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ORIGINAL RESEARCH

Cost-Effectiveness of SAPIEN 3 Transcatheter Aortic Valve Implantation Versus Surgical Aortic Valve Replacement in German Severe Aortic Stenosis Patients at Low Surgical Mortality Risk

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ABSTRACT

Introduction: In the randomized PARTNER 3 trial, transcatheter aortic valve implantation (TAVI) with the SAPIEN 3 device significantly reduced a composite of all-cause death, stroke, and rehospitalization, compared with surgical aortic valve replacement (SAVR), in patients with severe symptomatic aortic stenosis and low risk of surgical mortality. Furthermore, TAVI has been shown to be cost-effective in low-risk patients, compared with SAVR, in a number of countries. This study aimed to determine the cost-effectiveness of TAVI with SAPIEN 3 versus SAVR in Germany.

Methods: A previously published two-stage Markov-based model that captured clinical outcomes from the PARTNER 3 trial was adapted for the German context using the German Statutory Health Insurance perspective. The model had a lifetime horizon. The cost–utility analysis estimated changes in direct healthcare costs as well as survival and health-related quality of life using TAVI with SAPIEN 3 compared with SAVR.

Results: TAVI with SAPIEN 3 increased quality-adjusted life years (QALYs) by + 0.72 at an increased cost of €8664 per patient. The incremental cost-effectiveness/QALY ratio was €12,037, which fell below that of other cardiovascular interventions in use in Germany. The

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cost-effectiveness of TAVI over SAVR remained robust across multiple challenging scenarios and was driven by lower longer-term management costs compared with SAVR.
Conclusions: TAVI with SAPIEN 3 appears to be a clinically meaningful, cost-effective treatment option over SAVR for patients with severe symptomatic aortic stenosis and low risk for surgical mortality in Germany.
Clinical Trial Registration Number: www.clinicaltrials.gov identifier: NCT02675114.

Keywords: Tanscatheter aortic valve implantation (TAVI); Surgical aortic valve replacement; Cost–utility analysis; Cost-effectiveness; Aortic stenosis; Low risk

Key Summary Points

Why carry out this study?

Increasing evidence of the clinical benefits of transcatheter aortic valve implantation (TAVI) compared with surgical aortic valve replacement (SAVR) together with recent guideline updates recommending TAVI for patients 75+ years old regardless of surgical risk status are likely to lead to increased demand for the procedure.

This is the first study to provide cost-effectiveness information on TAVI versus SAVR in patients with severe symptomatic aortic stenosis who are at low risk of surgical mortality in Germany.

What was learned from the study?

The data from this analysis suggest that TAVI offers a cost-effective option in the low surgical-risk population over the longer term.

Healthcare providers and policy makers in Germany can use these data to inform their decisions on intervention selection for patients with severe symptomatic aortic stenosis.

INTRODUCTION

Aortic stenosis is a potentially life-threatening condition characterized by narrowing of the aortic valve opening and progressive obstruction of the left ventricular outflow tract [1]. Historically, severe symptomatic aortic stenosis (sSAS) was managed by surgical aortic valve replacement (SAVR) [1]. However, in the last 20 years, transcatheter aortic valve implantation (TAVI) has become increasingly established as a treatment option for selected patients with aortic stenosis [1, 2]. The multicenter randomized controlled trial PARTNER 3 has recently investigated TAVI using the latest-generation SAPIEN 3 transcatheter heart valve delivered via a transfemoral route in patients with sSAS considered at low risk of surgical mortality [3]. PARTNER 3 showed that, compared with SAVR, TAVI was associated with a reduction in the primary composite outcome of death, stroke, or rehospitalization after 1 and 2 years, significantly lower rates of stroke and new-onset atrial fibrillation (AF) within 1 month of the procedure, shorter hospital stays, functional benefits (including improvements in 6 min walk test difference and New York Heart Association functional class), and also greater improvement in the short term in quality of life [3].

On the basis of these findings, in 2020, TAVI was endorsed by the German Cardiac Society (DGK) and German Society of Thoracic, Cardiac and Vascular Surgery (DGTHG) as the recommended sSAS treatment approach among patients older than 75 years in all surgical risk groups (with suitable anatomy) [4]. The European Society of Cardiology (ESC)/European Association for Cardio-Thoracic Surgery (EACTS) guidelines were updated a year later, in 2021, to recommend that TAVI is considered for all patients with sSAS where feasible on the basis of individual clinical and anatomical characteristics [2]. Recognition of the potential benefits of TAVI appears strong in Germany, as highlighted by the country reporting the highest rate of TAVI procedures performed in 2019 in Western Europe (292 per million population compared with approximately 50–200 per million population across 15 other European

countries) [5]. This was despite Germany having a below-average number of TAVI centers (just over 1 per million population compared with the average of 1.59 centers per million population in Western Europe) [5]. Indeed, Germany is widely acknowledged as a key forerunner and contributor in the development and utilization of TAVI [6].

