

A Canadian cost-effectiveness analysis of SAPIEN 3 transcatheter aortic valve implantation compared with surgery, in intermediate and high-risk severe aortic stenosis patients

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Background and objectives: The treatment of severe aortic stenosis requires replacement of the defective native valve. Traditionally, this has been done via surgery, but in the last 10 years, transcatheter techniques have emerged. Transcatheter aortic valve implantation (TAVI) is a less invasive option compared to surgical aortic valve replacement (SAVR), and this study evaluates the cost-effectiveness of TAVI versus SAVR in intermediate and high surgical risk patients in Canada.

Methods: A Markov model was used to project the costs and quality-adjusted life years (QALYs) gained for TAVI using the SAPIEN 3 valve and SAVR over a 15-year time horizon. The PARTNER I and II studies were used to populate the model in terms of survival, clinical event rates and quality of life over time. The costs of TAVI with SAPIEN 3 and SAVR as well as the costs associated with events included in the model were derived from Canadian administrative and literature data. Costs were expressed in 2018 Canadian dollars and all future costs and QALYs were discounted at a rate of 1.5% annually. Probabilistic and one-way sensitivity analyses were conducted.

Results: The incremental cost-effectiveness ratios of TAVI using the SAPIEN 3 valve compared to surgery were \$28,154 per QALY gained in intermediate risk patients and \$17,237 per QALY gained in high-risk patients. The results of the probabilistic analyses indicated that at willingness-to-pay threshold of \$50,000 per QALY gained, the probability of TAVI to be cost-effective was greater than 0.9 in both intermediate-risk and high-risk patients. Sensitivity analyses showed the results were most sensitive to the time horizon used.

Conclusion: TAVI using the SAPIEN 3 valve is highly likely to be cost-effective in Canadian patients with severe aortic stenosis who are at intermediate and high surgical risk.

Keywords: aortic stenosis, economic evaluation, valve replacement, Canada

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Introduction

Aortic stenosis is a valvular heart disease that involves the narrowing of the aortic valve. In a recent systematic review, the prevalence of severe aortic stenosis amongst the elderly (>75 years old) was estimated to be 3.4%.¹ Severe aortic stenosis is associated with a very high mortality rate if left untreated with approximately 75% of patients likely to die within 3 years of symptoms.² Surgical aortic valve replacement (SAVR) has been the traditional treatment for severe aortic stenosis, although in many cases SAVR is not performed because patients are

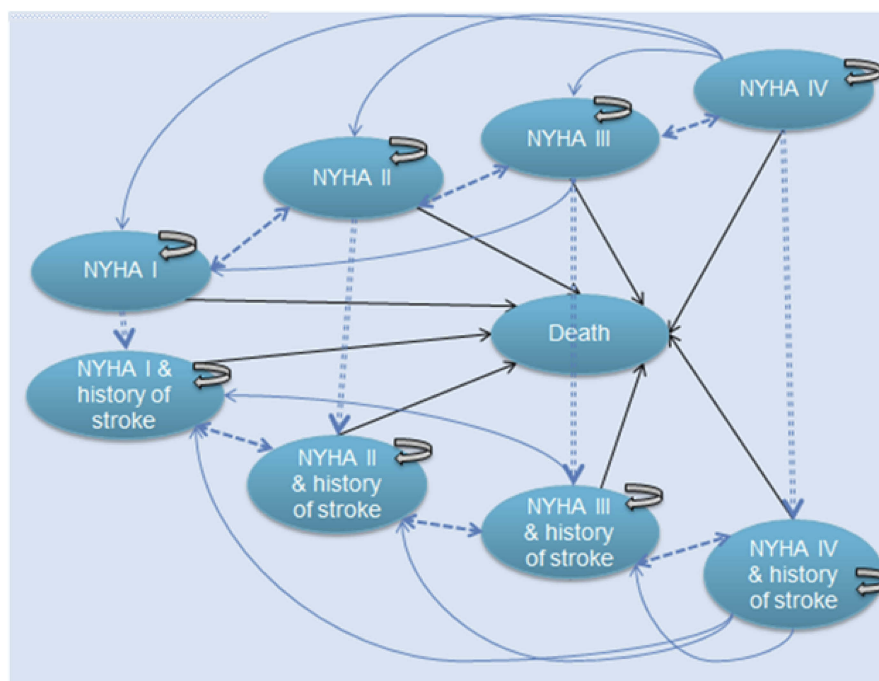


Figure 1 Graphical representation of the model structure.

