0.67 \pm 0.01 (30)
Stroke	0.46 \pm 0.01 (31)
Post-AVR	0.69 based on 10% disutility (31)
Post-transapical TAVI	0.66 \pm 0.43 (6)
Medical management	0.59 \pm 0.30 (6)
Transapical TAVI access site complications	-1 QAL week (32)
Post-AVR/Transapical TAVI complications	0.67 \pm 0.01*

*Assumed to be similar to that of NYHA functional class II and III

utility for functional classes II and III was derived from the Cardiovascular Outcomes Research Consortium (33), and subject to sensitivity analysis to compensate for the fact that our population was significantly older than those in the original report. Specific utilities for postoperative stroke are not well defined, so we used a utility for disabling stroke from a systematic review (34). Utilities regarding other post-AVR/TAVI complications are also not well established and were deemed equivalent to that of heart failure (33).

We applied a 10% reduction in utility for uncomplicated

AVR from that predicted of an age-matched population (31). Post-transapical TAVI utility was attributed the status reported in the European PARTNER transcatheter heart valve study (14). We anticipated a decrement in utility from access site complications concordant with the added hospital length-of-stay in patients developing hemorrhage post-coronary artery bypass grafting (32). Utility of the medical management group was assessed as being equivalent to the QALY before transapical TAVI in the European PARTNER transcatheter heart valve study (14).

Table 4 Costs associated with each health state

	Mean cost (US\$/yr; ±standard deviation)
Heart failure	Yearly costs after diagnosis: 10,832 (35)
Stroke	14,155±453 (acute treatment) (36) Annual follow-up costs: 14,561±14,690 (37)
TAVI	49,106±1283 (33) Cost of additional work-up: 374.35±500 Annual follow-up costs: 336.41**
AVR	49,106±1283 (33) Annual follow-up costs: 99.01* 1st 5 years Annual follow-up costs: 336.41 thereafter**
Medical management	Yearly costs after diagnosis: 10,832 (35)
TAVI access site complications	12,302 (32)
Post-AVR/TAVI complications	Yearly costs: 300 (38)

*Follow-up costs for one outpatient visit; **Follow-up costs for transthoracic echocardiogram plus one outpatient visit

Cost information

Cost analysis was taken from the perspective of the healthcare funding body, assuming that the amount reimbursed to the provider is the cost of care. Cost information was mainly obtained from diagnostic related groups (DRGs), and Medicare payments for current procedural terminology (CPT) codes (*Table 4*). Costs associated with AVR were gathered from weighted national estimates from the Healthcare Cost and Utilization Project (HCUP) nationwide inpatient sample 2010 (36). We assumed that reimbursement for transapical TAVI would be analogous to AVR (39). Costs of additional imaging, such as computed tomographic angiography, were included in screening for transapical TAVI. The costs of heart failure, including the costs of procedures and provider visits (35), were also attributed to patients in the medical management group, based on their assumed utility status. Peri-operative stroke was assigned the costs for acute treatment and follow-up (36,37). The average cost of hemorrhage post-coronary artery bypass was used as a surrogate for that of access site complications related to transapical TAVI (32). A weighted average of the relative incidences of post-AVR and TAVI complications was used to assign average annual cost (38).

Analyses

Beta distributions (continuous probability distributions defined on an interval of 0 to 1) were assigned to probabilities and utility weights, and gamma distributions

(continuous probability distributions potentially ranging from 0 to infinity) were assigned to costs based on standard errors derived from the associated literature. Means and 95% credible intervals (Bayesian confidence interval, 95% CI) were computed on the basis of 10,000 iterations. The willingness-to-pay (WTP) threshold of acceptable incremental cost-effectiveness was defined by an ICER of $\leq \$100,000/\text{QALY}$. Probabilistic sensitivity analyses were performed from the Markov model, and one-way sensitivity analyses were performed to identify the critical sources of variation in the input data.

Results

Health outcomes and costs of high-risk AVR and transapical TAVI

Outcomes of transapical TAVI and AVR were superior to medical management, although lifetime costs of transapical TAVI and AVR exceeded those of medical management. The cost-effectiveness ratios of transapical TAVI and AVR were respectively \$44,384/QALY and \$42,637/QALY. In the reference case (age 80, transition probabilities and outcomes in *Table 2*, 50% suitability for transapical TAVI), transapical TAVI was dominated by AVR, because lifetime costs were slightly higher for transapical TAVI (\$56,730 *vs.* \$56,630), with slightly fewer QALYs from TAVI (1.66 *vs.* 1.70).