Given the maturity of TAVI technology, the demonstrated clinical benefits for patients, the high numbers of procedures already performed, and the huge potential for further adoption with the move towards use in lower-risk patients wherein SAVR is more likely to have a favorable outcome, it is increasingly important to demonstrate the cost-effectiveness of TAVI in Germany. Using the same model as in our analyses, authors have previously shown TAVI to be cost-effective versus SAVR in low-risk patients with sSAS in France, Italy, and Spain [7–9]. Here, we report the first ever cost–utility analysis of TAVI with SAPIEN 3 versus SAVR from a German perspective in patients with sSAS at low risk of surgical mortality.

METHODS

Model Structure

A cost–utility analysis was conducted to estimate changes in direct healthcare costs and health-related quality of life with TAVI versus SAVR in the low-risk population of patients with sSAS. The two-stage model structure that formed the basis of this cost–utility analysis has been described in detail previously [7]. Briefly, the health economic model was developed in collaboration with York Health Economics Consortium and comprised an initial decision tree structure followed by a long-term Markov model with health states based around complications observed in patients with sSAS at low risk of surgical mortality. Early adverse events (AE) associated with the TAVI procedure using the SAPIEN 3 device were used in the decision tree to assign patients to a range of AE outcomes, alongside a death outcome (Fig. 1a) [7]. These rates were taken from the 30 days AE data set of the PARTNER 3 trial [3]. The outcomes from the decision tree were fed into a Markov model that included the following health states to capture longer-term outcomes post-TAVI and post-SAVR: "alive and well", "treated atrial fibrillation (treated AF)", "disabling stroke", and "dead" (Fig. 1b) [7, 8].

The model was adapted for the German context using cost data from the perspective of the German Statutory Health Insurance (SHI), with a lifetime horizon to account for the lifelong requirement for valve replacement in sSAS. A discounting factor of 3% was applied per year for both future costs and accrued benefits [10]. The conceptual model was validated by the authors on the basis of their clinical and health economics expertise. Details are published previously for input variable definitions [3, 7] and output definitions (www.yhec.co.uk/glossary/), and are summarized in the sections below.

Trial Overview

The multicenter randomized clinical trial PARTNER 3 (ClinicalTrials.gov number NCT02675114) included 1000 patients with sSAS who were considered at low risk of mortality from surgery (Society of Thoracic Surgeons-Predicted Risk of Mortality [STS-PROM] score $< 4\%$) [3]. Patients with clinical frailty, bicuspid aortic valves, or other anatomical features that increased the risk of complications associated with either TAVI or SAVR were excluded. In total, 503 patients were randomized to TAVI with SAPIEN 3 and 497 patients to SAVR, with the "as treated" groups comprising 496 and 454 patients, respectively. The average age of the trial population was 73 years, and 69% were male. The primary endpoint of PARTNER 3 was a composite of death from any cause, stroke, or rehospitalization at 1 year after the procedure.

Clinical Events

In the base case, clinical events over the short term ($\leq$ 30 days) were based on PARTNER 3 trial outcomes from the 30 days AE data set (Supplementary Material, Table S1). Input data for permanent pacemaker implantation (PPI) at 30 days were based on PARTNER 3 data for SAVR [3] and a real-world cohort study to reflect

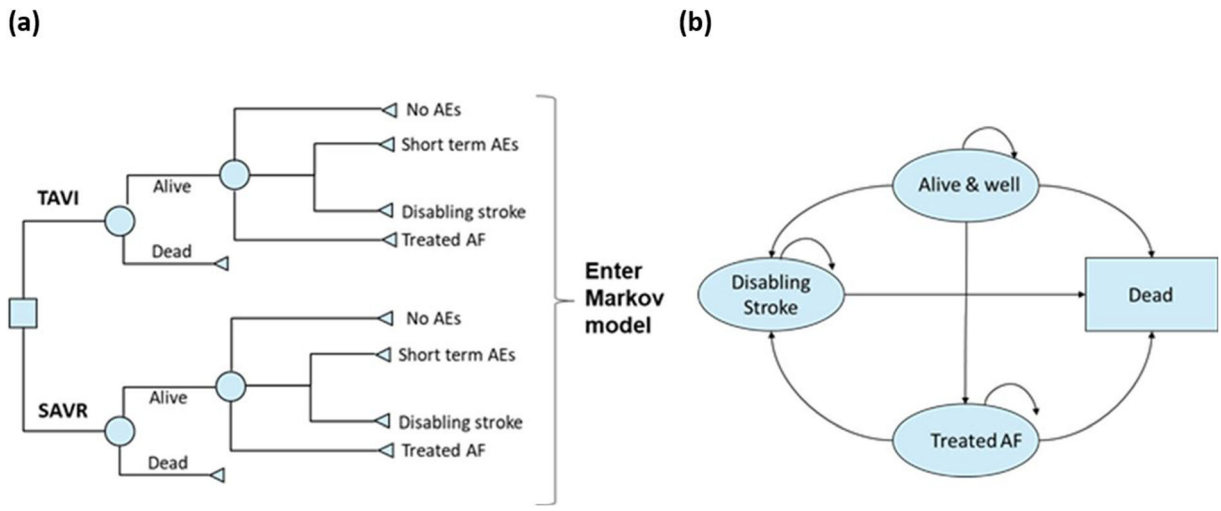

Fig. 1 The cost–utility model had two stages: **a** early AEs from the PARTNER 3 trial were captured in a decision tree, which fed into **b**, a Markov model that captured longer-term outcomes of patients, with four distinct health states

more recently available SAPIEN 3 TAVI data specific to the German population [11].

