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Cost-effectiveness of transcatheter aortic valve implantation versus surgical aortic valve replacement in low surgical risk aortic stenosis patients

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ABSTRACT

Background: The PARTNER 3 trial demonstrated clinical benefits of transcatheter aortic valve implantation (TAVI) with the SAPIEN 3 device, over surgical aortic valve replacement (SAVR) in patients with severe symptomatic aortic stenosis (sSAS) at low risk of surgical mortality. Using PARTNER 3 outcomes and Italy-specific costs data, this cost-utility analysis from the perspective of the Italian National Health System aimed to determine the cost-effectiveness of SAPIEN 3 TAVI versus SAVR in low risk sSAS patients in Italy.

Methods: A two-stage cost-utility model was developed to estimate changes in both direct healthcare costs and health-related quality of life using TAVI with SAPIEN 3 compared with SAVR. Early adverse events associated with TAVI were captured utilising the PARTNER 3 dataset. These data fed into a Markov model that captured longer-term outcomes of patients, following TAVI or SAVR intervention.

Results: Analysis findings estimated that TAVI with SAPIEN 3 offers benefits over SAVR in terms of increased quality-adjusted life years (QALYs) with only a small increase in costs, representing an incremental cost-effectiveness ratio/QALY gained of €2989 per patient. The results were robust, with TAVI with SAPIEN 3 remaining cost-effective across several scenarios and in probabilistic sensitivity analyses.

Conclusions: This model demonstrated that TAVI with SAPIEN 3 is likely to be cost effective compared with SAVR for the treatment of patients with sSAS who are at low risk of surgical mortality. These findings can inform policy makers to facilitate policy development in Italy on intervention selection for this patient population.

1. Introduction

Aortic valve replacement options for severe symptomatic aortic stenosis (sSAS) treatment include surgery (surgical aortic valve replacement; SAVR) or transcatheter aortic valve implantation (TAVI). Introduced initially as a treatment option for sSAS in patients considered inoperable or at high risk of surgical mortality [1], TAVI is now considered a viable option also for patients at intermediate or low risk of surgical mortality [2–7]. The PARTNER 3 study, a multicentre randomised controlled trial in sSAS patients considered at low risk of surgical mortality, showed that, compared with SAVR, TAVI (with SAPIEN 3 valve) reduced the composite outcome of death, stroke or rehospitalisation after 1 and 2 years [5,8]. Furthermore, the SAPIEN 3 device appeared to demonstrate efficacy benefits over earlier versions of the device used in the PARTNER (SAPIEN valve) and PARTNER 2 trials (SAPIEN-XT valve) [4,9,10].

As a result of recent data, the American College of Cardiology/American Heart Association guidelines have been updated and now

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[1] These authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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recommend the use of transfemoral TAVI for all sSAS patients, regardless of risk score and stratification by age, life expectancy and patient's anatomy [11]. The European Society of Cardiology (ESC)/European Association for Cardio-Thoracic Surgery (EACTS) guidelines also now state that TAVI can be considered in all sSAS patients following careful evaluation of individual clinical, anatomical and procedural characteristics by the Heart Team [12]. While SAVR remains the recommended treatment in younger (<75 years) patients considered low risk for surgery, TAVI can now be considered as an option in all other patients with sSAS and is the treatment of choice in older (≥75 years) patients [12]. In Italy, there are no national guidelines on the management of valvular heart disease; however, the Italian Society of Interventional Cardiology (SICI-GISE) has issued position papers that provide guidance to assess the potential of institutions and operators to initiate and maintain an efficient TAVI programme [13]. They have also provided a roadmap to attaining homogeneous nationwide access to cardiovascular interventions, including TAVI, as recommended by major internal guidelines [14]. According to the national data registry provided by SICI-GISE, the number of TAVI procedures performed in Italy has increased steadily since its introduction in 2007/2008, with a steeper rise between 2016 and 2019 (from 4592 to 8225 procedures) [14]. However, 2020 saw a decline with only 7592 TAVI procedures [15]. Furthermore, there is substantial variation across regions in the number of TAVI procedures performed. The highest penetration was 176 TAVI per million inhabitants in the Veneto region [15], which is less than the estimated value of 263 TAVI per million inhabitants [16]. This lower-than-expected number is probably due to financial and organisational issues [14]. Furthermore, the recent COVID-19 pandemic has highlighted the importance of optimising resources and limiting the length of hospitalisation stay to sustain healthcare systems whilst maintaining high-quality patient management.

