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Cost-effectiveness of transcatheter aortic valve implantation compared to surgical aortic valve replacement in the intermediate surgical risk population

Jennifer Zhou [a,1], Danny Liew [a,b,1], Stephen J. Duffy [a,b,1], Antony Walton [a,1], Nay Htun [a,1], Dion Stub [a,b,*,1]

[a] The Alfred Hospital, Melbourne, Australia
[b] School of Public Health and Preventive Medicine, Monash University, Melbourne, Australia

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ABSTRACT

Background: The recent PARTNER S3i trial compared transcatheter aortic valve implantation (TAVI) using the third-generation SAPIEN 3 device to surgical aortic valve replacement (SAVR) in intermediate-risk patients with severe symptomatic aortic stenosis. Using data from PARTNER S3i, we performed a contemporary cost-effectiveness analysis of current-generation TAVI versus SAVR from the Australian healthcare system perspective.
Methods: A Markov model with monthly cycles and a ten-year horizon was constructed to estimate costs, life-years and quality adjusted life-years (QALYs) associated with TAVI and SAVR. Efficacy inputs were derived from the PARTNER S3i study. Costs were estimated from published sources. Deterministic and probabilistic sensitivity analyses were performed to assess model uncertainty.
Results: TAVI was found to have higher immediate procedural costs than SAVR, driven primarily by the cost of the transcatheter valve. This was offset by a shorter length of hospitalisation following TAVI, such that the combined cost of initial procedure and hospitalisation was lower in TAVI compared to SAVR. With 5% annual discounting, total costs over ten-years were $50,515 AUD in TAVI and $60,144 AUD in SAVR, and TAVI was found to produce 0.33 more life years and 0.31 more QALYs than SAVR. Thus, from a health economic perspective, TAVI was dominant compared to SAVR. Results were robust to sensitivity analyses, with TAVI being dominant in 68% of 10,000 Monte Carlo iterations and cost-effective in 92% of iterations at a willingness-to-pay threshold of $50,000/QALY gained.
Conclusions: TAVI is likely to be highly cost-effective compared to SAVR in intermediate-risk patients with severe aortic stenosis.

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1. Introduction

Aortic stenosis (AS) is one of the most common valvular heart diseases in the developed world. Primarily affecting the elderly, its prevalence is expected to rise as the population ages [1]. Without aortic valve replacement, symptomatic severe AS carries a poor prognosis, with a two-year mortality nearing 50% [2]. Until recently, surgical aortic valve replacement (SAVR) was the only effective treatment option for patients with severe AS. However, in many patients, age and/or comorbidities mean that SAVR is associated with a high risk of operative morbidity or mortality.

Transcatheter aortic valve implantation (TAVI) is a less invasive alternative to conventional surgical therapy and has undergone rapid development over the past decade. Clinical trial data to date indicate that TAVI significantly improves survival and quality of life in patients with severe AS who are not suitable for surgery [3], and is non-inferior (and maybe superior) to surgical valve replacement in patients at high operative risk [4–6]. More recently, indications for TAVI have further expanded, as evidence emerges for its safety and efficacy in intermediate-risk and low risk patients [7–10].

As use of TAVI increases, the cost-effectiveness of this procedure has been the focus of growing interest. Existing economic analyses – mostly from North America and Europe – have yielded variable results [11–16]. Additionally, most previous studies have drawn data from clinical trials that used early-generation transcatheter devices in high-risk patients. In light of significant device refinements in recent years and expanding indications for TAVI towards lower-risk groups, findings from these studies may not accurately reflect contemporary practice.

Recently, the PARTNER S3i (Placement of Aortic Transcatheter Valve) trial compared outcomes of over 1000 intermediate-risk patients assigned to TAVI using the third-generation balloon-expandable SAPIEN 3 valve (Edwards Lifesciences, Irvine, CA) to a propensity score matched

* Corresponding author at: Heart Centre, Phillip Block, Level 3, The Alfred Hospital, 55 Commercial Road, Melbourne, VIC 3004, Australia.
E-mail address: dion.stub@monash.edu (D. Stub).
[1] This author takes responsibility for all aspects of the reliability and freedom of bias of the data presented and their discussed interpretation.