Monthly transition probabilities between health states for the Markov model, reflecting complications occurring after 30 days, were estimated on the basis of data from PARTNER 3 (up to 2 year outcomes) or other literature sources where there were too few events in PARTNER 3 for reliable estimates (Supplementary Material, Table S1). Rehospitalization rates were based on data from the PARTNER 3 study [3]. Reintervention rates due to value deterioration were based on PARTNER 3 data up to 2 years [3, 12] and by competing risk estimates for the 73 year-old cohort from a study by Bourguignon et al. from year 3 onwards [13]. The same reintervention rate was used for both TAVI with SAPIEN 3 and SAVR in the base case; this simplifying assumption allowed best use of the available data. We introduced multiple scenarios to test the robustness of our model. Scenario 1 assumed a higher reintervention rate for TAVI versus SAVR, based on data at 5 years from the PARTNER 2 trial [14] (Table 4). Scenario 2 assumed an increased risk of stroke with TAVI versus SAVR after 1 and 2 years, to align with PARTNER 3 outcomes [3, 12]. A number of scenarios explored alternative PPI rates: scenario 3a assumed a new PPI rate of 13.2% for TAVI and 3.3% for SAVR based on a recent study of over 38,000 patients enrolled in the German Aortic Valve Registry who received TAVI or SAVR between 2011 and 2015 [15], and scenario 3b assumed a new PPI of 6.5% for TAVI and 4.0% for SAVR based on PARTNER 3 [3] (Table 4).

Survival Extrapolation

Annual mortality risk for "alive and well" and associated relative risk for other health states are shown in Supplementary Material, Table S2. Two options for extrapolation of survival were considered. Option 1 (used as the base case) estimated transition probabilities using German general population mortality and published studies in German patients reporting relative risk (RR) of death with AF of 1.2 [16] and RR of death with disabling stroke of 2.3 [17]. Option 2 used parametric survival fitting based on Kapla–Meier data from PARTNER 3, with a choice of three parametric distributions (Weibull, exponential, Gompertz) adjusted to the German general population survival. Option 2 was explored in scenario analyses with alternative hazard ratios (HRs) for death: scenario 4 assumed a HR of 0.75 based on PARTNER 3 data at 2 years [12] whilst scenario 5 assumed no survival benefit with TAVI versus SAVR (HR = 1.0) (Table 4).

Health Utilities and Quality Of Life

Two options were considered here. In the base case (option 1), decrements were estimated on the basis of published literature to account for there being too few events in the PARTNER 3 trial. In this option, the description of health states was based upon the EuroQol-5 Dimensions-3 levels (EQ-5D-3L) questionnaire and health utilities were derived building upon choice-based methods, thereby producing the endpoint quality-adjusted life years (QALYs). For the health states, "disabling stroke" and "treated AF", the utility decrements were calculated using utilities reported by Walter et al. [18] for AF and Ali et al. [19] for disabling stroke and then finally adjusted for age and population norms for EQ-5D-3L according to Szende et al. [20].

Option 2 considered age-adjusted utility decrement by treatment arm from PARTNER 3 [3] and was considered within two scenario analyses (Table 4). Scenario 6 explored EQ-5D-5L descriptive responses individually extracted from PARTNER 3 at baseline, 30 days, 6 months, and 1 year converted to German health utilities using the value set from Ludwig et al. [21]. For the same descriptive responses in PARTNER 3, scenario 7 explored valuation by the visual analog scale (VAS) using the German experience-based value set from Leidl and Reitmeir [22]. With VAS values not being choice-based, the endpoint in scenario 7 is VAS-adjusted life years.

Cost Inputs

The cost perspective was based on information from the German Diagnostic-Related Groups (G-DRGs) and from published literature. For the base case, costs associated with TAVI and SAVR procedures were estimated from the 2021 reimbursement values of G-DRGs F98B for transfemoral TAVI and F03E for SAVR respectively. The total procedure costs for each treatment also accounted for the bedside nursing costs (Table 1). Follow-up costs, costs linked to postoperative complications, and acute and chronic rehospitalization costs were estimated from G-DRGs or relevant published literature (Table 2). All costs are actualized to 2021 euros using the consumer price index (CPI). Additional scenario analyses were performed on the total procedure costs assumptions, including SAVR procedure costs as a weighted average (by the corresponding actual number of cases in G-DRG 2021) of 2021 reimbursement values for G-DRGs F03E, F03D, and F03C (scenario 8, Table 4). There was a limitation of the current rehabilitation rates from the German Institute for the Remuneration System in Hospitals (InEK) used to derive the total procedural costs in the base case. Rehabilitation following release to home and ambulatory rehabilitation were not captured in the InEK data, leading potentially to procedure costs being underestimated in the base case. To address uncertainty arising from this, multiple scenario analyses were incorporated (Table 4), including assumption of 100% rehabilitation rates for TAVI (scenario 9a) and alternative rehabilitation rates for TAVI from the literature (scenarios 9b and 9c) [23, 24]. Finally, an additional scenario accounted for AE costs within 30 days (scenario 10).