Abbreviation: NYHA, New York Heart Association.

being considered inoperable due to frailty, co-morbidities or advanced age.² In recent years, transcatheter aortic valve implantation (TAVI) has emerged as a less invasive option to treat the disease, and in randomized clinical trials, it has been shown to be superior to best medical treatment³ in inoperable patients and at least noninferior to SAVR in high-risk^{4,5} and intermediate-risk^{6,7} patients.

Following the first in man use of TAVI in 2002 and commercialization in 2007, devices have undergone substantial development. The third generation of transcatheter heart valves such as the Edwards Lifesciences SAPIEN 3™ is now commercially available.⁸ A recent study evaluated outcomes for TAVI using the SAPIEN 3 device in inoperable, high-risk and intermediate-risk patients with severe aortic stenosis. In a propensity score-adjusted analysis, 1-year outcomes for intermediate-risk patients with SAPIEN 3 were compared to SAVR patients in the PARTNER II RCT.⁹ Mortality at 1 year with SAPIEN 3 was estimated to be 7.4% compared to 13% with SAVR and the 1-year risk of stroke was 4.6% for SAPIEN 3 compared to 8.2% for SAVR. Additionally, a recent economic evaluation in the US of PARTNER IIA and SAPIEN 3 results in intermediate-risk patients found that TAVI dominated SAVR (ie better outcomes and less costly than SAVR).¹⁰ In Canada, three recent economic evaluations have shown that TAVI was cost-effective in Canadian intermediate-risk^{11,12} and high-risk patients.¹³

However, no Canadian studies have evaluated the cost-effectiveness of TAVI using the SAPIEN 3 heart valve device compared to SAVR in intermediate-risk and high-risk Canadian patients.

Methods

Model overview

An economic model was used to estimate the costs and quality adjusted life years (QALYs) of patients with severe aortic stenosis undergoing either 1) TAVI using the SAPIEN 3 prosthesis or 2) SAVR in Canada. Two different patient populations were evaluated: patients at intermediate and patients at high surgical risk. The analysis was made from a Canadian third-party payer perspective. The model used a 15-year time horizon and a 1.5% discount rate for costs and outcomes (ie QALYs).

Figure 1 presents the structure of the economic model. In each monthly cycle of the model, patients can be in 1 of 9 mutually exclusive health states primarily defined by NYHA (New York Heart Association) class and whether the patient has suffered a stroke during the model. In addition to health states defined by NYHA class and stroke status, patients are also at risk of death every monthly cycle. Patients can transition between any of the non-death health states each cycle and different costs and

utility values can be assigned to each of these. Patients are assigned the cost of treatment (SAVR, TAVI) including the device cost and associated hospitalization cost during the first cycle of the model. Thereafter, simulated patients are at risk of acute events each cycle from any of the nondeath health states including stroke, transient ischemic attack (TIA), pacemaker implantation, endocarditis, new-onset atrial fibrillation, myocardial infarction, renal replacement therapy, major bleeding, re-hospitalization and reinterventions with TAVI using SAPIEN 3 or SAVR.

Model inputs

Clinical inputs

The distribution of patients by NYHA class, mortality rates and clinical event rates used in the model was derived from 3 main sources of data: 1) PARTNER IA study¹⁴ for the SAVR high-risk population; 2) PARTNER IIA study⁶ for the SAVR intermediate-risk population and 3) PARTNER II study for TAVI with the SAPIEN 3 valve in intermediate- and high-risk populations.^{9,15} Tables 1 and 2 present for TAVI using SAPIEN 3 and SAVR the 30-day and 1-year observed event rates for intermediate- and high-risk patients, respectively. For TAVI using SAPIEN 3, outcome data were available up to 12 months for both the intermediate- and the high-risk populations. For SAVR, data on all clinical outcomes was available up to 2 years for intermediate-risk and 5 years for high-risk arms. Mortality rates beyond those observed in the trials were extrapolated and a range of survival statistical functions were tested. Based on goodness of fit tests (Akaike

information criterion and Bayesian information criterion) and clinical plausibility comparing predictions to general population mortality data, a linear function and a Weibull distribution were selected to model mortality in the intermediate-risk and high-risk populations, respectively. Trial data and extrapolations based on the last observed data were used for the other clinical events included in the model.