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group of SAVR patients [9]. This study revealed promising outcomes for TAVI using current valve technology, reporting that SAPIEN 3 TAVI was superior to SAVR at one year for the primary composite endpoint of death, stroke and aortic regurgitation.

We aimed to use data from PARTNER S3i to conduct a contemporary cost-effectiveness analysis of SAPIEN 3 TAVI compared to SAVR from the Australian healthcare system perspective. Our focus was on patients with severe symptomatic AS at intermediate surgical risk.

2. Methods

A decision-analytic Markov model with monthly cycles was constructed to estimate costs and benefits associated with TAVI and SAVR from the Australian healthcare system perspective [17]. The model followed a hypothetical cohort of intermediate-risk patients (Society of Thoracic Surgeons 30-day predicted risk of mortality 4 to 8%) [9] with severe symptomatic AS over a time horizon of ten years. Costs were measured in 2018 Australian dollars, and benefits measured in life-years (LYs) and quality adjusted life-years (QALYs) gained. The incremental cost-effectiveness ratio (ICER) was calculated by dividing the difference in costs between the two treatment groups by differences in LYs and QALYs.

In Australia, no specific ICER threshold has been established for acceptable cost-effectiveness. However, interventions costing up to $50,000 per QALY gained are generally considered cost-effective [18]. Thus, in the economic evaluation, an ICER of less than $50,000 per QALY gained was used as the willingness-to-pay (WTP) threshold of acceptable cost-effectiveness. All outcomes and costs beyond the first year of the model were discounted at 5% annually per Australian guidelines [19].

2.1. Model structure

The basic structure of the Markov model is presented in Fig. 1. All patients entered the model in the 'Procedure' health state at age 82, the mean age of patients in the PARTNER S3i trial. This represented their undergoing either a TAVI or SAVR. Potential acute events were death, stroke and short-term complications, which included vascular injury, major bleeding, myocardial infarction, permanent pacemaker insertion, atrial fibrillation, acute kidney injury and moderate to severe paravalvular leak. Event rates were derived from data reported in the PARTNER S3i study, capturing differences in treatment-related complications between the TAVI and SAVR groups.

Following TAVI or SAVR, patients transitioned into one of three long-term health states. Those who died moved to the 'Dead' state. Those who lived transitioned into either the 'Alive and well' state or the 'Alive with previous stroke' state. For the remainder of the model, patients transitioned between long-term states based on event rates reported in the literature. Each health state was associated with unique costs and utilities, which patients accrued over the course of the model. In the first year post-procedure, patients could also experience further short-term complications. These would incur a one-off cost and utility decrement, the latter reflecting a transient decrease in quality of life associated with that complication. It was assumed that no further short-term complications occurred beyond one year.

2.2. Model inputs

2.2.1. Trial overview

PARTNER S3i was a single-arm, non-randomised, historical-controlled study in which 1077 intermediate-risk patients with severe symptomatic AS at 51 sites across the United States and Canada were assigned to SAPIEN 3 TAVI between February and September 2014 [9]. 30-day and one-year outcomes in these patients were compared – using a pre-specified propensity score analysis – with a historical cohort of 944 patients from the PARTNER 2A randomised trial who underwent SAVR between December 2011 and November 2013 [7].

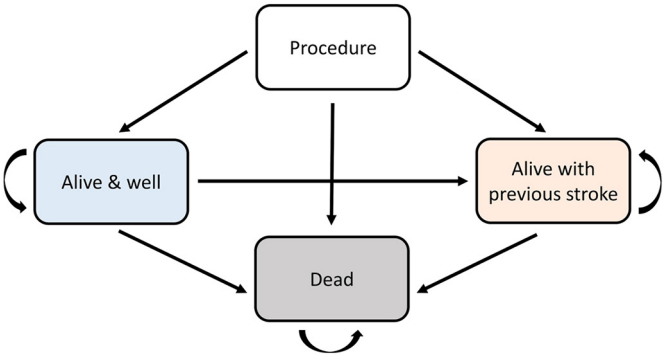

Fig. 1. Model schematic. All patients entered the model in the 'Procedure' state and transitioned into one of three long-term health states one month after the procedure. Patients moved between long-term states based on event rates reported in the PARTNER S3i study.