Table 1 Breakdown of TAVI and SAVR procedure costs

	TAVI with SAPIEN 3	SAVR
G-DRG	F98B	F03E
Cost weight per case 2021	6.17	3.84
Federal base rate 2021	€3748.98	€3748.98
Procedure cost excluding bedside nursing costs	€23,136.28	€14,395.99
Nursing cost weight per day 2021	1.1916	1.3567
Base rate bedside nursing 2021	€163.09	€163.09
DRG average LoS 2021	11.1	11.3
Bedside nursing cost	€2157.15	€2500.29
Total procedure cost	€25,293.43	€16,896.28

G-DRG German Diagnostic-Related Group, *SAVR* surgical aortic valve replacement, *TAVI* transcatheter aortic valve implantation, *LoS* length of stay

Table 2 Costs associated with TAVI and SAVR (procedure, complications, long-term)

Unit cost components	TAVI with SAPIEN 3	SAVR	Source
Procedure			
Intervention	€25,293	€16,896	Estimated 2021 revenue values for G-DRG F98B and G-DRG F03E [34]
Rehabilitation	€169	€626	Karoff et al. [35]
Acute postoperative complications			
Reintervention	€25,463	€25,452	Assumed equal to cost of initial procedure plus rehabilitation associated with procedure
Associated to health states			
Treated AF—month 1	€229	€229	Reinhold et al. [36]
Treated AF ≥ month 2	€28	€28	
DS—month 1	€8834	€8834	Mensch et al. [16]
DS ≥ month 2	€1076	€1076	
Caregiver for DS—month 1	€1309	€1309	Albrecht et al. [37]
Caregiver for DS ≥ month 2	€740	€740	
Alive and well—year 1	€54	€54	Kaier et al. [38]
Alive and well—year 2+	€39	€40	
Other costs considered			
Pacemaker procedure	€1584	€1584	Gutmann et al. [39]
Pacemaker complications (monthly)	€123	€123	Hadwiger et al. [26]
Rehospitalization	€5787	€5787	2019 G-DRG F62B [40]
Reintervention	€25,463	€25,452	Assumed equal to cost of initial procedure plus rehabilitation associated with procedure

AF atrial fibrillation, *DS* disabling stroke, *SAVR* surgical aortic valve replacement, *TAVI* transcatheter aortic valve implantation

Model Outputs

Details of the model outputs and assumptions have been published previously [7]. The cost–utility model generated total per-patient costs and QALYs for each intervention over the patients' lifetime, and an incremental cost-effectiveness ratio (ICER) for TAVI with SAPIEN 3 compared with SAVR in a population of German patients with sSAS at low risk of surgical mortality. Scenario 7 included life years adjusted by VAS instead of QALYs as the effectiveness outcome.

As Germany has no official cost-effectiveness threshold, we assumed a hypothetical willingness to pay (WTP) threshold of €35,000/QALY. This threshold has also been used by other cost–utility studies for cardiovascular disease conditions in Germany and reflects the upper threshold boundary of the UK National Institute for Health and Care Excellence (NICE) [25, 26].

To evaluate uncertainty in the results, one-way deterministic sensitivity analyses were

performed by varying inputs using confidence intervals and ranges from the literature where available and, plausible ranges where data were unavailable as specified in Supplementary Material, Table S3. Overall parameter uncertainty was addressed by a probabilistic sensitivity analysis. Probability distributions for all input parameters were specified and 1000 Monte Carlo simulations were run using random draws of all parameters from within their assigned distributions (Supplementary Material, Table S4). Finally, multiple scenario analyses were conducted to explore the impact of major structural assumptions (Table 4), as detailed throughout. The model was fully developed, adapted, and validated by the authors. All analyses were performed using Microsoft Excel (Microsoft Corporation, Redmond, WA).

Compliance with Ethics Guidelines

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

RESULTS

Base Case

Compared with SAVR (lifetime cost per patient €28,878, lifetime QALY per patient 7.84), TAVI with SAPIEN 3 (lifetime cost per patient €37,542, lifetime QALY per patient 8.56) improves QALYs per patient by + 0.72 with a slight increase in costs of approximately €8664 per patient, yielding an ICER per QALY of €12,037. Our estimated ICER per QALY of €12,037 is lower than the assumed WTP of €35,000/QALY. The base case results over a 50-year time horizon are shown in Table 3. A cost breakdown revealed higher initial procedure costs with TAVI compared with SAVR, but lower long-term costs related to hospitalizations, treated AF, and disabling stroke (Supplementary Material, Fig. S1).

Deterministic Sensitivity Analyses

The univariate sensitivity analysis showed that TAVI with SAPIEN 3 remains cost-effective regardless of changes in individual model parameters (Fig. 2, tornado diagram displaying the 10 parameters with greatest influence on the model). The parameters that most influence the model are patient age, procedure costs, and transition probabilities toward treated AF.

Probabilistic Sensitivity Analyses

The results of the probabilistic sensitivity analysis corroborate the base case results. At the assumed cost-effectiveness threshold of €35,000/QALY or higher, TAVI remains cost-effective in 99.6% of cases compared with SAVR (Fig. 3a). Additionally, the cost-effectiveness acceptability curve shows that TAVI still has a high probability (99%) of being cost-effective at a lower threshold of €30,000/QALY (Fig. 3b).