Given the increased clarity on the clinical benefits of TAVI in patients with sSAS and the move towards use in lower risk patients, it is important to evaluate the associated implications for policymakers and healthcare resource allocation. Specifically, it is important to evaluate the cost-effectiveness of this approach and whether TAVI presents a potential solution to treating sSAS with a relatively lower requirement for hospital resources compared with SAVR. This article thereby reviews the data from the PARTNER 3 trial alongside economic data from Italy to assess the cost-effectiveness of TAVI versus SAVR in sSAS patients at low risk of surgical mortality. In doing so, this study aims to address the lack of evidence on cost-effectiveness of TAVI with SAPIEN 3 in the low-surgical-risk population of sSAS patients in Italy. This evidence would be timely as, compared with SAVR, transfemoral TAVI with SAPIEN 3 has been shown to be cost-effective in the high-risk population and even more favourable in the intermediate-risk population in Italy [17].

2. Methods

A cost-utility analysis was developed to estimate changes in both direct healthcare costs and health-related quality of life with use of TAVI with SAPIEN 3 compared with SAVR in sSAS patients at low risk of surgical mortality (STS < 4%) from the perspective of Italian National Health System. Costs were measured in 2020 Euros and benefits measured in quality-adjusted life years (QALYs) gained. The incremental cost-effectiveness ratio was calculated by dividing the difference in costs between the two treatment groups by differences in QALYs. In Italy, interventions costing up to €30,000 per QALY gained are generally considered cost effective [18]. Thus, an incremental cost-effectiveness ratio of less than €30,000 per QALY gained was used as the willingness-to-pay (WTP) threshold of acceptable cost-effectiveness [18].

2.1. Model structure

Details of the two-stage model structure have been described previously [19] and the model was considered appropriate by all authors for the Italian context based on their clinical and health-economic expertise. Briefly, early adverse events (AEs) linked to the TAVI procedure were first captured utilising the 30-days AEs dataset from the PARTNER 3 trial [5] in a decision tree (Fig. 1a). Subsequently, these data were fed into a Markov model that included four distinct health states ('alive and well', 'treated atrial fibrillation [treated AF]', 'disabling stroke', and 'dead') to capture longer-term outcomes of patients, post TAVI or SAVR intervention (Fig. 1b).

One of the co-authors adapted the model for Italy context and costings and the adaptation was further validated by all the co-authors based on their expertise. Given that sSAS requires life-long valve replacement, a lifetime horizon of 50 years was selected for the cost-utility analysis with a discounting factor per year of 3% applied for both future costs and benefits following Italian pharmaceutical guidelines [18]. This time horizon was chosen to reflect all potential consequences to individuals with sSAS over their lifetime.

Health-related quality of life was included using QALYs. These were measured using EQ-5D for the different health states in the model, with utility decrements taken from a published study [20] and adjusted for age and population norms [21].

2.2. Model inputs

2.2.1. Trial overview

The model was informed by the PARTNER 3 trial population, which excluded patients with clinical frailty, bicuspid aortic valves or other anatomical features that increased the risk of complications associated with either surgery or TAVI. In PARTNER 3, 503 patients were randomised to TAVI and 497 to SAVR, with the 'as treated' groups comprising 496 and 454 patients, respectively [5]. The primary endpoint was a composite of death from any cause, stroke, or rehospitalisation at 1 year after the procedure.

2.2.2. Clinical events

Monthly transition probabilities between health states of the Markov model were estimated. For the transition from 'alive and well' to 'treated AF', data from PARTNER 3 on new-onset treated AF between 30 days and 1 year were used [5] (Table A1, Appendix). Other literature sources provided a more realistic estimate of the remaining two transitions due to too few of these events in PARTNER 3: the transition from 'alive and well' to 'disabling stroke' was informed by Stroke Alliance For Europe (SAFE) data from 2017 on burden of stroke in Italy [22], and 'treated AF' to 'disabling stroke' was informed by a systematic review and meta-analysis involving 104 eligible cohort studies with more than 9.5 million participants [23] (Table A1, Appendix). Myocardial infarction, transient ischaemic attack and severe or life-threatening bleeding were captured as intercurrent events between 30 days and 1 year from the PARTNER trial [5].