Though not a randomised trial, study arms used identical inclusion and exclusion criteria, were carried out at the same clinical sites, and used the same clinical events committee and echocardiographic laboratory. Thus, baseline characteristics were comparable between groups. The mean ages of patients in the TAVI and SAVR arms were 81.9 and 81.6 years and mean Society of Thoracic Surgeons risk scores were 5.2 and 5.4, respectively.

2.2.2. Clinical events

Most transition probabilities for death, stroke and short-term complications following TAVI and SAVR were estimated from 30-day and one-year event rates reported in the PARTNER S3i study. These are summarised in Supplemental Table 1. All probabilities were converted to reflect the monthly cycle length of the model. Relative risks reported in the literature were used to reflect higher rates of stroke and mortality in patients with a history of previous stroke [20–22].

As PARTNER S3i only reported outcomes to one year, age and sex-matched mortality from Australian Life Tables were used to estimate mortality in the SAVR group beyond this time [23]. This was based on reports indicating that SAVR restores life-expectancy to that of an age-matched population [24]. A hazard ratio (HR) comparing TAVI and SAVR mortality was applied to estimate mortality in the TAVI arm. As no HR was reported in PARTNER S3i, this was assumed to be 1.0 in the base case, and varied in the sensitivity analysis using the 95% confidence interval reported in the PARTNER 2A trial [7].

Long-term risk of stroke was estimated from a systematic review examining stroke incidence in the elderly [25]. Again, due to lack of longer-term follow up in PARTNER S3i, we assumed that risk of stroke was equal in both arms after one year, based on previous studies showing no difference in long-term stroke rates between TAVI and SAVR [4,7]. Finally, we assumed short-term complications did not occur in either group beyond one year.

2.2.3. Cost inputs

Cost and utility inputs used in the model are summarised in Supplemental Table 2. The cost of the TAVI prosthesis was estimated at $23,932 based on costs recorded on the Australian Medicare Benefits Schedule (MBS) [26]. The cost of the SAVR valve was estimated at $6858 based on prosthesis costs in the Australian National Hospital Costs Data Collection (NHCDC) database for cardiac valve procedures [27]. Costs of the TAVI and SAVR procedures were estimated from MBS item numbers, assuming that the amount reimbursed by Australian Medicare was equal to the cost to the healthcare system [26].

The cost of index hospitalisation was estimated by obtaining the average daily cost of hospitalisation for cardiac valve procedures reported in the NHCDC [27], and multiplying this by the median length of stay reported in the PARTNER S3i trial for TAVI and SAVR (four and nine days, respectively) [9]. Monthly costs for the long-term state of stroke were estimated from an Australian study [28]. Finally, acute costs for short-term complications were estimated from relevant DRG codes in the NHCDC database [27]. All costs were inflated to 2018 Australian dollars using the Australian Reserve Bank Consumer Price Index.

2.2.4. Utilities

QALYs were calculated by multiplying time spent in a particular health state by the quality of life weight (utility) for that health state. Baseline, one-month and 12-month EuroQol 5-dimensional utility weights reported in PARTNER S3i were used to estimate utility values for the 'Alive and well' state following TAVI and SAVR [29]. In the absence of longer-term data, we assumed utilities were equal between study arms after 18 months.

Utility for the 'Alive with previous stroke' state was estimated from an Australian study reporting quality of life among stroke survivors [30]. For short-term complications, we applied a one-time disutility representing a transient decrease in quality of life associated with that complication. These disutilities were not reported in PARTNER S3i, so were estimated from other studies [31–34], as summarised in Supplemental Table 2.

2.3. Sensitivity analyses

To evaluate effects of individual parameter uncertainty on the results, one-way deterministic sensitivity analyses (DSAs) were performed by varying inputs over a range of their 95% confidence intervals. Threshold analyses were also conducted to assess the degree to which parameters needed to change in order to influence model outcomes.