The anticipated survival curves from 10,000 simulations (*Figure 2*) showed both interventions to be superior to medical therapy. The incremental cost-effectiveness plot

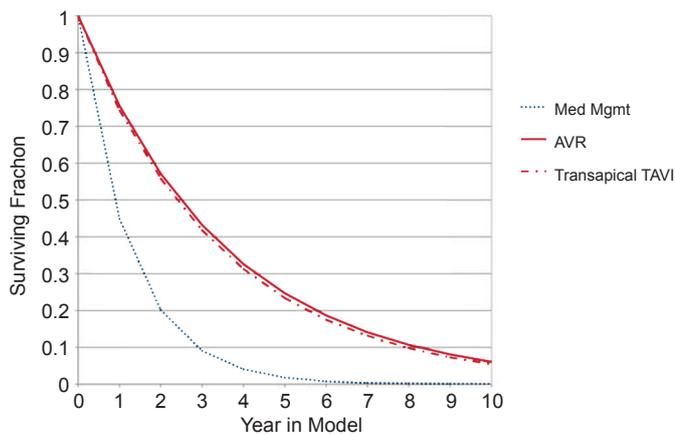


Figure 2 Survival of the patients in the Monte Carlo simulation. AVR = Aortic valve replacement; TAVI = Transcatheter aortic valve implantation

from simulation comparison of transapical TAVI relative to AVR (*Figure 3*) showed that at a WTP \leq \$100,000/QALY gained, transapical TAVI is incrementally cost-effective relative to AVR in a minority (47%) of simulations.

Sensitivity analyses

Analysis of each factor across a clinically plausible range was used in threshold analyses to understand the limits of transition probabilities, mortalities, costs, and utilities that could influence model outcome. These factors, together with the threshold at which they alter model outcome are shown in *Table 5*. The favored strategy was mainly determined by variation in the probabilities of peri-operative and annual mortality after each procedure, and the probability of annual stroke post-AVR. The thresholds of annual mortality post-AVR and post-transapical TAVI are near their reference case values noted in *Table 2*. *Figure 4*, showing a two-way sensitivity analysis comparing the impact of varying these annual mortality rates, emphasizes that slight alterations, such as a reduction of annual mortality from transapical TAVI to 20% while keeping the annual mortality post-AVR near that of the reference case, can change the outcome of the model. Likewise, *Figure 5*, a two-way sensitivity analysis demonstrating the interaction between the utility post-AVR and utility post-transapical TAVI, emphasizes how the utilities of each health state are also important determinants of variation in net health benefit.

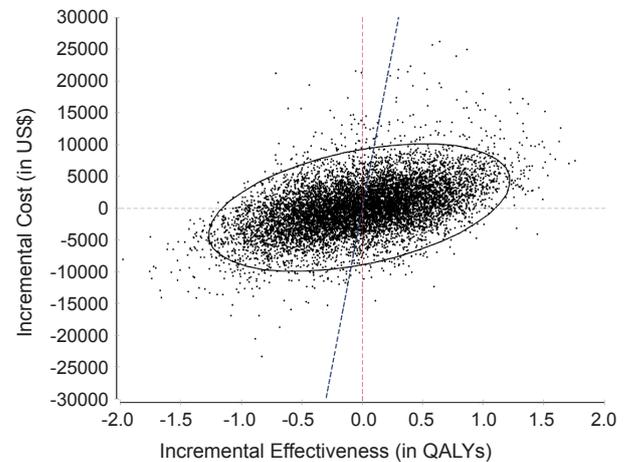


Figure 3 Scatter plot of incremental cost-effectiveness of transapical TAVI relative to AVR from 10,000 simulations of the decision-analytic model. Ellipse represents 95% confidence interval. Line represents the willingness to pay with slope of \$100,000/QALY. In this scatter plot, transapical TAVI is incrementally cost-effective relative to AVR in 47% of simulations. AVR = Aortic valve replacement; TAVI = Transcatheter aortic valve implantation; QALY = Quality-adjusted life years

Variation in net monetary benefit is influenced by the initial cost attributed to transapical TAVI. The net monetary benefit from AVR exceeds transapical TAVI as long as transapical TAVI cost exceeds \$41,904.

Discussion

Using existing registry data, we have shown that transapical TAVI fails to achieve incremental cost-effectiveness compared to AVR. However, with sensitivity analyses of this data, we have identified thresholds that may be helpful in identifying particular groups that would achieve greater benefit from transapical TAVI versus the population incorporated in the reference case. This model reinforces the importance of considering mortality, non-fatal adverse events, and cost in the selection between high-risk AVR and transapical TAVI.

