Structural Heart
The Journal of the Heart Team

ISSN: 2474-8706 (Print) 2474-8714 (Online) Journal homepage: https://www.tandfonline.com/loi/ushj20

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To cite this article: Benjamin P. Geisler, Simone A. Huygens, Michael J. Reardon, Nicolas Van Mieghem, Arie Pieter Kappetein, Ruben L. J. Osnabrugge & Jan B. Pietzsch (2017) Cost-Effectiveness and Projected Survival of Self-Expanding Transcatheter Versus Surgical Aortic Valve Replacement for High Risk Patients in a European Setting: A Dutch Analysis Based on the CoreValve High Risk Trial, Structural Heart, 1:5-6, 267-274, DOI: 10.1080/24748706.2017.1381357

To link to this article: https://doi.org/10.1080/24748706.2017.1381357

STRUCTURAL HEART
2017, VOL. 1, NOS. 5–6, 267–274
https://doi.org/10.1080/24748706.2017.1381357

ORIGINAL RESEARCH

Cost-Effectiveness and Projected Survival of Self-Expanding Transcatheter Versus Surgical Aortic Valve Replacement for High Risk Patients in a European Setting: A Dutch Analysis Based on the CoreValve High Risk Trial

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ABSTRACT

Background: Clinical and economic outcomes of self-expanding bioprosthetic transcatheter aortic valve implantation (TAVI) in high-risk surgical candidates are unknown in the European setting. The objective of this study was to project life expectancy and to estimate the cost-effectiveness of TAVI in a European setting.

Methods: Cost-utility analysis via probabilistic Markov modeling was performed. A simulated cohort of 83-year-old men and women (53 and 47%, respectively) with severe aortic stenosis at high but not extreme surgical risk were observed in the CoreValve High Risk Trial. Costs were based on resource use data from a Dutch academic medical center and costing guidelines. Undiscounted life expectancy and discounted costs, quality-adjusted life years (QALYs), incremental cost-effectiveness ratio (ICER), and proportion cost-effective at a willingness-to-pay threshold of €50,000/QALY were evaluated. Beyond the base case, further analyses explored a "lean scenario" that considered a shorter TAVI procedure time and hospital stay.

Results: Mean projected survival increased by 0.65 life years (5.62 for TAVI vs. 4.97 for SAVR). TAVI was projected to add 0.41 (3.69 vs. 3.27) QALYs at an increased cost of €9048 (€51,068 vs. €42,020), resulting in an ICER of €21,946 per QALY gained. The probability of TAVI being cost-effective was 71%. Further cost reduction of approximately €5400 in addition to the "lean" assumptions would make TAVI the dominant strategy.

Conclusion: A self-expanding TAVI system for high-risk surgical candidates increases quality-adjusted life expectancy at an economically acceptable cost in the Dutch setting. Reductions in procedure time and length of hospital stay will further improve the value of TAVI.

ARTICLE HISTORY Received 20 July 2017; Revised 12 September 2017; Accepted 14 September 2017

KEYWORDS Aortic valve stenosis; CoreValve High Risk Trial; cost-benefit analysis; decision support techniques; health-related quality of life; heart valve prosthesis implantation; self-expandable catheter; surgical aortic valve replacement; transcatheter aortic valve replacement; utility

Introduction

Transcatheter aortic valve implantation (TAVI) for severe aortic stenosis has recently experienced rapid adoption in clinical practice and its use has extended beyond patients at extreme operable risk.[1,2] Two-year follow-up data of the CoreValve High Risk Trial have demonstrated a sustained higher survival rate and a reduction in stroke rate in patients with high operable risk compared with surgical aortic valve replacement (SAVR).[3]

In contrast to its efficacy, the cost-effectiveness of TAVI compared to SAVR is still under debate.[2,4–6] Except for one study in the United States,[7] most economic evaluations of TAVI compared to SAVR were conducted for a balloon-expandable TAVI system (Edwards SAPIEN, Irvine, CA). The cost-effectiveness of TAVI using the self-expanding CoreValve system (Medtronic plc, Dublin, Ireland) for high-risk patients outside the US remains uncertain. The objectives of the present study were to project the life expectancy, health-related quality of life, and costs of TAVI and SAVR in high-risk operable candidates beyond the 2-year data and to determine the cost-effectiveness of TAVI in a European setting.

Materials and methods

Model structure

A decision-analytic model was developed using a combination of a decision tree and a state-transition model (Markov model) with a life-long time horizon and an interval between each follow up (cycle length) of one month (Figure 1). The model was developed in consultation with interventional cardiologists, cardiothoracic surgeons, and decision scientists. In the base case, patients enter the model at age 83, which was the mean age in the CoreValve High Risk Trial. The model starts with the index procedure for which pre-