Overall parameter uncertainty was addressed by means of a probabilistic sensitivity analysis (PSA). Probability distributions for all input parameters were specified and 10,000 Monte Carlo simulations were run using random draws of all parameters from within their assigned distributions. Parameter distributions used in the PSA are presented in Supplemental Table 3.

Finally, several scenario analyses were performed to examine the impact of major structural assumptions. The model was run using alternative time horizons, discount rates and patient subgroups. All analyses were performed using Microsoft Excel (Microsoft Corporation, Redmond, Washington, USA) and @RISK version 7.6 (Palisade Corporation, New York, New York, USA).

3. Results

The base case results are presented in Table 1. Immediate procedural costs were higher for TAVI compared to SAVR, driven primarily by the increased cost of the transcatheter valve. This was offset by a shorter

Table 1
Base case results.

	Costs	LYs	QALYs	ICER ($ per LY)	ICER ($ per QALY)
TAVI	$50,515	5.43	4.13	–	–
SAVR	$60,144	5.10	3.82	–	–
Incremental	-$9629	0.33	0.31	TAVI dominant	TAVI dominant

All values are reported in 2018 Australian dollars.
TAVI, transcatheter aortic valve implantation; SAVR, surgical aortic valve replacement; LYs, life years; QALYs, quality adjusted life years; and ICER, incremental cost-effectiveness ratio.

length of hospital stay in the TAVI group, such that the combined cost of the index procedure and hospitalisation was lower in TAVI compared to SAVR ($41,615 versus $47,384).

With 5% annual discounting, total projected costs over a ten-year horizon were lower in the TAVI group compared to SAVR ($50,515 versus $60,144), and TAVI was estimated to produce 0.33 more life years and 0.31 more QALYs than SAVR. Thus, from a health economic perspective, TAVI was dominant compared to SAVR.

3.1. Deterministic sensitivity analysis

One-way DSA found the model to be robust to changes to most inputs over clinically reasonable ranges. As shown in Fig. 2, factors that most strongly influenced model outcomes were the length of hospitalisation following TAVI and SAVR, the cost per day of hospitalisation, the cost of the valve prostheses, and the hazard ratio of mortality between groups. TAVI remained cost-effective (ICER less than $50,000 per QALY gained) when each of these parameters was varied over the range of their 95% confidence intervals.

In keeping with one-way DSA results, threshold analysis found that significant variations to individual parameters were required to meaningfully alter model outcomes. For example, the ICER exceeded $50,000 per QALY gained only if the length of hospitalisation following TAVI exceeded that of SAVR (compared to a base case of four versus nine days) or if the cost of the TAVI valve exceeded $47,962.

3.2. Probabilistic sensitivity analysis

PSA revealed a moderate to high degree of certainty in the cost-effectiveness findings. TAVI was dominant compared to SAVR in 68% of 10,000 Monte Carlo iterations and was cost-effective at a WTP threshold of $50,000 per QALY gained in 92% of iterations. When the WTP threshold was increased to $100,000 per QALY gained, TAVI was cost-effective in 97% of iterations. This is illustrated on the cost-effectiveness plane and cost-effectiveness acceptability curve (Fig. 3).

3.3. Scenario analysis

Scenario analyses found that changing the annual discount rate did not significantly affect model outcomes, nor did reducing the time horizon of the model to one or five years. When analysis was restricted to the transfemoral cohort of PARTNER S3i, the model produced similar results to the base-case analysis. This is likely due to the high percentage of PARTNER S3i participants who underwent transfemoral TAVI. Finally, when the cost of TAVI prosthesis was inflated by 50%, TAVI was no longer dominant, but remained cost-effective compared to SAVR in all scenarios. These results are summarised in Supplemental Table 4.

4. Discussion

In this cost-effectiveness analysis using contemporary evidence, we found that from the perspective of the Australian healthcare system, TAVI using the third-generation SAPIEN 3 system would be economically dominant compared to SAVR in treatment of intermediate-risk patients with severe symptomatic AS. Over a ten-year horizon, SAPIEN 3 TAVI was associated with greater quality adjusted life expectancy and lower long-term costs compared with SAVR.