Scenario Analyses

The scenario analyses demonstrate the comparative robustness of the reported results. On the basis of a wide-ranging series of scenarios, which included varying the time horizon (5, 10, 15, 20, and 30 years in scenarios 11–15) and the use of VAS-adjusted life years (scenario 7), TAVI with SAPIEN 3 remained cost-effective compared with SAVR despite changing various assumptions. The resultant ICERs from all the tested scenarios are reported in Table 4.

DISCUSSION

The findings of this cost–utility analysis support the use of TAVI with SAPIEN 3 as a cost-effective valve replacement option in patients with sSAS at low risk of surgical mortality in Germany. TAVI with SAPIEN 3 showed an improvement in QALYs (+ 0.72) that was associated with slightly increased costs (+ €8664 per patient) compared with SAVR. The ICER benefits for TAVI with SAPIEN 3 shown in this model represent a highly cost-effective intervention (ICER

Table 3 Base case results with acute and lifetime costs

Summary results	TAVI with SAPIEN 3	SAVR	Incremental
Cost per patient	€37,542	€28,878	€8664
Life year gained (undiscounted)	12.83	12.38	0.45
Median survival (years)	15.00	13.17	1.83
QALYs per patient	8.56	7.84	0.72
Incremental cost effectiveness ratio (ICER)			€12,037
Incremental net monetary benefit (NMB)			€16,529
Incremental net health benefit (NHB)			0.47
Acute phase cost (first hospitalization and rehabilitation)			
Index hospitalization	€25,293	€16,896	€8397
Rehabilitation	€169	€626	− €457
Acute phase costs	€25,463	€17,522	€7940
Additional costs at 1 year			
MI	€134	€117	€18
Costs of pacemaker complications	€148	€52	€96
Costs of hospitalizations	€396	€591	− €195
Reintervention costs	€117	€117	€1
Alive and well health state costs	€607	€407	€200
Treated AF health state costs	€25	€187	− €162
Disabling stroke costs	€9	€137	− €129
Death costs	€0	€0	€0
Total costs at 1 year	€26,898	€19,130	€7769
Additional lifetime costs			
Costs of pacemaker complications	€1542	€526	€1016
Costs of hospitalizations	€645	€623	€21
Reintervention costs	€3600	€3340	€260
Alive and well health state costs	€3911	€2545	€1365
Treated AF health state costs	€304	€1232	− €927
Disabling stroke costs	€642	€1482	− €840
Additional lifetime costs	€10,644	€9749	€896
Total lifetime costs	€37,542	€28,878	€8664

AF atrial fibrillation, *ICER* incremental cost-effectiveness ratio, *MI* myocardial infarction, *NHB* net health benefit, *NMB* net monetary benefit, *QALY* quality-adjusted life year, *SAVR* surgical aortic valve replacement, *TAVI* transcatheter aortic valve implantation

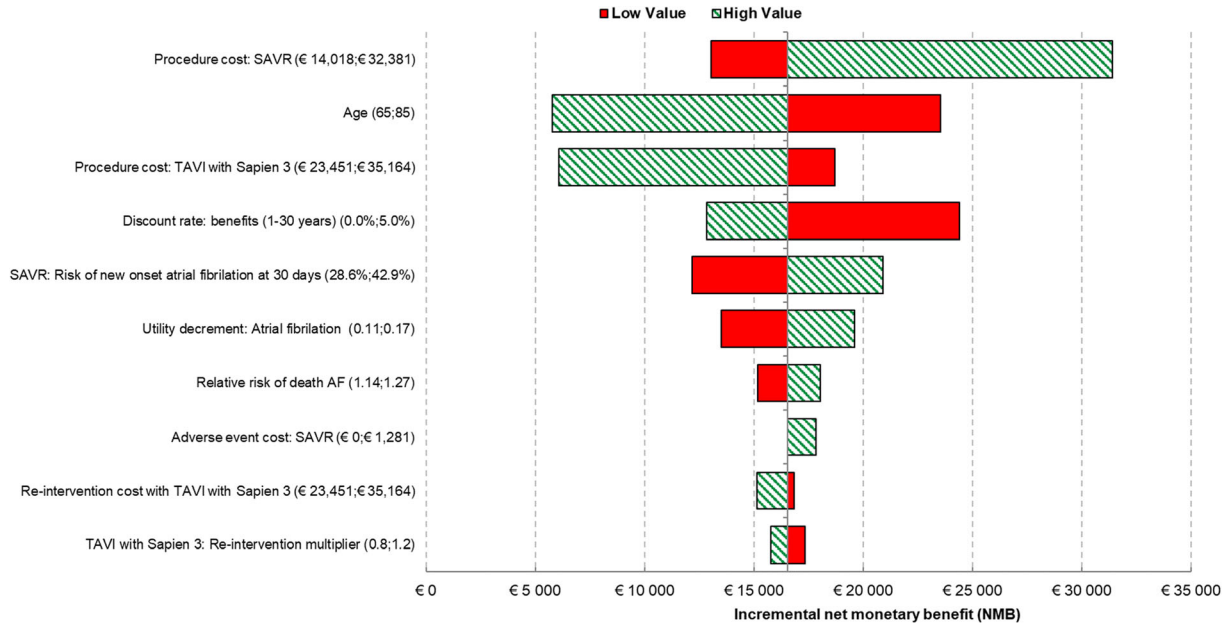

Fig. 2 Tornado diagram showing the 10 parameters with greatest influence on the model (deterministic sensitivity analysis)

of €12,037/QALY) when considered in relation to the assumed WTP threshold of €35,000/QALY. The robustness of the analysis was confirmed through various sensitivity analyses. Indeed the ICER falls well towards the lower range of those reported in previously published cost-effectiveness studies of other cardiovascular procedures in Germany, which range from €24,659/QALY for additional defibrillator use for cardiac resynchronization [26] to €50,570/QALY for radiofrequency catheter ablation to treat paroxysmal AF [27].