Registry data

Given the recent development of transapical TAVI, we did not include data from registries emphasizing results of

Table 5 Threshold analyses. The threshold to alter model outcome, the resultant net health benefit or net monetary benefit (at a willingness to pay of \leq \$100,000) at that threshold, and the favored strategy are listed for all factors that modified model outcome

Factor	Threshold value	Favored strategy (below threshold)	Net health benefit*
Transition probabilities/mortality rates			
Annual mortality post-AVR	25.53%	AVR	1.06
Annual mortality post-transapical TAVI	24.00%	TAVR	1.13
Peri-operative mortality AVR	14.53%	AVR	1.06
Peri-operative mortality transapical TAVI	5.05%	TAVR	1.13
Annual stroke post AVR	4.93%	AVR	1.06
Cost			
Transapical TAVI	\$41,904	TAVR	\$112,821
Utilities			
AVR	0.62	TAVR	1.63
Transapical TAVI	0.70	AVR	1.69

*Net health benefit (for willingness to pay of \$100,000) is that which is obtained at the stated threshold

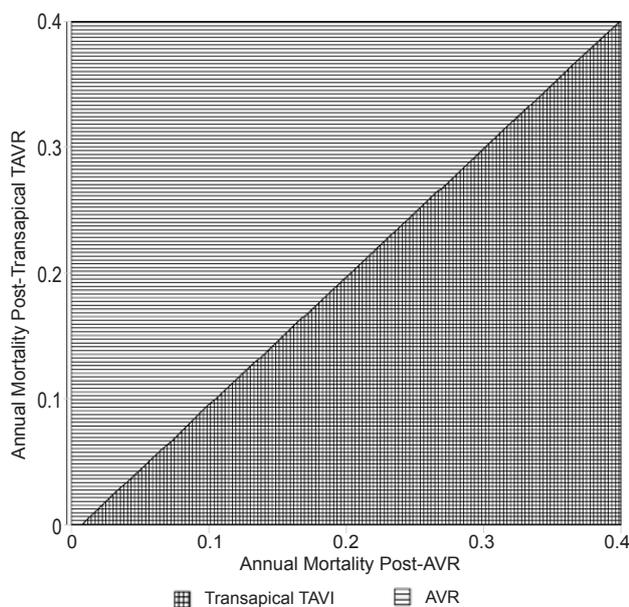


Figure 4 Two-way sensitivity analysis – Annual mortality post-AVR versus annual mortality post-transapical TAVI. Strategy favored with regards to net health benefit is that noted by the legend. AVR = Aortic valve replacement; TAVI = Transcatheter aortic valve implantation

a “learning curve.” Only registries that separated recent procedures, once proper proctoring and training had been completed, were included in the data employed in the model (13). In order to ensure our analysis would compare

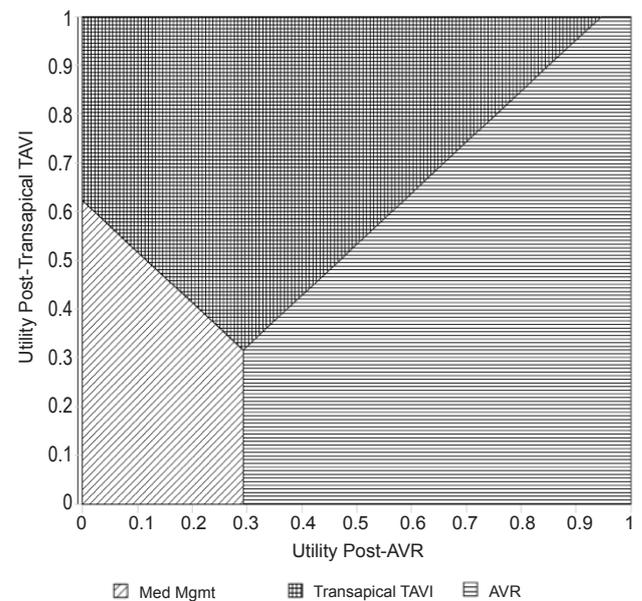


Figure 5 Two-way sensitivity analysis - Utility post-AVR versus utility post-transapical TAVI. Strategy favored with regards to net health benefit is that noted by the legend. AVR = Aortic valve replacement; Med Mgmt = Medical management; TAVI = Transcatheter aortic valve implantation

similar groups, we also did not include registries that failed to discern between transapical TAVI performed in inoperable versus high-risk patients.

Based on the clinical features assessed in *Table 1*, the

transapical TAVI and AVR groups were similar, except for two variables, the actual ejection fraction and the percentage of patients with peripheral arterial disease. The difference in ejection fraction is unlikely to influence outcomes, given that comparative differences in ejection fraction, when values are greater than 45%, have been shown to not influence mortality (40). Given clinical circumstance surrounding the decision to proceed with transapical TAVI, at times involving the exclusion of transfemoral access due to severe peripheral arterial disease, the high rate of peripheral arterial disease in the transapical TAVI group is concordant with current clinical practice.