Results were robust to sensitivity analyses, with TAVI being dominant in two-thirds of 10,000 Monte Carlo simulations and cost-effective in over 90% of simulations. Major cost drivers identified were the length of hospitalisation following TAVI and SAVR, the cost of the valve prostheses, and the hazard ratio of mortality between treatment arms. TAVI remained cost-effective even when each of these parameters was varied over the range of their 95% confidence intervals.

In keeping with previous studies, we found that immediate procedural costs were higher in the TAVI group compared to SAVR, driven by the higher cost of the transcatheter system. However, our model demonstrated that the greater cost of the TAVI prosthesis was offset by cost-savings associated with a shorter length of hospital stay in TAVI patients, such that the combined cost of initial procedure and hospitalisation was lower in TAVI compared to surgery.

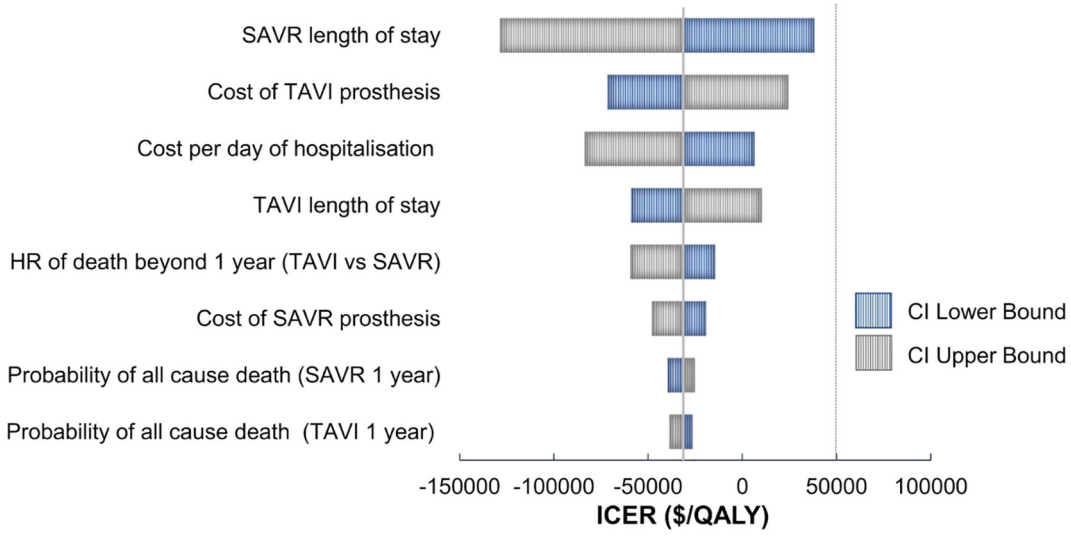

Fig. 2. Tornado plot illustrating the effect on the incremental cost-effectiveness ratio (ICER) of changing input parameters across their 95% confidence interval range. Inputs with the strongest effect on the ICER are presented. TAVI was cost-effective with an ICER below $50,000/QALY (indicated by the dotted line) when each parameter was varied across its 95% confidence interval range. TAVI, transcatheter aortic valve implantation; SAVR, surgical aortic valve replacement; QALY, quality adjusted life year; and CI, confidence interval.