Costs input

The cost estimates of TAVI using SAPIEN 3 and SAVR procedures were comprised of various components. These included the cost of the device for each procedure, the post-procedural inpatient costs, physician fees related to the procedure and to specialist consultations during the inpatient stay, along with workup costs that occurred in an emergency room or ambulatory setting just prior to admission. The cost of the TAVI using SAPIEN 3 device was based on the manufacturer list price (\$25,000). The cost of the SAVR device (\$6,000) was derived from a recent Canadian cost-effectiveness study comparing TAVI to SAVR in intermediate-risk patients.¹¹ Post-procedural inpatient costs (eg hospitalization costs) were calculated using unpublished patient level data from the Canadian Institute of Health Information (CIHI) for more than 8,000 individuals undergoing TAVI or SAVR for severe aortic stenosis between April 1, 2014 and March 31, 2016 (Hamilton Integrated Review Ethics Board approval #2018-3141). Work-up costs were also identified using the same CIHI data. Physician fees associated with SAVR and TAVI using SAPIEN 3 procedures were based on

Table 1 Clinical outcomes for intermediate-risk patients

Outcomes	30-Day outcomes		1-Year outcomes	
	TAVI using SAPIEN 3	SAVR	TAVI using SAPIEN 3	SAVR
Mortality	1.03%	3.53%	8.81%	12.83%
Major stroke	1.10%	4.29%	2.38%	5.78%
Transient ischemic attack	0.46%	0.41%	1.92%	1.79%
Atrial fibrillation	5.42%	27.08%	6.34%	27.08%
Renal replacement therapy	0.46%	3.16%	0.46%	5.26%
Myocardial infarction	0.28%	1.84%	0.28%	3.33%
New pacemaker	10.02%	6.95%	10.56%	8.74%
Major bleeding	10.57%	31.57%	11.02%	36.98%
Repeat hospitalization	4.87%	7.05%	13.03%	17.81%
Heart failure hospitalization	1.74%	1.74%	6.90%	9.42%
Endocarditis	0.19%	0.00%	0.73%	0.31%
Redo with TAVI	0.00%	0.00%	0.27%	1.82%
Redo with SAVR	0.00%	0.00%	0.73%	0.44%

Abbreviations: TAVI, transcatheter aortic valve implantation; SAVR, surgical aortic valve replacement.

Table 2 Clinical outcomes for high-risk patients

Outcomes	30-Day outcomes		1-Year outcomes	
	TAVI using SAPIEN 3	SAVR	TAVI using SAPIEN 3	SAVR
Mortality	3.11%	5.68%	11.36%	20.01%
Major stroke	1.26%	1.21%	2.79%	1.55%
Transient ischemic attack	0.76%	0.30%	2.55%	1.28%
Atrial fibrillation	5.80%	17.18%	8.88%	17.18%
Renal replacement therapy	1.01%	4.22%	1.01%	5.86%
Myocardial infarction	0.50%	0.30%	1.99%	0.30%
New pacemaker	10.60%	4.22%	12.64%	4.85%
Major bleeding	13.37%	23.20%	16.95%	27.87%
Repeat hospitalization	6.81%	5.42%	18.58%	17.83%
Heart failure hospitalization	3.02%	3.02%	10.79%	13.09%
Endocarditis	0.25%	0.00%	1.28%	0.63%
Redo with TAVI	0.00%	0.00%	0.26%	0.26%
Redo with SAVR	0.00%	0.00%	2.92%	0.00%

Abbreviations: TAVI, transcatheter aortic valve implantation; SAVR, surgical aortic valve replacement.