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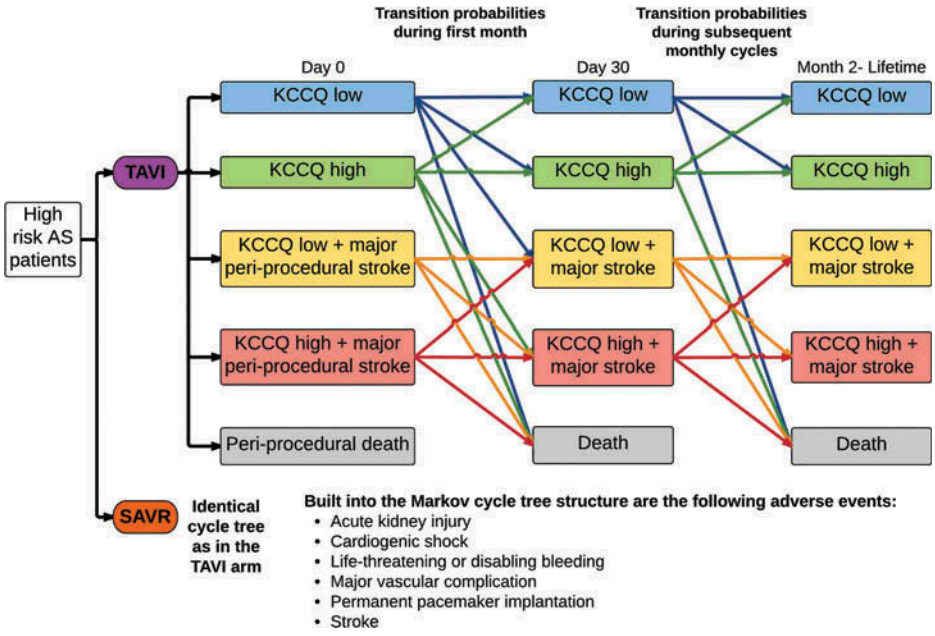

Figure 1. Model Structure. Simplified model structure for high risk aortic stenosis (AS) patients who enter either one of two strategies: transaortic valve implantation (TAVI) or surgical aortic valve replacement (SAVR). On day 0, the time of the index procedure, patients can either die (grey box, periprocedural death) or enter a combination of high or low Kansas City Cardiomyopathy Questionnaire (KCCQ) status with or without a new stroke. Patients can over time change to other disease states. Built into the model are also the adverse events given in the bullet list.

operative and procedural costs are being incurred regardless of potential periprocedural death. After the intervention, all patients who are alive incur hospitalization costs and, after the hospitalization, costs for outpatient follow-up care. During each month, patients can either die (absorbing state) or experience a stroke. All patients who were alive were stratified by Kansas City Cardiomyopathy Questionnaire (KCCQ) scores above or below 60. The transition probabilities for the combination of KCCQ stratum and whether a patient had experienced a stroke were taken from the CoreValve High Risk trial. KCCQ scores were chosen as this disease-specific questionnaire integrates patients' symptoms, functional status, and health-related quality of life (HRQoL) into one metric and is also inversely correlated with long-term mortality after TAVI.[5] The stratification by stroke events was applied to reflect the excess mortality, reduced HRQoL and often relatively high health care costs incurred by stroke patients.[8] After they experience a stroke in the model, patients spent the first one month and then the remaining 11 months in separate tunnel states that reflected the increased costs and decreased utility in the more immediate time after the stroke event (see Table 1). Besides stroke, the following adverse events were included in the model: major vascular complication, life-threatening or disabling bleeding, acute kidney injury (AKI), cardiogenic shock, and permanent pacemaker (PPM) implantation.[3,9,10] To effectively capture the most relevant drivers of mortality, HRQoL, and health care costs, we only included separate health states for stroke. Health care costs were calculated for each of the adverse events, but only stroke constituted a separate health state. This means, that all impact that other adverse events aside from stroke had on mortality and HRQoL are included in the four combined KCCQ/stroke states based on the patient-level data from the CoreValve High Risk trial. All resource use and cost data were taken either from the trial or a single institution in the Netherlands (see details below). This study was performed from a health care perspective; only costs and effects within the health care sector are taken into account.[2] The model was run until 99.9% of all patients had died and was implemented in TreeAge Pro 2009 (TreeAge, Inc., Waltham, MA).

Clinical events and health-related quality of life

Clinical event probabilities and HRQoL measurements were derived from the 2-year follow-up data of the CoreValve High Risk Trial.[3,9] This multicenter controlled trial randomized 750 patients with severe aortic stenosis and New York Heart Association (NYHA) class II or higher to TAVI via a self-expanding bioprosthesis (CoreValve, Medtronic plc, Dublin, Ireland) or SAVR (valve type chosen by surgeon). At baseline, the mean age of the enrolled patients was 83 years, 48% of whom patients were female, the mean logistic EuroSCORE was 18%, and the Charlson comorbidity index was at least five in 56% of the enrolled patients. The available patient-level data included follow-up at 1, 6, 12, and 24 months after the index procedure.[9] Clinical input parameters and HRQoL were analyzed in SAS 9.4 (SAS Institute, Cary, NC). Table 1 shows the key input parameters; see Supplemental Material (online only) for a complete list.

As described in the section on the model structure, the trial data was stratified by the index procedure, KCCQ score above or below 60, and status prior or post stroke. Mortality and adverse event rates were extracted and converted to monthly probabilities. Based on the trial data, cardiogenic shock and AKI were only considered in the first month after the index

Table 1. Input parameters.