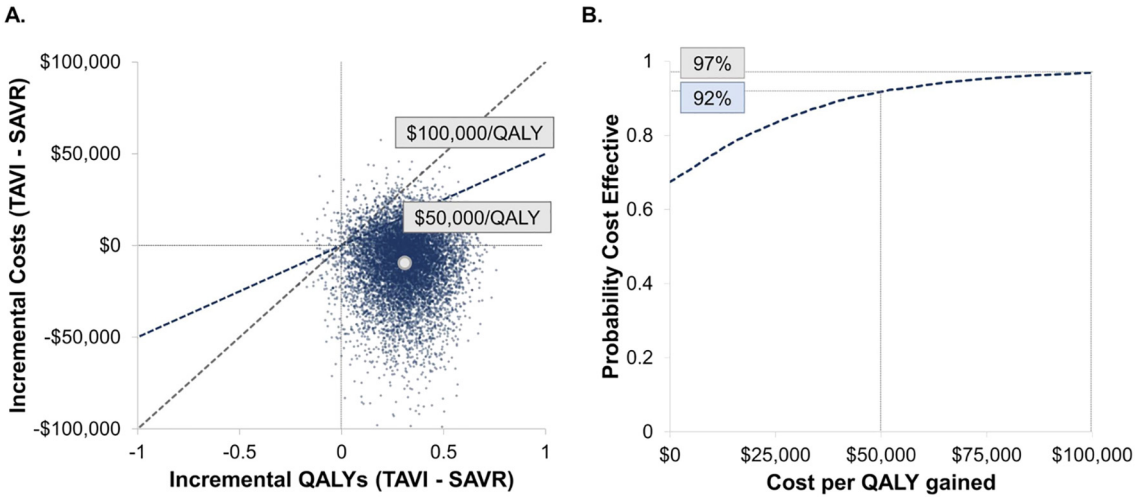

Fig. 3. (A) Cost-effectiveness plane showing results from 10,000 Monte Carlo simulations. Each small dot represents the incremental cost and incremental QALY from one simulation. The solid circle represents the base-case estimate. The dashed lines represent willingness-to-pay thresholds of $50,000/QALY and $100,000/QALY. The majority of Monte Carlo simulations fell below a WTP threshold of $50,000/QALY. (B) Cost-effectiveness acceptability curve of TAVI versus SAVR. The probability that TAVI is cost-effective (calculated as the proportion of Monte Carlo simulations that fall below a given WTP threshold) is plotted against a range of WTP thresholds. TAVI, transcatheter aortic valve implantation; SAVR, surgical aortic valve replacement; QALY, quality adjusted life years; and WTP, willingness-to-pay.

4.1. Comparison to previous studies

TAVI was originally developed as a less invasive alternative to SAVR in patients at high surgical risk. Thus, most studies of TAVI cost-effectiveness focused on the high-risk and inoperable populations. In recent years, indications for TAVI have expanded, and intermediate-risk patients now form one of the largest patient groups eligible for TAVI [35]. As these patients differ from higher risk groups in terms of comorbidities and life-expectancy, findings from previous economic analyses may not be applicable.

To date, only a few studies have specifically examined the cost-effectiveness of TAVI relative to SAVR in intermediate-risk patients. The first of these, a single-centre Dutch analysis that followed 42 pairs of patients over a one-year period, concluded that in-hospital and one-year costs were higher for TAVI compared to SAVR [36]. While this study provided some insights into the real-world costs associated with TAVI, it was conducted relatively early in the 'learning curve' for TAVI and was restricted to only a small group of patients, limiting the generalisability of results.

More recently, Tam and colleagues published two studies from the Canadian perspective, in which costs associated with TAVI and SAVR were estimated using a Markov model [15,16]. In these studies, inputs were derived from earlier trials of intermediate-risk patients, which used first or second-generation transcatheter devices in their TAVI arms. Both studies concluded that in the Canadian healthcare system, TAVI may be cost-effective relative to SAVR in intermediate-risk patients. However, there was significant uncertainty in the reported results.

Like Tam and colleagues, we also used a Markov model to capture costs and benefits associated with TAVI and SAVR. However, we based our analysis primarily on the PARTNER S3i study, which could explain the more favourable cost-effectiveness estimates produced in our model. PARTNER S3i, in contrast to earlier trials, used a newer generation transcatheter device. Compared to earlier systems, the third-generation SAPIEN 3 device features a lower profile delivery system designed to improve transfemoral delivery and reduce access site complications, and an outer polyethylene terephthalate skirt, to prevent paravalvular leak [37].

Several multi-centre registries have reported lower rates of death, stroke and severe paravalvular regurgitation using the SAPIEN 3 device compared to earlier systems [38–40], in keeping with outcomes observed in the PARTNER S3i trial. This is likely to reflect advances in valve technology, as well general advances in procedural techniques and post-procedural care. As the bulk of TAVI procedures are now performed using third-generation technology, we felt that data from PARTNER S3i provided the most accurate representation of contemporary practice.