Other relevant events, such as rehospitalisation rates (using data from PARTNER 3 [5]) and reintervention rates due to valve deterioration (using data up to 2 years from PARTNER 3 [5,8] and from 3 years onwards from a study on 20-year outcomes of pericardial aortic tissue valve bioprosthesis [24]) were also considered (Table A1, Appendix). In the base case, the same reintervention rate was used for both the TAVI and SAVR arms; this simplifying assumption allowed best use of the available data. In Scenario 1, higher reintervention rates were assumed for TAVI than SAVR (based on data from PARTNER 2 at 5 years [6]), while in Scenario 2, an increased risk of stroke was assumed, to align with PARTNER 3 outcomes.

Two options were considered for extrapolation of survival. Option 1: transition probabilities were estimated for each health state using general population mortality data and literature reports of hazard ratio (HR) for death with AF (HR = 1.46) [23] and for death with disabling stroke (HR = 2.05) [25]; option 2: parametric survival analysis based on Kaplan-Meier data from the PARTNER 3 study was undertaken, with a

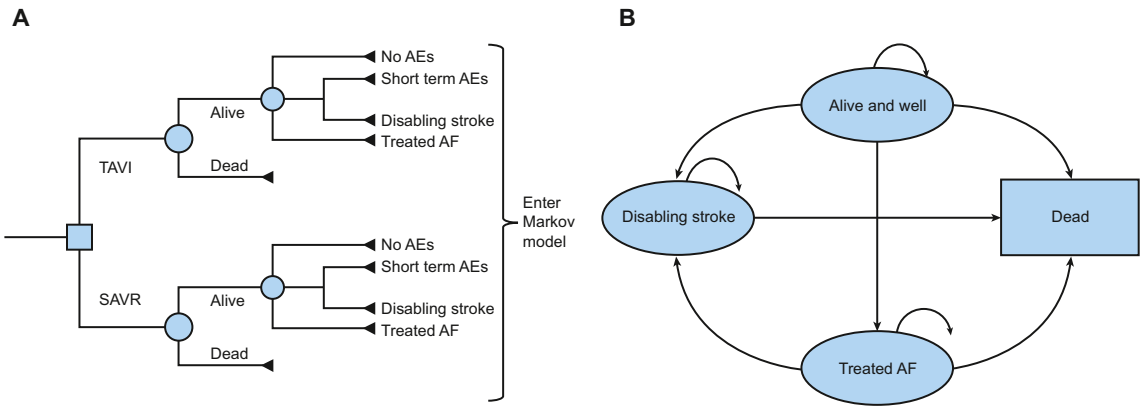

Fig. 1. The cost-effectiveness model had two stages: *(a)* early AEs from the PARTNER 3 trial were captured in a decision tree, which fed into *(b)* a Markov model that captured longer-term outcomes of patients, with four distinct health states[a].
Reproduced from Gilard M, et al. *Value Health* 2021; doi:https://doi.org/10.1016/j.jval.2021.10.003 [19] under the terms of the creative commons license (Creative Commons Attribution License (CC BY)).
[a] 'Alive and well'=patients have undergone the procedure and survived with only short-term or no AEs; patients in this health state can transition to 'disabling stroke', 'AF' or 'dead' at any point during the model time horizon. 'Treated AF' = patients have undergone the procedure and survived but developed AF requiring specific treatment; this can either occur within the first 30 days or during the rest of the time horizon of the model, and patients in this health state can transition to 'disabling stroke' or 'dead' at any point during the model time horizon. 'Disabling stroke' = patients have undergone the procedure and survived but had a disabling stroke; this can either occur within the first 30 days or during the rest of the time horizon of the model, and patients in this health state can only transition into the 'dead' state at any point during the model time horizon. 'Dead' = this is the absorbing state in the model: all patients in the model are at risk of dying due to general all-cause mortality; patients with treated AF and stroke are at an increased risk of dying.
AE, adverse event; AF, atrial fibrillation; SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation.

choice of three parametric distributions applied (Weibull, exponential, Gompertz). The survival estimates were adjusted using Italian general population survival to ensure that people in the model did not live longer than expected for the general population. It is worth noting, however, that parametric survival analysis produced clinically implausible estimates in the model due to a low death rate in the trial (and therefore immature survival data with which to extrapolate). Thus, in the base case, all-cause mortality estimates were determined using the first option (using general population mortality risk, with relative risks applied from published literature corresponding to each health state [Table A2, Appendix]). Option 2 (parametric survival analysis) was explored in scenario analysis using alternative HRs (Scenario 3). An additional Scenario 4 assumed no survival benefits with TAVI.