expert opinion and the Ontario Schedule of Benefits for Physician Services.¹⁶ Hospitalization costs associated with TAVI and SAVR were estimated separately for intermediate- and high-risk patients. The logistic EuroScore I (log ES),¹⁷ which can be approximated using administrative data from CIHI, was used to predict the operative risk group for each patient. High-risk patients were defined as those with a log ES greater or equal to 15% while intermediate-risk patients were defined as those with a log ES score between 5% and less than 15%. Table 3 provides the total and breakdown of procedure-related costs for TAVI with SAPIEN 3 and SAVR used in the model per surgical risk levels. In addition, all TAVI patients as well as SAVR patients with non-mechanical heart valves were assigned costs of 75 mg OD clopidogrel for the first 6 months after their procedure at a cost of \$73.¹⁸ SAVR patients who received mechanical valves, approximately 15% of all valves, were assumed to receive on average 5.8 mg of warfarin per day for the rest of their lives,¹⁹ which was calculated at \$278 per year (including drug and INR testing costs^{16,20}). Canadian-specific costs of events were derived from published literature,²¹ the CIHI patient cost calculator²² and Alberta Health costing²³ (Table 4). All costs are presented in 2018 Canadian dollars, and the Canadian Consumer Price Index²⁴ was used when required to inflate costs to 2018 values.

Utilities input

Health state utility values considered in the model were derived from patient-level EQ5D-3L data collected in the PARTNER studies, which were valued using the Canadian

EQ5D-3L algorithm.²⁵ For intermediate-risk patients, EQ5D-3L utility values of 0.80 and 0.72 were assigned to TAVI using SAPIEN 3 and SAVR patients for the first year postprocedure. Beyond 1 year, these utility values were 0.79 and 0.78, respectively. EQ-5D-3L utility values for high-risk patients were lower for both the first-year post procedure (ie TAVI with SAPIEN 3: 0.75; SAVR: 0.69) and beyond 1 year (ie TAVI using SAPIEN 3: 0.76; SAVR: 0.74). For patients with stroke, a utility weight of 0.68²⁶ was applied to the procedure and time-specific utility values. In the base case analysis, no additional dis-utilities were applied for other clinical events as the utilities used in the model were based on trial data collected over time, therefore already accounting for the impact of clinical events on quality of life. To test the impact of this assumption, event-specific dis-utilities were applied in the model in a sensitivity analysis (Table 4).

Treatment of uncertainty

Uncertainty in the model was evaluated in several ways. The overall parameter uncertainty of the cost-effectiveness results was assessed using probabilistic sensitivity analysis (PSA). In PSA, the model is run a large amount of times using Monte Carlo simulation. In each simulation, different values of model input variables (eg mortality rates, costs) are drawn based on their specified distribution and parameters. Beta distributions were used to define mortality and other clinical event rates, along with utility variables. Gamma distributions were used to define cost variables. The overall parameter uncertainty is expressed

Table 3 Procedural cost by patient risk population*

	Intermediate risk		High risk		Combined population (sensitivity analysis)**	
	TAVI using SAPIEN 3	SAVR	TAVI using SAPIEN 3	SAVR	TAVI using SAPIEN 3	SAVR
Device costs	\$25,000	\$6,000	\$25,000	\$6,000	\$25,000	\$6,000
Non-device costs (ie hospitalizations)	\$34,395	\$37,611	\$45,497	\$59,507	\$39,466	\$44,142
Total costs	\$59,395	\$43,611	\$70,497	\$65,507	\$64,466	\$50,142

Notes: *Surgical risk categories based on logistic EuroScore I values. Non-device costs (ie hospitalization costs) were derived from the Canadian Institute for Health Information (CIHI) admission data from April 1, 2014 to March 31, 2016. **Independent of surgical risk status.

Abbreviations: TAVI, transcatheter aortic valve implantation; SAVR, surgical aortic valve replacement.