The findings of the current study from a German perspective are consistent with cost-effectiveness outcomes for the use of TAVI with SAPIEN 3 versus SAVR in low-risk patients in other countries. In cohorts comparable to ours, ICER/QALYs range from €2989 (Italy) [8], Australian $3521 (Australia) [28], Canadian $27,196 (Canada) [29] to economic dominance in France (potential cost saving of €12,742 and + 0.89 QALYs gained per patient) [7, 30] and Norway (cost saving of NOK 35,000 and 0.05 QALYs gained) [31]. TAVI also appears to be cost-effective over SAVR in low-risk patients from the perspective of other TAVI devices. ICER/QALY for TAVI using a self-expandable device (Evolut) was Canadian $59,641 in Canada [29] and showed dominance in Australia [28], while an ICER/QALY of DKK 696,264 was reported for TAVI using the CoreValve device versus SAVR in a low-risk Danish population [32]. Furthermore, TAVI was considered highly cost-effective in an Irish Health Technology Assessment in both low- and intermediate-risk patients aged 70 years or older (cost-effectiveness probability at the €20,000/QALY national threshold of 57.1% and 62.8%, respectively) [33]. Caution should be taken when comparing ICERs between different countries because of variations in model assumptions and country healthcare system costs. For example, the recent analysis conducted from a Canadian third-party payer perspective estimated the cost-effectiveness of balloon-expandable TAVI relative to SAVR using data from the PARTNER 3 trial with up to 1-year follow-up [29]. The estimated ICER of Canadian $27,196/QALY for TAVI versus SAVR was below the Canadian WTP threshold of Canadian $50,000. While both the Canadian analysis and our German analysis show TAVI to be cost-effective versus SAVR, there were differences between the models. In contrast to the Canadian model, treated AF was included as a health state in our German model because of the large