	Procedure day		Periprocedural (0–30 days after procedure)		Post-procedure year 1 (monthly)		Post-procedure year 2 (monthly)		Relative risks beyond post-procedure year 2	
Clinical event probabilities	TAVI	SAVR	TAVI	SAVR	TAVI	SAVR	TAVI	SAVR	TAVI	SAVR
Death	0.013	0.000	0.021	0.045	0.010	0.014	0.007	0.007	0.977	1.135
Acute kidney injury			0.061	0.150						
Cardiogenic shock			0.023	0.031						
Life-threatening or disabling bleeding			0.136	0.365	0.003	0.005				
Major vascular complication			0.061	0.017	0.000	0.000				
Permanent pacemaker implantation			0.200	0.070	0.003	0.004	0.003	0.001		
Stroke	0.021	0.020	0.036	0.045	0.003	0.005	0.005	0.002	2.3	
KCCQ<60 (month 2–5/6–12)			0.369	0.620	0.052/0.003[a]	0.002[a]	0.000[a]	0.000[a]		
KCCQ>60			0.631	0.380	0[a]	0	0.001[a]	0.007[a]		

Index procedure costs	TAVI	SAVR
Pre-operative care	€1809	€1555
Procedure	€25,437	€12,550
Index hospitalization	€6116	€14,302

	Month 1		*Month 2–6*		*Month 6–12*		*Month 12–24*	
	TAVI	SAVR	TAVI	SAVR	TAVI	SAVR	TAVI	SAVR
Outpatient follow-up (including re-hospitalization)	€604	€690	€400	€465	€241	€201	€163	€130

Adverse events costs	During index hospitalization	After index hospitalization
Acute kidney injury	€2162	
Cardiogenic shock	€3888	
Life-threatening or disabling bleeding	€1912 (TAVI); €1864 (SAVR)	€2925 (TAVI); €2877 (SAVR)
Major vascular complication	€4545	€5445
Permanent pacemaker implantation	€8421	€11,088
Stroke	€1770	€6657
Stroke, additional monthly costs	€384 (year 1); (€98 subsequent years)	

	Month 1		*Month 6*		*Month 12*		*Month 24*	
Utilities per post-procedure months	TAVI	SAVR	TAVI	SAVR	TAVI	SAVR	TAVI	SAVR
KCCQ<60, no stroke (TAVI/SAVR)	0.67	0.57	0.65	0.68	0.64	0.63	0.58	0.62
KCCQ>60, no stroke (TAVI/SAVR)	0.84	0.85	0.85	0.85	0.84	0.84	0.83	0.82
KCCQ<60, stroke[b]	0.31		0.55		0.61		0.6	
KKCQ>60, stroke[b]	0.77		0.83		0.8		0.7	

Note. [a]These probabilities are not the absolute probabilities but denote the probability of moving from the other KCCQ stratum to this one.
[b]No distinction in utilities in patients with strokes after TAVI or SAVR because of small number of patients in these subgroups. TAVI, transcatheter aortic valve implantation; SAVR, surgical aortic valve replacement; KCCQ, Kansas City Cardiomyopathy Questionnaire.

procedure. Likewise, life-threatening or disabling bleeding and major vascular complications only occurred during the first year of follow-up. PPM was considered up to the end of the available clinical follow-up data of 2 years. To extrapolate mortality rates beyond the 2-year follow-up data, the mortality in the second year of the trial was used to derive relative mortality risks of 0.98 and 1.13 for TAVI and SAVR, respectively. These relative mortality risks were applied to age- and sex-adjusted mortality rates in the general population.[11] In the base case, the difference in survival between TAVI and SAVR remained constant over time. The projected TAVI survival was compared to recently published results from TAVI registry data.[12] An elevated mortality risk of 2.3 was applied to patients post-stroke.[13] The mortality for all other events was also accounted for.

Quality-adjusted life years (QALY) were based on the EuroQoL-5D (EQ-5D) values measured in the trial and converted to utilities using the appropriate value set for the Netherlands (Table 1).[14] The EQ-5D questionnaire was assessed in all patients and in subgroups of patients with or without major stroke at 1, 2, 6, 12, and 24 months post-procedure. For all other adverse events besides stroke, utility decrements were assumed to be temporary only and were included in the utilities of the overall KCCQ/stroke health states. We did not separate the adverse events in different health states with specific utilities as this would have decreased the number of subjects per group derived from the CoreValve High Risk Trial further. Beyond year two, we assumed the same utility as in the second year of follow-up.

Resource use and costs

The input parameters for costs are provided in Table 1 and the Supplemental Material. All costs are expressed in 2015 Euros by inflating costs from other years using the consumer price index.[15] Costs and effects were discounted at 4% and 1.5% per annum, respectively.[2]

Costs of pre-operative diagnostics, respective index procedures, index hospitalization (including intensive care unit [ICU] and regular ward length-of-stay [LOS] and periprocedural adverse events), and long-term care were included. Clinical resource use was based on the CoreValve High Risk Trial. When information on resource use of pre-operative diagnostics, personnel and materials used during TAVI and SAVR procedures was not available in the trial, micro-costing at a single institution, Erasmus University Medical Centre (Rotterdam, the Netherlands), was performed.[16] LOS was determined based on an analysis of recent data from this center and was compared with Dutch, other European, and US CoreValve High Risk Trial LOS data (please see the Supplemental Material for details). In the base case, a LOS of 7.0 and 15.1 days for TAVI and SAVR were assumed, respectively, including 1.0 and 2.5 days in the ICU. In the trial, data were collected about resource use of rehabilitation and chronic care facilities after index hospitalization. These costs were not included in our analysis because in the Netherlands patients often stay in the hospital longer rather than going to another facility. However, other postoperative costs including re-hospitalizations were included in the analysis; they differed slightly between TAVI and SAVR: in the first 6 months, follow-up costs were lower for TAVI but after the 6-month mark they were higher due to a higher rate of re-hospitalizations.