Table 4 Costs and dis-utilities applied to model events

Event	Value	Source
Costs		
Stroke (ischemic or hemorrhagic)		
First year	\$57,024	Mittman ³³
2nd year and beyond	\$7,085	Blackhouse ³⁴
Transient ischemic attack	\$3,716	CIHI PCE ²² CMG029
Major bleeding (not cerebral)	\$4,700	CIHI PCE ²² CMG187
Pacemaker implant	\$12,177	CIHI PCE ²² CMG187
Myocardial infarction	\$7,524	CIHI PCE ²² CMG 193,194
Acute onset atrial fibrillation	\$4,555	CIHI PCE ²² CMG201,202
Other hospitalization (not included in the above)	\$6,098	CIHI average hospitalization cost ²¹
Heart failure hospitalization	\$7,426	CIHI PCE ²² CMG195,196
Renal failure needing replacement therapy	\$743	Alberta Health ²³ C471,C472
Endocarditis	\$35,084	Alberta Health ²³ CMG+219
Balloon valvuloplasty	\$29,304	Alberta Health ²³ CMG+178
Vascular complication (not included in bleeding)	\$10,320	Alberta Health ²³ CMG+213
Dis-utilities (used in sensitivity analysis)		
Stroke	0.68 (utility weight)	Tengs ²⁶
Transient ischemic attack	0.033	Sullivan ³⁵
Major bleeding (not cerebral)	0.181	Sullivan ³⁵
Vascular complication (not included in Bleeding)	0.06	Fairbairn ²⁸
Heart failure hospitalization	0.1167	Sullivan ³⁵
Acute onset atrial fibrillation	0.0384	Sullivan ³⁵
Renal replacement therapy	0.1104	Sullivan ³⁵
Myocardial infarction	0.0626	Sullivan ³⁵
Endocarditis	0.0289	Sullivan ³⁵

Abbreviations: CIHI PCE, Canadian Institute for Health Information patient cost estimator; CMG, case mix group.

through cost-effectiveness acceptability curves (CEACs) which present the probability that an intervention (TAVI) is cost-effective over a range of willingness-to-pay thresholds (eg \$50,000 or \$100,000 per QALY gained). Additionally, several one-way sensitivity analyses were undertaken in which the cost-effectiveness of TAVI using

SAPIEN 3 compared to SAVR was evaluated when changing the value of a single model variable at a time. This included changing the time horizon of the model, changing the discount rate, using initial hospitalization costs based on all patients regardless of surgical risk, changing the cost of the SAVR device, changing non-device procedure costs

Table 5 Base-case cost-effectiveness results

	Costs	QALYs	Incremental cost per QALY gained
<i>Intermediate risk</i>			
TAVI using SAPIEN 3	\$70,556	5.10	
SAVR	\$57,083	4.62	
Difference	\$13,473	0.48	\$28,154
<i>High risk</i>			
TAVI using SAPIEN 3	\$84,348	3.57	
SAVR	\$76,986	3.15	
Difference	\$7,362	0.43	\$17,237

Abbreviations: TAVI, transcatheter aortic valve implantation; SAVR, surgical aortic valve replacement; QALYs, quality-adjusted life years.

(ie hospitalization costs) by $\pm 20\%$, excluding management costs related to clopidogrel or warfarin costs and applying event-specific dis-utilities to the model.

Results

With incremental cost-effectiveness ratios (ICERs) lower than \$30,000 per QALY gained, TAVI with the SAPIEN 3 valve was found to be cost-effective compared to SAVR in both intermediate- and high-risk populations. Table 5 presents the details of the base case analyses for both populations. For patients at an intermediate surgical risk, TAVI using SAPIEN 3 was found to generate 0.48 more QALYs than SAVR and cost an additional \$13,473, yielding an ICER of \$28,154 per QALY gained. For patients at high surgical

risk, TAVI was estimated to generate 0.43 more QALYs than SAVR at an additional cost of \$7,362. The resulting ICER for the high-risk population was \$17,237 per QALY gained.

The CEACs for TAVI using SAPIEN 3 in the intermediate- and high-risk groups are shown in Figure 2. For patients at intermediate surgical risk, the probability of TAVI with SAPIEN 3 being cost-effective was 0.91 and 0.99 at willingness-to-pay thresholds of \$50,000 and \$100,000 per QALY gained, respectively. These probabilities were 0.93 and 0.99 in the high-risk patient group, respectively. Table 6 presents the cost-effectiveness results under various one-way sensitivity analyses. As shown in this table, the only sensitivity analysis in which the ICER became higher than \$50,000 per QALY gained was when the time horizon of the model was