2.2.3. Costs

These were based on costing information from Italian Diagnostic-Related Groups (DRGs) and regional tariffs. In the base case, costs associated with procedures, rehabilitation and complications were estimated from the DRGs and regional tariffs (all costs actualised to 2020) (Table A3, Appendix). Scenarios for alternative procedural cost estimates included using data from the Italian administrative database 2016–2017 (Scenario 6) and using real-world hospital length-of-stay data for low-risk TAVI patients in 2019 from two co-authors' hospitals (Scenario 7) (Table A3, Appendix). Furthermore, a Scenario 8 was included to account for AEs costs within 30 days.

2.2.4. Utilities

Utility values used age-adjusted population utility norms. An EQ-5D-3L index value (time trade-off [TTO] value set) was used for the age adjusted population utility norms [21]. Utility decrements were estimated using two approaches, to account for there being too few events in the PARTNER 3 trial. Option 1, the preferred approach based on realistic estimates from the literature, estimated utility decrements by health states (AF and disabling stroke) using data reported by Pradelli et al. [20] on the pharmacoeconomic assessment of apixaban versus standard-of-care for stroke prevention in Italian patients with AF. Option 2 estimated age-adjusted utility decrement by treatment arm from PARTNER 3 (individually extracted data at baseline, 30 days, 6 months and 1 year, which was then converted to Italian Health Utilities based on Scalone et al. [26]). The base case applied the estimates determined from the literature, while Scenario 5 applied utility decrements estimated by option 2.

2.3. Sensitivity analyses

To evaluate uncertainty, 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 (see Table A4, Appendix). Overall parameter uncertainty was addressed by a probabilistic sensitivity analysis (Table A5, Appendix). 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. Several scenario analyses were conducted to explore the impact of major structural assumptions, as described in Table A6 (Appendix). All analyses were performed using Microsoft Excel (Microsoft Corporation, Redmond, Washington, USA).

3. Results

3.1. Base case

Compared with SAVR, TAVI with SAPIEN 3 is estimated to offer meaningful benefits by increasing QALYs (incremental improvement of 1.11 per patient) at a slightly increased cost (+€3317 per patient) over a lifetime horizon. This represents an incremental cost-effectiveness ratio (ICER) of €2989 per QALY gained. This is lower than the typically used Italian willingness-to-pay (WTP) threshold value of €30,000 per QALY gained [18] (Table 1). Closer examination of the breakdown of costs for TAVI versus SAVR revealed that although initial procedural costs in the model were higher with TAVI, costs related to 'disabling stroke' and 'treated AF' were somewhat lower (Table 1 and Fig. A1, Appendix).

3.2. Deterministic sensitivity analyses

Univariate sensitivity analyses demonstrate that TAVI with SAPIEN 3

Table 1
Base case results with acute and lifetime costs.

Summary results	TAVI with SAPIEN 3	SAVR	Incremental
Cost per patient	€ **42,587**	€ **39,269**	€ **3317**
Life year gained (undiscounted)	13.58	12.76	0.82
Median survival (years)	16.00	14.08	1.92
QALYs per patient	**8.94**	**7.83**	**1.11**
Incremental cost effectiveness ratio (ICER)			€ **2989**
Incremental net monetary benefit (NMB)			€ 29,974
Incremental net health benefit (NHB)			1.00
Acute phase cost (first hospitalisation and rehabilitation)			
Index hospitalisation	€ 30,634	€ 24,675	€ 5959
Rehabilitation	€ 1160	€ 2755	−€ 1594
Acute phase costs	€ **31,794**	€ **27,430**	€ 4365
Additional costs at 1 year			
MI	€ 197	€ 129	€ 68
Costs of pacemaker complications	€ 40	€ 24	€ 16
Costs of hospitalisations	€ 471	€ 703	−€ 232
Reintervention costs	€ 147	€ 143	€ 4
Alive & well health state costs	€ 666	€ 446	€ 220
Treated AF health state costs	€ 37	€ 285	−€ 249
Disabling stroke costs	€ 6	€ 74	−€ 68
Death costs	€ 0	€ 0	€ 0
Total costs at 1 year	€ **33,357**	€ **29,234**	€ 4123
Additional lifetime costs			
Costs of pacemaker complications	€ 435	€ 252	€ 183
Costs of hospitalisations	€ 806	€ 761	€ 45
Reintervention costs	€ 5089	€ 4382	€ 707
Alive & well health state costs	€ 1960	€ 1234	€ 727
Treated AF health state costs	€ 713	€ 2945	−€ 2233
Disabling stroke costs	€ 226	€ 461	−€ 235
Additional Lifetime Costs	€ 9229	€ 10,035	−€ 806
Total Lifetime Costs	€ 42,587	€ 39,269	€ 3317

remains cost-effective regardless of plausible changes in individual model parameters (Fig. 2, Tornado diagram displaying the 20 parameters with greatest influence on the model). The model was most sensitive to procedure costs of TAVI with SAPIEN 3 and the starting age of patients entering the model.