Unit costs were mainly derived from the Dutch Manual for Cost-Analysis in Healthcare.[6] If unit costs were not available in this manual, updated estimates from a previously published micro-costing analysis,[16] diagnosis-related groups tariffs, internal costs prices at the center studied, or published literature (Supplemental Material) were used. An average wholesale TAVI device price of €18,661 was assumed based on the country-specific list price of the CoreValve system. For SAVR, it was assumed that in all cases a bioprosthesis (and not a mechanical valve) was used given the patients' age; therefore, we did not analyze excess bleeding events from anticoagulation. The price of €2862 was based on the invoiced price at Erasmus University Medical Centre.[17] The calculations of the costs of adverse events are described in more detail in the Supplemental Material.

Willingness-to-pay threshold

In the Netherlands, the cost-effectiveness threshold depends on the disease burden of the patients of interest with the current standard of care; the higher the disease burden, the higher the cost-effectiveness threshold (varying between €20,000 to €80,000 per QALY).[10] Disease burden can be expressed in proportional shortfall—the fraction of QALYs that people lose relative to their remaining life expectancy—which can take a value between 0 (minimal burden of disease) and 1 (maximum burden of disease).[18] In this study, disease burden in terms of proportional shortfall is calculated using the iMTA Disease Burden Calculator (iDBC) version 1.3.[19] This tool uses age- and sex-adjusted life expectancy[20] and utilities[21] of the general Dutch population, and compares this with (quality-adjusted) life expectancy of standard care to calculate the burden of disease for a given condition (see results for details).

Scenario analysis

A "lean" scenario was explored for TAVI assuming a shorter LOS of 0.5 days in the ICU and 2.5 days on a regular ward, as opposed to 1 and 6 days in the base case, and one instead of two interventional cardiologists and technicians present during the procedure. Further, threshold analysis was performed to determine by how much the costs of TAVI need to be decreased to be considered cost-effective compared to SAVR. In addition, scenario analyses were performed varying the assumption of extrapolation of survival beyond the results of the CoreValve High Risk Trial. Instead of proportional hazards, two alternative scenarios with either a gradually declining survival benefit or no survival benefit of TAVI after 2 years were simulated (see Supplemental Material for details).

Sensitivity and threshold analyses

The effects of parameter uncertainty on the cost-effectiveness results were evaluated in deterministic sensitivity analyses by varying each parameter by at least 30% (Supplemental Material). Threshold analysis was performed to quantify costs that would be associated with an incremental cost-effectiveness ratio (ICER) of 0. To study the overall effect of parameter uncertainty on the results, probabilistic sensitivity analysis (PSA) for the base-case and "lean scenario" were performed. In the PSA, all input parameters were varied simultaneously by drawing from their probability distributions (available upon request) with costs and effectiveness results generated for 50,000 simulations. The results are shown in cost-effectiveness planes and cost-effectiveness acceptability curves.

Results

Survival

Mean model-projected survival increased by 0.65 life years after TAVI compared to SAVR (5.62 vs. 4.97 life years, respectively). The quality-adjusted life expectancy increased by 0.41 QALYs after TAVI compared to SAVR (3.69 vs. 3.27 QALYs, respectively). The survival curves in Figure 2 show that the proportion of patients alive decreases more rapidly after SAVR compared to TAVI. The survival probability remains higher after TAVI compared to SAVR during the remainder of the patients' lifetime. However, the difference in survival probability slowly decreases over time. Compared to recently published registry results, the survival of TAVI in this registry was, per visual analysis, reasonably similar to the survival of SAVR in the trial and our extrapolation (see Supplemental Material for details).[12,22] Shortly after completion of our study, the 3-year results of the CoreValve High Risk Study became available; as likewise shown in the Supplemental material, the present model predicts mortality similarly compared to the 3-year trial data.[15]

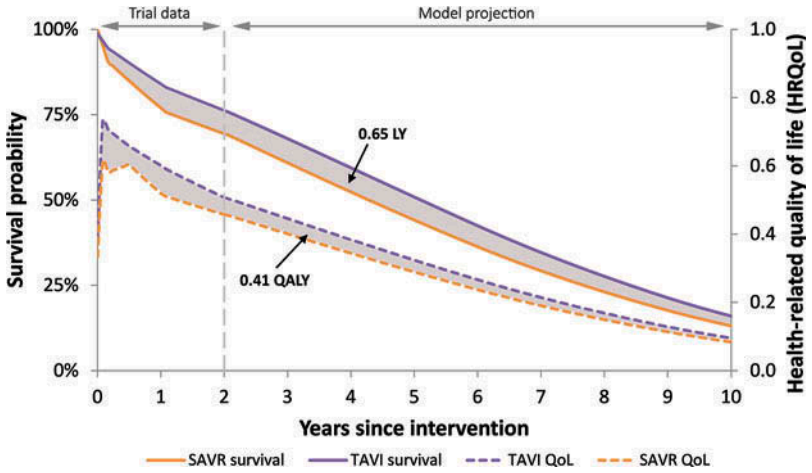

Figure 2. Projected Unadjusted and Quality-adjusted Survival. Kaplan-Meier-style Survival Curves depicting the proportion alive (y-axis) after surgical aortic valve replacement (SAVR, purple line) or transaortic valve implantation (TAVI, yellow curve). Dashed lines represent the annualized health-related quality of life (HRQoL) gain by strategy.