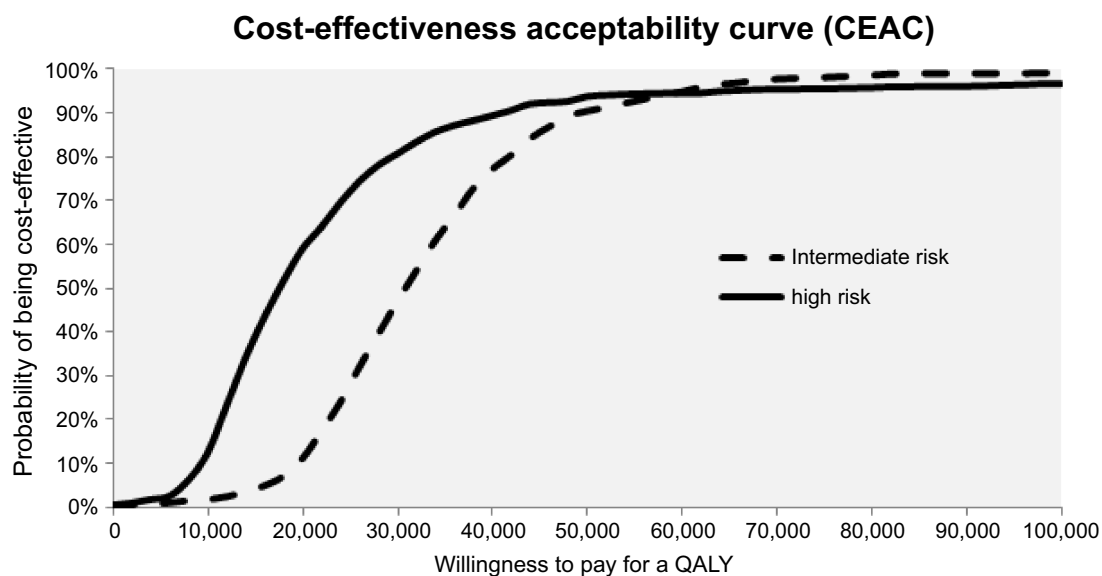


Figure 2 Cost-effectiveness acceptability curves for TAVI (SAPIEN 3) versus SAVR.

Abbreviations: TAVI, transcatheter aortic valve implantation; SAVR, surgical aortic valve replacement; QALY, quality-adjusted life year.

Table 6 One-way sensitivity analysis: TAVI using SAPIEN 3 versus SAVR

	Incremental cost per QALY gained: intermediate risk	Incremental cost per QALY gained: high risk
Base case results	\$28,154	\$17,237
Time horizon (base case: 15 years)		
10 years	\$35,505	\$17,737
5 years	\$65,562	\$20,970
Discount rates (base case: 1.5%)		
0%	\$25,675	\$16,667
3%	\$30,699	\$17,812
Initial hospitalization costs based on all patients independent of risk level (base case: different costs based on risk level)	\$25,278	\$38,136
SAVR costs (base case: \$6,000)		
\$4,000	\$32,334	\$21,920
\$8,000	\$23,975	\$12,554
\$12,000	\$15,616	\$3,188
Exclude non stroke management costs (base case: included)	\$28,280	\$17,369
Non-device procedure costs		
-20% of base case costs	\$29,256	\$23,065
+20% of base case costs	\$27,052	\$11,410
Event dis-utilities included (base case: excluded)	\$18,518	\$13,853

Abbreviations: TAVI, Transcatheter aortic valve implantation; QALY, quality-adjusted life year; SAVR, surgical aortic valve replacement.

reduced to 5 years for the intermediate-risk population. Under this scenario, the ICER for the intermediate-risk group became \$65,562 per QALY gained. Changes in SAVR device costs, procedural or non-procedural costs, excluding pharmacological management costs following procedures, or including event-specific dis-utilities had a minimal impact on the cost-effectiveness results.

Discussion

Our results indicate that TAVI using the SAPIEN 3 heart valve is cost-effective compared to SAVR in Canadian patients with symptomatic severe aortic stenosis who are at intermediate or high surgical risk. In Canada, access to TAVI varies considerably with only 7 of the 10 Canadian provinces offering access to TAVI in the fiscal year 2013/2014, which is the most recent data available.²⁷ The same data indicated that the average Canadian rate of TAVI procedures per million was 34 with rates varying from 16 in Manitoba (population of 1.3 million or 4% of the Canadian population) to 61 in British Columbia (population of 4.6 million population or 13% of the Canadian population). Due to health care system structures in Canada, TAVI reimbursement status also varies between

Canadian provinces but TAVI, when reimbursed, has generally been restricted to inoperable or high-risk patients.