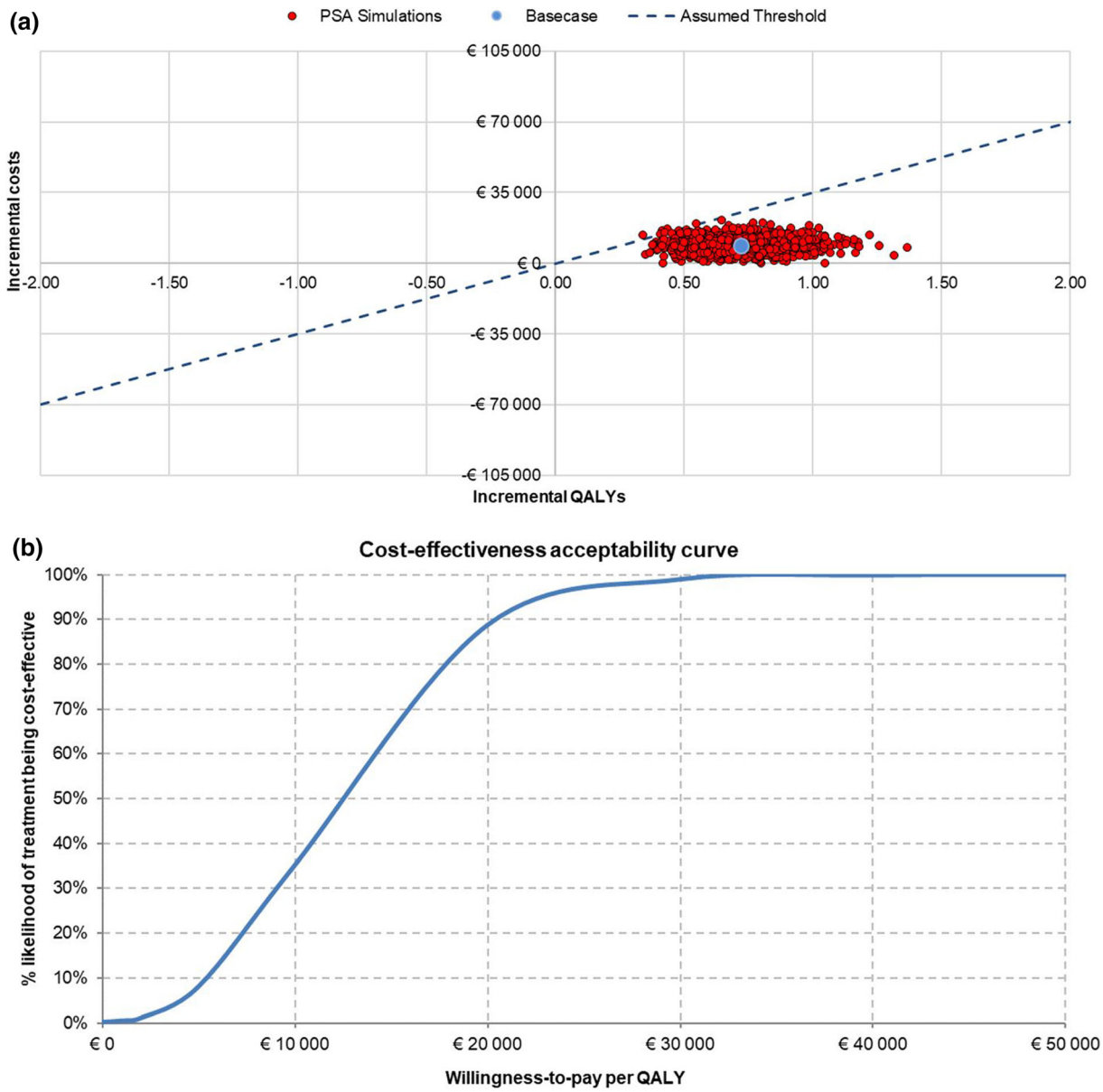

Fig. 3 Probabilistic sensitivity analysis (PSA). **a** Cost-effectiveness scatter plot; 99.6% of cases in the model fell below the €35,000/QALY threshold. **b** Cost-effectiveness acceptability curve. Cost-effectiveness of TAVI with SAPIEN 3 across several willingness-to-pay thresholds: 99% probability of being cost-effective at €30,000/QALY threshold

difference in incidence of this event between treatment arms in PARTNER 3 (4.1% TAVI vs 35.8% SAVR at 30 days [3]). Another difference was that the Canadian model was based on the PARTNER 3 data at 1 year, with the assumption thereafter of similar event ratios. As such, accounting only for differences in model structure and utilities, it is only feasible to compare the incremental QALYs at 1 year between the two models, which were 0.1 and 0.05, respectively, so actually even more conservative in the German model. Similarly, cost-effectiveness analyses using the same model have been run in France, Italy, and Spain, which

Table 4 Scenario analyses results

		Incremental costs (TAVI vs SAVR)	Incremental QALYs (TAVI vs SAVR)	ICER
	Base case	€8664	0.72	€12,037/QALY
Scenario 1	Increase in risk of reintervention with TAVI (RR from PARTNER 2A)	€16,570	0.71	€23,487/QALY
Scenario 2	Increase in risk of stroke to align with PARTNER 3 outcomes	€13,643	0.53	€25,934/QALY
Scenario 3a	Alternative new PPI rates: 13.2% for SAPIEN 3 and 3.3% for SAVR [15]	€9056	0.72	€12,582/QALY
Scenario 3b	Alternative new PPI rates: 6.5% for SAPIEN 3 and 4.0% for SAVR (from PARTNER 3 [3])	€7944	0.72	€11,037/QALY
Scenario 4	Survival data from PARTNER 3 (HR = 0.75)	€10,162	1.48	€6848/QALY
Scenario 5	No survival benefit with TAVI	€7886	0.55	€14,222/QALY
Scenario 6	Use of health-related quality of life data by treatment from PARTNER 3	€8664	0.27	€32,541/QALY
Scenario 7	Valuation from derived VAS model	€8664	0.28	€31,168/QALY
Scenario 8	SAVR procedure costs as a weighted (by the corresponding actual number of cases in G-DRG 2021) average* of 2021 reimbursement values for DRGs F03E F03D and F03C	€6064	0.72	€8425/QALY
Scenario 9a	100% rehab rates for TAVI and SAVR from the literature	€9305	0.72	€12,927/QALY
Scenario 9b	Alternative rehab rates for TAVI from the literature (60.4%) [23]	€10,223	0.72	€14,203/QALY
Scenario 9c	Alternative rehab rates for TAVI from the literature (72.4%) [24]	€10,452	0.72	€14,521/QALY
Scenario 10	Inclusion of adverse event costs within 30 days	€7885	0.72	€10,954/QALY
Scenario 11	Time horizon = 5 years	€7927	0.24	€32,518/QALY
Scenario 12	Time horizon = 10 years	€8111	0.45	€18,161/QALY

Table 4 continued

		Incremental costs (TAVI vs SAVR)	Incremental QALYs (TAVI vs SAVR)	ICER
Scenario 13	Time horizon = 15 years	€8330	0.60	€13,936/QALY
Scenario 14	Time horizon = 20 years	€8543	0.68	€12,482/QALY
Scenario 15	Time horizon = 30 years	€8662	0.72	€12,042/QALY

AE adverse event, *CABG* coronary artery bypass graft, *ICER* incremental cost-effectiveness ratio, *LoS* length of stay, *PCI* percutaneous coronary intervention, *PPI* permanent pacemaker implantation, *QALY* quality-adjusted life years, *rehab* rehabilitation, *RR* relative risk, *SAVR* surgical aortic valve replacement, *TAVI* transcatheter aortic valve implantation
*Table S8 in the supplementary material details the costs breakdown

showed dominance of TAVI in France, and cost-effectiveness of TAVI in Italy and Spain with ICERs of €2989 and €6952, respectively [7–9]. Comparing the total QALYs generated for TAVI with SAPIEN 3 from each study, we observe similar outcomes: 8.44 for France, 8.94 for Italy, 8.66 for Spain, and 8.56 for Germany, with differences being mostly due to utility input differences.