Table 2. Cost-effectiveness results of base-case and scenario analyses.

	Effectiveness, QALY (LY)			Costs, €			
	TAVI	SAVR	Δ TAVI-SAVR	TAVI	SAVR	Δ TAVI-SAVR	ICER, €/QALY
Base-case	3.69 (5.62)	3.27 (4.97)	0.41 (0.65)	51,068	42,020	9048	21,946
Gradually declining survival benefit of TAVI >2 years	3.68 (5.26)	3.33 (4.75)	0.35 (0.51)	51,034	42,138	8895	25,688
No survival benefit of TAVI >2 years	3.65 (5.23)	3.45 (4.92)	0.20 (0.31)	50,960	42,429	8531	42,235
"Lean" TAVI scenario	3.69 (5.62)	3.27 (4.97)	0.41 (0.65)	47,386	42,020	5347	12,971

Note. All results are discounted with 4% and 1.5% for costs and effectiveness, respectively.
QALY, quality adjusted life year; LY, life year; ICER, incremental cost-effectiveness ratio; TAVI, transcatheter aortic valve implantation; SAVR, surgical aortic valve replacement.

Base case analysis

The results of the base-case analysis are provided in Table 2. The increased life years after TAVI translated to 0.41 additional QALYs. The distribution of costs over types of health care is illustrated in the Supplemental Material. The additional costs for the transcatheter valve prosthesis and increased survival were partly compensated by a shorter hospitalization and blood product use, resulting in incremental discounted costs for TAVI of €9048. This resulted in an ICER of €21,946 per QALY gained.

Willingness-to-pay threshold

The results of this study showed that patients who undergo SAVR can expect to incur 3.27 QALYs, compared to a normal QALY expectancy of 5.69 for an 83-year-old.[20] Hence, 2.42 QALYs are lost due to the condition with standard care or 43% of normal life expectancy. Therefore, the disease burden in terms of proportional shortfall is 0.43. For a disease burden between 0.41 and 0.70 the appropriate cost-effectiveness threshold is €50,000/QALY in the Netherlands.[10] In addition, an alternative willingness-to-pay threshold of €80,000/QALY was explored (see Supplemental Material).

Sensitivity, scenario, and threshold analyses

Sensitivity analyses revealed that the cost-effectiveness results were robust and relatively insensitive to changes in input parameters. Variations in the discount rate for effectiveness between 0% and 10%, patient age between 80 and 86 years, and the proportion of female patients were most influential on the cost-effectiveness results (see Supplemental Material).

The ICER in the "lean" scenario was considerably lower than the base-case analysis: €12,971/QALY (see Table 2). A threshold analysis of the "lean" scenario indicated that a further cost reduction of approximately €5400 would make TAVI the dominant strategy, i.e., result in a higher QALY gain and lower costs of TAVI compared to SAVR.

We also quantified the size of reductions in TAVI procedure-related costs that would make TAVI not only associated with improved patient outcomes, but also lower health care costs. Even with the base case LOS, a decreased TAVI device price of €12,000 would make TAVI dominant.

The PSA revealed that most samples were scattered in the quadrant that indicates higher effectiveness at higher costs (see Figure 3 and Supplemental Material). The median ICER was similar (€20,914/QALY) to the deterministic base case. The cost-effectiveness acceptability curve shows that 70.6% of simulations fell below the willingness-to-pay threshold of €50,000/QALY and 76.0% below €80,000/QALY (95% credible interval: 0 to ∞), indicating the likelihood that TAVI is cost-effective. The separate PSA conducted for the "lean" scenario indicated that 75.5% and 78.7% of simulations, for €50,000/QALY and €80,000/QALY respectively, were cost-effective (95% credible interval: 0 to ∞; see Supplemental Material).

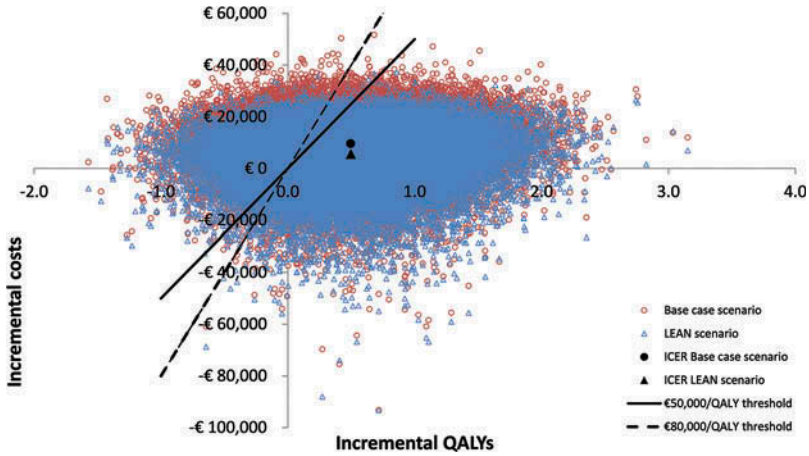

Figure 3. Incremental Cost-effectiveness Scatter Plot of the Probabilistic Sensitivity Analyses. Depicted are two different probabilistic analyses, one using the base case assumptions and distributions for all parameters (red dots), and one where the lean scenario is assumed (blue triangles).