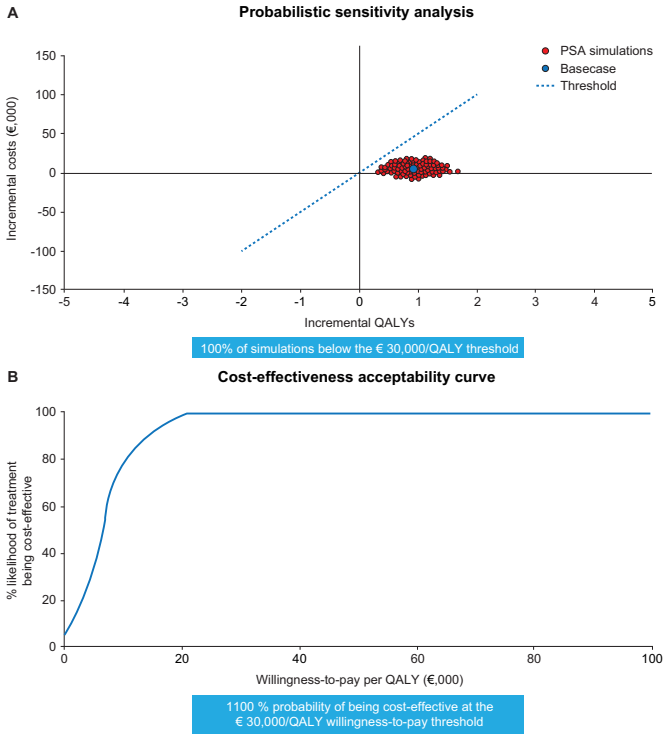

Fig. 3. Probabilistic sensitivity analysis. *(a)* Cost-effectiveness scatter plot. *(b)* Cost-effectiveness acceptability curve.

3.3. Probabilistic sensitivity analyses

The findings of the probabilistic sensitivity analyses confirm the results of the base case analysis. At the conventional WTP threshold of €30,000/QALY or above, TAVI with SAPIEN 3 remains cost-effective compared with SAVR in 100% of simulations (Fig. 3a). In addition, the cost-effectiveness acceptability curve (Fig. 3b) indicates that TAVI with SAPIEN 3 still has a high probability (99%) of being cost-effective at a lower threshold of €20,000/QALY.

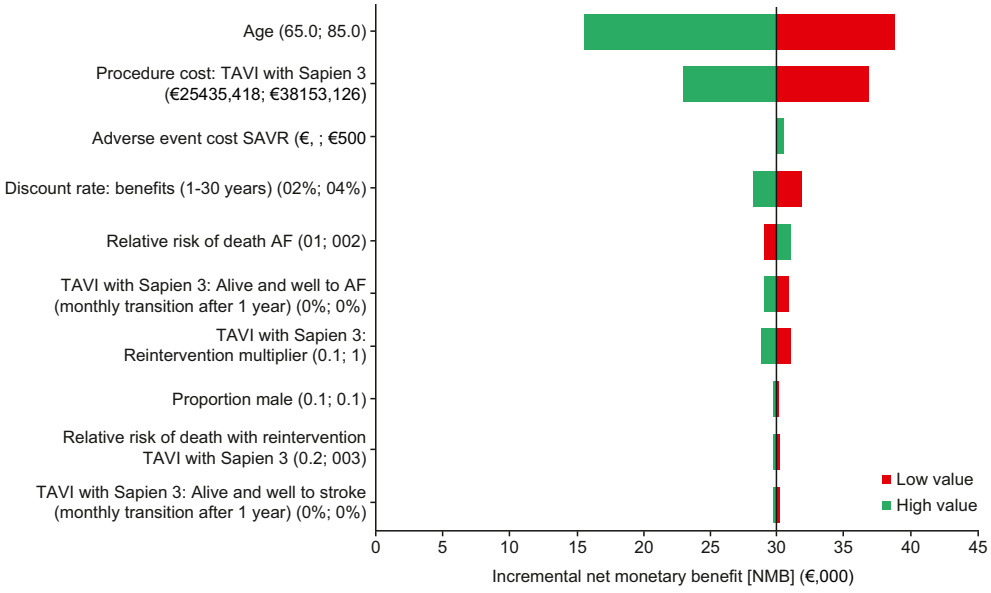

Fig. 2. Tornado diagram showing the 20 parameters with greatest influence on the model (deterministic sensitivity analysis).