Results from our study are consistent with findings reported in another recently published economic analysis using PARTNER S3i data. In a patient-level analysis using in-trial costs, utilities and survival data, Baron and colleagues concluded that from the United States healthcare system perspective, SAPIEN 3 TAVI was economically dominant compared to SAVR in intermediate-risk AS patients [41]. In line with our findings, the study projected life-time cost-savings of around $10,000 USD per patient and incremental benefits of 0.27 QALYs per patient.

4.2. Study implications

In an era of rising healthcare costs, policy-makers and clinicians must make difficult decisions regarding resource allocation. While TAVI has received Therapeutic Goods Administration approval in Australia for use in patients with severe AS at intermediate, high and prohibitive surgical risk, reimbursement for TAVI under the Australian MBS is currently restricted to high-risk and inoperable patients only [26]. This is perhaps due to previous lack of evidence surrounding the cost-effectiveness of TAVI in intermediate-risk patients.

Our study adds to the growing body of data supporting use of TAVI in patients with severe symptomatic AS at intermediate surgical risk. We provide the first Australian-specific evidence that, in addition to its clinical benefits, TAVI is also an economically attractive treatment option in this patient group. Expanding eligibility for MBS reimbursement to include lower-risk patients appears cost-effective, and would increase accessibility of TAVI in Australia.

The sensitivity of our model to particular variables also identifies areas in which further meaningful improvements to TAVI cost-effectiveness may be achievable. Implementation of early discharge algorithms post-TAVI may serve to significantly reduce length of hospital stay, one of the major drivers of TAVI cost [42–44]. As more competitors enter the market, it could be expected that the acquisition cost of transcatheter valves will fall. Finally, with improved operator experience and device technology, we may see a further improvement in TAVI outcomes.

4.3. Study limitations

Findings from this study should be interpreted in light of several important limitations. First, there is an inherent uncertainty to any model-based analysis, as various assumptions must be made in the modelling process. Nevertheless, our sensitivity analysis showed that changing input parameters over the range of their 95% confidence intervals exerted only a modest effect on model outcomes, and the PSA demonstrated a high degree of certainty in our findings.

Secondly, although cost inputs were derived from Australian sources, benefits were based on a North American population (PARTNER S3i). Reassuringly, registry data indicate that similar 'real-world' outcomes are achievable following TAVI in the Australian setting when compared to major international registries [45]. Furthermore, consistent results using the SAPIEN 3 device have been reported across various healthcare settings, suggesting that modern TAVI technology has evolved towards more predictable implantation results [38].

Thirdly, this was not an 'in-trial' cost analysis, but a model-based analysis based on published data. Costs inputs were estimated from hospital data reports and Australian Medicare reimbursement fees. Using this approach, it is possible that not all factors with impact on cost-effectiveness were taken into account, such as patient-to-patient variability in procedure length, intensive care unit stay and ventilation time.

Fourthly, our study did not consider the long-term durability of the TAVI prosthesis, as PARTNER S3i only followed patients to one year. To date, the best data to support TAVI valve durability is derived from the PARTNER 1A trial, which reported no cases of structural valve deterioration at five years in high-risk patients [4]. As the projected life-expectancy of intermediate-risk patients is around seven years, we assumed valve durability would not be an issue over the lifetime of these patients. This may become more important in future studies as the focus shifts towards younger, lower-risk patients.

Finally, our model was based on a clinical trial population with strict inclusion and exclusion criteria and a single modern TAVI device. It cannot be assumed that results would be the same in different patient subgroups or with different TAVI systems. The latter is of particular importance due to well-recognised differences between transcatheter devices, particularly with regard to pacemaker insertion rates.

5. Conclusions

We conclude that in patients with severe symptomatic AS at intermediate surgical risk, TAVI using the current-generation SAPIEN 3 valve is likely to be highly cost-effective compared with SAVR from the perspective of the Australian healthcare system.

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Declaration of Competing Interest

Associate Professor Antony Walton serves as a proctor and advisory board member for Medtronic and as a proctor for Abbott. Professor Stephen Duffy serves as a proctor for Medtronic.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2019.06.057.

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