Discussion

Our results show that TAVI adds approximately 8 months to the life of an 83-year-old with severe aortic stenosis at high operable risk compared with SAVR which represents 13% of their average remaining life expectancy. This patient benefit can be realized at higher costs compared to SAVR, but at a level that can be considered economically acceptable for the Dutch health care system. Although there was uncertainty around our results, the probability of TAVI being cost-effective at a willingness-to-pay threshold of €50,000 is between two thirds and three quarters in the probabilistic sensitivity analysis.

Our assumptions can be justified as conservative and the comparison with the 3-year trial data shows that our model predicts incremental life years similarly; in fact, the model might under-predict incremental life year gain slightly at year three which would make it more conservative. However, we did explore an alternative "lean" scenario and quantified the threshold when TAVI would become dominant. As an example, a Canadian group has proposed that TAVI patients should be cared for in a highly streamlined process and be grouped into standard and early discharge groups, analogous to our base case and "lean" scenarios; their median LOS was 3.4 and 1.2 days in the standard and early discharge groups, respectively.[23] Consequently, our base case LOS after TAVI appears to be a rather conservative assumption and the "lean" scenario with an LOS of 3 days still appears to be on the upper end of the Canadian benchmark, even when considering a mix of standard and early discharge group patients. In addition, procedure time is likely to decrease further as TAVI centers gain additional experience. These changes in resource utilization and efficiency gains, in conjunction with potential gradual reductions in device cost over time, might contribute to meaningful reductions in overall procedure cost. It therefore seems reasonable to assume that TAVI, in the not-too-distant future, might become a treatment strategy that is not just clinically appropriate for many patients, but also economically dominant, providing the same or improved clinical outcomes at overall reduced costs to the healthcare system.

Recently, Reynolds and colleagues published a cost-effectiveness analysis performed alongside the CoreValve High Risk Trial.[7] Individual patient-level data was extrapolated based on US life tables and a multiplicative factor for SAVR group mortality compared to age- and-sex matched members of the US population. In their base case analysis, the mortality hazard ratio was assumed to be equal for TAVI and SAVR patients. Their projected incremental effectiveness of 0.41 life years or 0.32 QALYs is somewhat lower compared to 0.60 life years and 0.41 QALYs in our study. Given that the cost structures are substantially different between the US and European countries we did not compare the costs and ICERs. There are other published decision-analytic models that have studied the cost-effectiveness of TAVI versus SAVR.[24–26] In most of these studies, TAVI was dominated by SAVR (i.e., TAVI had lower QALY gain at higher costs compared to SAVR) or they reported high ICERs. Compared with these studies, we found a substantially higher QALY gain, resulting in a lower ICER. However, the previous studies are not comparable with our study, because most of these studies used data on a single balloon-expandable instead of a self-expandable TAVI system.[27] More importantly, the operative risk of the patient population of the current study was lower compared to other studies.

The extrapolation of survival estimates of patients undergoing TAVI seems reasonably comparable with the survival observed in the referenced UK registry.[12] The slightly lower 3- and 5-year mortality probability estimated in our study may be explained by the fact that we studied patients at high surgical risk, while the UK registry also included patients at extreme operable risk. Another explanation may be that the UK registry tracks patients who underwent procedures between 2007 and 2009, whereas the proportion of procedure success and long-term survival might have increased since newer generations of devices have become available, including the CoreValve system.[1]

Our study has several limitations. First, the data are based on a clinical trial that was not performed in Europe, but in the US. However, while health care systems and costs are considerably different, it might be reasonable to assume that clinical data from US centers are applicable to European centers. To control for differences in valuation of health states and clinical care, utilities were based on a validated Dutch value set and the estimates of