The overall cost-effectiveness of TAVI with SAPIEN 3 in low-risk patients in Germany appears to be driven by lower long-term management costs, particularly those associated with treating AF and disabling stroke; cost savings in these areas were also seen in the studies in France and Italy [7, 8]. Our analysis showed that initial procedure costs for TAVI with SAPIEN 3 were higher than for SAVR in Germany; this was also the case in Italy [8], whereas the initial cost for performing TAVI was lower than for SAVR in France [7].

It is likely that the demand for TAVI will increase in coming years, particularly given the recent change in treatment guidelines that recommend consideration of TAVI in all patients 75 years and older regardless of their surgical risk level [2, 4]. Patients tend to prefer a minimally invasive treatment option with lower risk of complications and/or rehospitalization, faster recovery rate, and quality of life gains. From a societal perspective, there may be additional benefits of TAVI over SAVR that have not yet been accounted for, such as a faster return to normal activities leading to a reduced need for caregivers; further investigation into this may be valuable. German healthcare providers face the pressure of ensuring that limited healthcare resources are used as efficiently as possible. To be sustainable within healthcare budgets, the demand for TAVI must be balanced with a favorable overall cost. Despite the initial procedure being more costly than SAVR, our analysis supports TAVI with SAPIEN 3 as a cost-effective treatment option in the low surgical-risk population, driven by lower long-term management costs.

As far as we are aware, this is the first cost-effectiveness analysis of TAVI in Germany. As such, this analysis may also provide useful insights into the potential cost-effectiveness of TAVI with SAPIEN 3 in patients with intermediate or high risk of surgical mortality in Germany. By demonstrating cost-effectiveness in the population most likely to have favorable outcomes with SAVR (i.e., low-risk patients), it is plausible to speculate that TAVI with SAPIEN 3 may be even more cost-effective in patients with intermediate or high risk of surgical mortality, as the anticipated treatment benefits of TAVI versus SAVR can be expected to increase.

Finally, this lifetime horizon cost-effectiveness analysis may be useful for policy makers in Germany when considering the benefits of TAVI over SAVR from an overall societal-medical perspective. Our analysis provides a comprehensive and long-term overview of cost-effectiveness, which may be more helpful for informing policy decisions on the management of sSAS than distinct reports on procedure costs, rehabilitation costs, etc.

Limitations

There are a number of limitations to this study. A first limitation is that the conclusions cannot be generalized to the overall population with aortic stenosis as patients with bicuspid aortic valves or other unsuitable anatomical features that augmented the likelihood of complications post intervention were excluded from PARTNER 3. Furthermore, caution is required when attempting to generalize any findings from this model to populations outside Germany.

Other limitations pertain to those inherent in any cost-effectiveness analysis and include assumptions made in the presence of "best fit" data or paucity of data, extrapolations modelled for time horizons beyond the scope of existing input data, and potential for under- and over-estimations owing to differences in healthcare systems or by the intervention and treatment selection criteria within a specific system. In the current model, assumptions for hospitalization data were based on PARTNER 3 outcomes at 1 and 2 years, with a simplifying assumption that this rate remained constant over the time horizon of the model after 2 years. The reintervention rate was also assumed to remain constant after 22 years, on the assumption that only a small proportion of patients would still be alive after this time, with limited need for reintervention. However, given that there remains some uncertainty about the longer-term durability of the TAVI device, it is possible that reintervention rates for younger patients could be higher than modelled. The considerable uncertainty about long-term side effects and likely need for subsequent TAVI in younger patients may require modelling of another procedure to explore this. To avoid a potential risk of double counting with the health state utilities being applied to patients in the "treated AF" and "disabling stroke" states, disutility data were not included for intercurrent events. Furthermore, there were few cases of the short-term AEs and they were assumed to be treated successfully within 30 days while not incurring any disutility. This assumption was considered conservative as, apart from pacemaker complications, rates of intercurrent events are generally lower for TAVI with SAPIEN 3 compared with SAVR. Also, the literature data used to calculate the utility decrements for AF and disabling stroke could imply a limitation. The two studies used, though being the best available option and methodologically sound, were either based on data that differ from typically used German utility data or were based on Austrian patients. Finally, it is worth noting that the cost data from the DRG matrix is an average value. This is positive from a general methodological perspective. However, it also implies that possible differences in in-hospital care and resultant costs for low-risk patients versus high-risk patients may not be visible.

CONCLUSIONS

Compared with SAVR, TAVI with SAPIEN 3 is associated with clinical benefits in patients with sSAS at low risk of surgical mortality, based on data from the pivotal, randomized PARTNER 3 trial. Furthermore, TAVI appears to present a potentially cost-effective option over SAVR for this patient population in Germany, with an estimated ICER value of €12,037/QALY. The findings of this cost-effectiveness analysis in conjunction with PARTNER 3 data can inform policy makers and healthcare budget holders in Germany in their decision-making to optimize management of patients with sSAS.

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