Cost-effectiveness comparison with PARTNER data

This analysis focused on the comparison of outcomes between high-risk tissue AVR and transapical TAVI with the Edwards-Sapien valve. In contrast to PARTNER Cohort A, which was a randomized-control trial, we sought to study the incremental cost, health, and monetary benefit related to transapical TAVI from registries that may be more reflective of “everyday life” because of freedom from trial inclusion/exclusion criteria. In contrast to the PARTNER Cohort A cost effectiveness analysis, which assessed costs and outcomes accrued over one year post-intervention (41), a modeling approach also allows development of a longer-term perspective with the additive morbidity and mortality of each intervention assessed over a number of years. This could be important as although the patient population has a limited lifespan, the cost assessed beyond one-year post-intervention could have important economic ramifications and impact the feasibility of either intervention.

The initial part of this analysis showed that the outcome of our model is consistent with previous work showing that both AVR and transapical TAVI are cost-effective when compared to standard medical management in high-risk patients, based on the superior utility derived from either strategy (42). Importantly, this confirmed the published cost-effectiveness data from PARTNER, but using separate data to inform the medical management cohort, derived from a study where patients opted for medical management (25). The second component showed TAVI to be less cost-effective than AVR, under our assumed scenario. The cost-effectiveness analysis from PARTNER Cohort A data showed the change in utility with the transapical approach was -0.07 QALYs; we show a similar decrement in QALYs. However, our threshold analysis (detailed in *Table 5*) highlights factors, that when altered from reference case

values, may produce a model outcome more favorable to transapical TAVI.

Costs in our decision-analytic model were based on reimbursement determined by the weighted 2010 national estimates from the Healthcare Cost and Utilization Project (HCUP) nationwide inpatient sample. Given uncertainties in the future reimbursement and thus the actual cost of TAVI, the impact of the initial cost of TAVI, which does influence model outcome, was subject to sensitivity analysis. These results are heavily dependent on the assumption of equal reimbursement for transapical TAVI and AVR (39), and we would expect AVR to remain dominant unless lower costs pertained to transapical TAVI – perhaps this might be attainable with a shorter length of stay.

Assumptions and limitations

The modeling process is based upon assumptions regarding transition probabilities, outcomes and costs, which are informed by literature and clinical experience. Bleeding and vascular access complications overlap in various trials and registries, especially since the transapical approach itself may many times incur both types of complications in the same procedure. Accordingly, they were assessed as a single complication. Reassuringly, threshold analysis did not show the probability of transapical TAVI access site complications to have an important influence on the outcome of the model. Other post-AVR and post-transapical TAVI complications were analyzed as a single entity. The assessment of outcomes derived from weighted averages is a simplification of a variety of complications of varying severity. However, the low frequency of severe complications within an already low incidence of post-AVR complications renders this of limited influence over health outcomes (27). Similarly, in relation to transition probabilities, costs, and utilities, other less morbid conditions, such as subsequent atrial fibrillation, renal failure, or need for pacemaker placement after AVR or transapical TAVI were considered to be part of the costs and utility of the post-operative state and not included separately in our model. An analysis of the registry data employed showed no significant difference in the need for permanent pacemaker placement post-operatively (6.94% post-AVR versus 6.41% post-transapical TAVI; $P=0.714$), as well as the occurrence of renal failure (8.97% post-AVR versus 5.16% post-transapical TAVI; $P=0.219$). Given there is no comparison of these outcomes to those of patients with severe aortic stenosis receiving medical management, it is unclear how these factors would impact cost-effectiveness

of transapical TAVI or AVR in this population.

Patient-prosthetic mismatch is also an important determinant of morbidity and mortality post-AVR and has also been shown to predict adverse outcomes post-transapical TAVI (43). Similarly, paravalvular aortic insufficiency has also been linked to post-operative adverse events after transapical TAVI (44). Both the occurrence of these complications and their clinical impact were assumed to be incorporated in the transition probabilities and health utilities in the model, given their limited distinction in registry data.

The most appropriate strategy to define utility for patients with two disease conditions is controversial (45). Given the high annual mortality post-AVR and post-transapical TAVI, the annual mortality of patients developing heart failure and stroke were not deemed to be significantly different than those without those conditions, and this philosophy was also applied to utilities. Thus, stroke and heart failure post-AVR and post-transapical TAVI were ascribed the mortality and utility of the worst condition. No studies have detailed the risk of post-transapical TAVI heart failure, thus this was assumed to be similar to that post-AVR.

Conclusions

With a developing technique, decision-analytic models are able to provide unique perspective not easily obtained even through clinical trials. The ICER of transapical TAVI does not satisfy standard criteria for cost-effectiveness in an unselected, non randomized-controlled trial, population defined by the literature. However, this decision-analytic model identifies patient populations that may derive superior utility at an acceptable cost with transapical TAVI, relative to surgical AVR.

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