LOS were not based on trial data. Extensive sensitivity analyses were performed to quantify the remaining uncertainties. Second, the lifetime horizon of the analysis made it necessary to extrapolate mortality beyond the 2-year trial data and therefore actual survival might differ from our projections. However, we explored scenarios in which the continued survival benefit of TAVI compared to SAVR would gradually decline or stop after 2 years, and performed external validation of the projected survival to 5-year real-world data.[12] Furthermore, our estimated 3-year survival rates are in accordance with the 3-year follow-up data from the CoreValve High Risk Trial (TAVI: 68.0% vs. 67.1% and SAVR: 60.9% vs. 60.9% in our study vs. 3-year CoreValve High Risk Trial data, respectively).[22] Third, we did not apply utility decrements for adverse events other than stroke as this might have resulted in a slight overestimation of the utilities in our study given that the utility decrements are already included in the estimates for the entire cohort except for stroke cases. Fourth, some of our cost estimates were derived from a single academic center in the Netherlands. However, per expert opinion, there is currently not much practice variation and therefore the observed costs can be expected to be comparable at other centers in the Netherlands and other European countries. Resource utilization in non-academic centers is likely to be somewhat lower in the future which makes our analysis more conservative. In addition, we took potential differences into account by performing extensive sensitivity analyses to explore the effect of changes in cost parameters. Fifth, the source of the relative risk multiplier used to reflect the elevated long-term event probabilities of patients with a stroke is relatively dated, leading to a possible overestimation. However, this would have effected both treatment arms and the difference in stroke incidence between TAVI and SAVR is relatively small, limiting the possible effect of this limitation on our endpoints. Sixth, the proportion of AKI cases requiring dialysis, about one-third, is rather high and was derived from an aggregate of TAVI and SAVR cases. However, the proportion of patients requiring dialysis for TAVI is likely to be lower than SAVR which would make our model estimates more conservative. Seventh, most post-procedure atrial fibrillation cases did not necessitate a pacemaker as they either resolved spontaneously or were just treated with antinodal agents at costs that were not included in the model. However, the costs for these drugs are relatively small and would not have impacted the strategies very differently. Eighth, we did not assess the effects of late manifestations of decreased hemodynamic performance including valve durability, mismatch, performance, and leakage as well as thrombosis and prosthetic valve endocarditis. However, we did not have access to such data. Finally, our results might only be applicable to self-expandable and not to balloon-expandable systems.

Conclusion

In conclusion, TAVI via a self-expandable catheter system is a treatment that modestly prolongs life and improves quality of life for elderly high-risk surgical candidates compared to SAVR at a cost that is deemed acceptable in the Dutch health care system. The favorable health-economic value proposition of TAVI is in agreement with recent findings from the US and can be expected to further improve in future years.

Acknowledgments

The co-authors are indebted to Rachele Busca, MBA, MSc, PharmD, Sharla Chenoweth, MSc, Abigail Garner, MSc, Amir Ansaripour, PharmD, and William Ken Redekop, PhD for their assistance and support. We would also like to thank the US CoreValve Clinical Investigators for granting access to the clinical trial data.

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Funding

This work was supported by Medtronic plc, a manufacturer of aortic valves for transcatheter implantation.

Disclosure statements

Wing Tech Inc. (J.B.P., B.P.G.) provided health-economic consulting services to Medtronic plc, a manufacturer of aortic valves for transcatheter implantation. Erasmus University Medical Center (A.P.K, R.L.J.O., S. A.H.) received an unrestricted research grant for the costing part of this study from Medtronic plc. M.J.R. serves on a medical advisory board for Medtronic plc.

References

1. Reinöhl J, Kaier K, Reinecke H, et al. Effect of availability of transcatheter aortic-valve replacement on clinical practice. *N Engl J Med*. 2015;373(25):2438–2447. doi:10.1056/NEJMoa1500893.
2. Mylotte D, Osnabrugge RL, Windecker S, et al. Transcatheter aortic valve replacement in Europe: adoption trends and factors influencing device utilization. *J Am Coll Cardiol*. 2013;62(3):210–219. doi:10.1016/j.jacc.2013.03.074.
3. Adams DH, Popma JJ, Reardon MJ, et al. Transcatheter aortic-valve replacement with a self-expanding prosthesis. *N Engl J Med*. 2014;370(19):1790–1798. doi:10.1056/NEJMoa1400590.
4. Busca R, Geisler BP, Pietzsch JB. Cost-effectiveness of transcatheter aortic valve replacement: current decision-analytic models and future opportunities. *Value Health*. 2015;18(7):A359. doi:10.1016/j.jval.2015.09.686.
5. Statistisches Bundesamt. Fallpauschalenbezogene Krankenhausstatistik (DRG-Statistik) Diagnosen, Prozeduren, Fallpauschalen und Case Mix der vollstationären Patientinnen und Patienten in Krankenhäusern 2015. Fachserie 12 Reihe 6.4. 2016; https://www.destatis.de/DE/Publikationen/Thematisch/Gesundheit/Krankenhaeuser/FallpauschalenKrankenhaus.html. Accessed March 2, 2016.
6. Huygens SA, Takkenberg JJ, Rutten-Van Molken MP. Systematic review of model-based economic evaluations of heart valve implantations. *Eur J Health Econ*. 2017. [Epub ahead of print]. doi:10.1007/s10198-017-0880-z.
7. Reynolds MR, Lei Y, Wang K, et al. Cost-effectiveness of transcatheter aortic valve replacement with a self-expanding prosthesis versus surgical aortic valve replacement. *J Am Coll Cardiol*. 2016;67(1):29–38. doi:10.1016/j.jacc.2015.10.046.
8. Buisman LR, Tan SS, Nederkoorn PJ, Koudstaal PJ, Redekop WK. Hospital costs of ischemic stroke and TIA in the Netherlands. *Neurology*. 2015;84(22):2208–2215. doi:10.1212/WNL.0000000000001635.
9. Reardon MJ, Adams DH, Kleiman NS, et al. 2-Year outcomes in patients undergoing surgical or self-expanding transcatheter