Two recent Canadian studies in intermediate-risk patients^{11,12} have reported lifetime ICERs of \$46,083¹¹ per QALY gained (TAVI with SAPIEN XT versus surgery) and \$76,736 per QALY gained (self-expandable TAVI devices versus surgery).¹² In comparison to these two studies, we reported lower ICERs when we evaluated TAVI with the newer SAPIEN 3 valve against surgery. This is in line with recent published US data which indicated that economic outcomes were more favorable with the SAPIEN 3 valve in intermediate-risk patients.¹⁰ Consistent with several other cost-effectiveness analyses conducted in Canada¹³ or the United States,²⁸⁻³¹ our results confirm that TAVI is cost-effective in patients at a high surgical risk.

There are several limitations with our current analysis that should be considered when interpreting the results. Firstly, mortality and clinical events used in this evaluation were based on non-randomized evidence, which may bring into question the validity of the relative effects (eg mortality) assumed in the model. To deal with this uncertainty, we conducted probabilistic analyses in which all model

parameters were simultaneously varied according to pre-specified distributions. Results indicated that there was a probability greater than 0.9 that TAVI with SAPIEN 3 was cost-effective in patients at intermediate or high surgical risk if governments' willingness-to-pay was \$50,000 or \$100,000 per QALY gained, two commonly cited thresholds for health care decision-making. Secondly, in common with most economic analyses, outcomes such as mortality had to be extrapolated from data that was shorter than the 15-year time horizon of the model. To evaluate the impact of these extrapolations, we truncated the base case time horizon to 10 and 5 years in sensitivity analyses, which increased the cost-effectiveness ratios to values still deemed cost-effective. The results of several other one-way sensitivity analyses indicated that the results were not sensitive to change in other key variables (eg hospitalization costs, SAVR costs, utility data).

Another limitation of our study is the use of Canadian administrative data to estimate the cost of the initial hospitalization associated with TAVI and SAVR. As such, the hospitalization costs associated with TAVI and SAVR were not adjusted for differences in baseline characteristics (eg TAVI patients older than SAVR patients). We however believe that this is a great strength of our study as it reflects the real-world use of TAVI and SAVR in Canada. This may also explain why the difference in hospitalization costs between TAVI and SAVR was found to be much greater than that found in the US analysis of the PARTNER II trial in which TAVI with SAPIEN 3 was found to dominate SAVR.¹⁰ Finally, we compared TAVI using SAPIEN 3 to standard surgical repair and not against other surgical techniques such as minimal invasive aortic valve surgery, fast-track processing of surgical patients or rapid deployment valves such as Intuity or Perceval. However, minimal invasive aortic valve surgical technique and the rapid deployment valves are not widely used yet.³² Another limitation of our study is that the long-term durability of TAVI using SAPIEN 3 is unknown, and while our analyses included re-interventions for TAVI using SAPIEN 3 based on the trial data, the long-term cost of TAVI treatment could have been potentially underestimated. This also applies to SAVR.

Finally, while the STS score has been used in the PARTNER trials to classify patients into intermediate and high surgical risk patients, it was not available in CIHI administrative databases. For this reason, we used the information contained in the administrative database to create a proxy of the log ES to stratify patients at

intermediate or high surgical risk, which is less than ideal. In addition, the log ES is out of date and it is currently recommended to use the EuroScore2 to classify AS patients into intermediate or high risk.¹⁷ However, the conversion from the clinical laboratory values required for the calculation of the EuroScore2 to administrative data proxies of ICD-10 CA codes (used in Canada) has not yet been derived. It should be acknowledged that any attempt to define patients retrospectively from administrative data is limited as the final decision on therapy is made by the heart team based on several factors not necessarily captured in administrative databases (eg frailty status). To deal with this issue, we conducted a sensitivity analysis in which we varied the hospitalization costs associated with patients at intermediate or high surgical risk by $\pm 20\%$ and also conducted a sensitivity analysis using similar hospitalization costs for the two populations. Results indicated that TAVI with SAPIEN 3 valve was still cost-effective in the two populations under study.

Within these limitations and consistent with previous studies, our results and sensitivity analyses confirmed that TAVI using the SAPIEN 3 valve is cost-effective compared to SAVR in Canadian patients with symptomatic aortic stenosis at intermediate or high surgical risk.

Disclosure

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