aortic valve replacement. *J Am Coll Cardiol*. 2015;66(2):113–121. doi:10.1016/j.jacc.2015.05.017.
10. Leon MB, Piazza N, Nikolsky E, et al. Standardized endpoint definitions for transcatheter aortic valve implantation clinical trials: a consensus report from the valve academic research consortium. *Eur Heart J*. 2011;32(2):205–217. doi:10.1093/eurheartj/ehq406.
11. Centraal Bureau voor de Statistiek. Overlevingskansen; geslacht, leeftijd (op 31 december). 2015; http://statline.cbs.nl/Statweb/selection/?VW=T&DM=SLNL&PA=70701ned&D1=0-1%2c10%2c20%2c30%2c40%2c50%2c60%2c70&D2=a&D3=0-2%2c11%2c21%2c31%2c41%2c51%2c61&D4=(l-3)-l&HDR=G1%2cT&STB=G2%2cG3. Accessed September 16, 2015.
12. Duncan A, Ludman P, Banya W, et al. Long-term outcomes after transcatheter aortic valve replacement in high-risk patients with severe aortic stenosis: the U.K. Transcatheter aortic valve implantation registry. *JACC Cardiovasc Interv*. 2015;8(5):645–653. doi:10.1016/j.jcin.2015.01.009.
13. Pilgrim T, Englberger L, Rothenbuhler M, et al. Long-term outcome of elderly patients with severe aortic stenosis as a function of treatment modality. *Heart*. 2015;101(1):30–36. doi:10.1136/heartjnl-2014-306106.
14. Lamers LM, McDonnell J, Stalmeier PF, Krabbe PF, Busschbach JJ. The Dutch tariff: results and arguments for an effective design for national EQ-5D valuation studies. *Health Econ*. 2006;15(10):1121–1132. doi:10.1002/(ISSN)1099-1050.
15. Ruparelia N, Latib A, Buzzatti N, et al. Long-term outcomes after transcatheter aortic valve implantation from a single high-volume center (The Milan Experience). *Am J Cardiol*. 2016;117(5):813–819. doi:10.1016/j.amjcard.2015.12.014.
16. Osnabrugge RL, Head SJ, Genders TS, et al. Costs of transcatheter versus surgical aortic valve replacement in intermediate-risk patients. *Ann Thorac Surg*. 2012;94(6):1954–1960. doi:10.1016/j.athoracsur.2012.07.002.
17. Financial advisor at Erasmus Medical Centre. Invoiced price of the Carpentier-Edwards Perimount Magna Ease Pericardial. 2014. Rotterdam, Erasmus Medical Centre.
18. Stolk EA, Van Donselaar G, Brouwer WBF, Busschbach JJV. Reconciliation of economic concerns and health policy. *Pharmacoeconomics*. 2004;22(17):1097–1107. doi:10.2165/00019053-200422170-00001.
19. Versteegh MM The iMTA disease burden calculator. Software version 1.3 beta. Downloaded from www.imta.nl/idbc. Institute of Medical Technology Assessment (iMTA), Erasmus University Rotterdam; 2016. Accessed November 12, 2015.
20. Centraal Bureau voor de Statistiek (CBS). Gezonde levensverwachting: vanaf 1981. 2014; http://statline.cbs.nl/. Accessed April 11, 2015.
21. Heijink R, Van Baal P, Oppe M, Koolman X, Westert G. Decomposing cross-country differences in quality adjusted life expectancy: the impact of value sets. *Popul Health Metr*. 2011;9(1):1. doi:10.1186/1478-7954-9-17.
22. Deeb GM, Reardon MJ, Chetcuti S, et al. 3-year outcomes in high-risk patients who underwent surgical or transcatheter aortic valve replacement. *J Am Coll Cardiol*. 2016;67(22):2565–2574. doi:10.1016/j.jacc.2016.03.506.
23. Lauck SB, Wood DA, Baumbusch J, et al. Vancouver transcatheter aortic valve replacement clinical pathway: minimalist approach, standardized care, and discharge criteria to reduce length of stay. *Circ Cardiovasc Qual Outcomes*. 2016;9(3):312–321. doi:10.1161/CIRCOUTCOMES.115.002541.
24. Neyt M, Van Brabandt H, Devriese S, Van De Sande S. A cost-utility analysis of transcatheter aortic valve implantation in Belgium: focusing on a well-defined and identifiable population. *BMJ Open*. 2012;2(3):e001032. doi:10.1136/bmjopen-2012-001032.
25. Fairbairn TA, Meads DM, Hulme C, et al. The cost-effectiveness of transcatheter aortic valve implantation versus surgical aortic valve replacement in patients with severe aortic stenosis at high operative risk. *Heart*. 2013;99(13):914–920. doi:10.1136/heartjnl-2013-303722.
26. Orlando R, Pennant M, Rooney S, et al. Cost-effectiveness of Transcatheter Aortic Valve Implantation (TAVI) for aortic stenosis in patients who are high risk or contraindicated for surgery: a model-based economic evaluation. *Health Technol Assess*. 2013;17(33):1–86. doi:10.3310/hta17330.
27. Smith CR, Leon MB, Mack MJ, et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. *N Engl J Med*. 2011;364(23):2187–2198. doi:10.1056/NEJMoa1103510.