3.4. Scenario analysis

A series of scenario analyses were conducted to determine the robustness of the findings, by assessing whether changing various assumptions altered the results of the model. TAVI with SAPIEN 3 remained cost-effective regardless of the time horizon (assessed for various time lengths up to 30 years). TAVI with SAPIEN 3 also remained more cost-effective than SAVR in other scenarios, despite modelling various challenging assumptions (full list of scenarios shown in Table A6, Appendix):

- o A more aggressive reintervention rate for TAVI (based on PARTNER 2A trial data at 5 years)
- o An increased rate of stroke with TAVI after 1 and 2 years
- o Using PARTNER 3 trial data for survival at 2 years (HR = 0.75), adjusted to the Italian general population mortality rate
- o No survival benefit (HR = 1)

4. Discussion

This analysis suggests that TAVI using the SAPIEN 3 device may be a cost-effective valve replacement option for sSAS patients at a low risk of surgical mortality, treated in the contemporary Italian setting. TAVI with SAPIEN 3 showed an improvement in QALYs (+1.11) associated with slightly increased costs (+€3317) per patient compared with SAVR. The ICER indicates TAVI with SAPIEN 3 as a highly cost-effective intervention (ICER/QALY €2989) when considered in relation to the Italian healthcare system WTP threshold of €30,000/QALY. The ICER benefits for TAVI with SAPIEN 3 remained robust across a range of input modifications and challenging scenarios. Our findings are consistent with cost-effectiveness analyses of TAVI with SAPIEN 3 versus SAVR in other countries using the same model structure [19]. For example, TAVI with SAPIEN 3 was shown to be dominant in France (cost saving of €12,742 and generating +0.89 QALYs per patient). Reassurance on the robustness of our findings was further achieved from various sensitivity analyses.

Our analyses revealed that, while the initial procedure costs for TAVI with SAPIEN 3 are higher than SAVR in Italy, the overall cost-effectiveness of TAVI is driven by lower long-term management costs, particularly those associated with treated AF and disabling stroke. In our model, transitions to 'treated AF' and 'disabling stroke' states were assumed to remain constant over the time horizon from 2 years onwards, regardless of time in the model or patient age. Given that stroke risk increases with age [27], this assumption understates transitions between the disease states in later years. For TAVI with SAPIEN 3 outcomes, this represents a conservative assumption because it is anticipated that stroke risk would be higher in the SAVR arm due to increased incidence of treated AF—the incidence of new-onset AF is 31–64% after SAVR and 4–32% after TAVI [28]; this would, therefore, likely increase the incremental difference in stroke incidence between treatment arms.

Our findings are supported by other publications reporting cost-effectiveness of TAVI versus SAVR in patients at low risk of surgical mortality. An analysis conducted from a Canadian third-party payer perspective used data from the PARTNER 3 and Evolut LR trials to estimate the cost-effectiveness of TAVI with balloon-expandable and self-expandable devices compared with SAVR, and reported an ICER/QALY of Ca$27,196 and Ca$59,641, respectively [29]. The main difference between the Canadian model and our model was their choice of '≥moderate paravalvular leak' rather than 'AF' as a health state. Also, costs linked to AF and rehabilitation were not factored in this Canadian analysis. A Markov model-based Australian cost-effectiveness study that used data from PARTNER 3 and Evolut LR showed economic dominance over SAVR for TAVI with Evolut (self-expandable device) and an ICER of $3521/QALY gained for TAVI with SAPIEN 3 [30]. Other published analyses that have shown TAVI to be cost-effective versus SAVR in low-risk patients include an Irish cost-utility analysis in patients ≥70 years (TAVI was less costly and delivered more QALY) [31], and Norwegian and French Health Technology Assessments (both showed dominance of TAVI over SAVR) [32,33]. The positive French Health Technology Assessment was informed by a cost-utility analysis that used the same Markov model structure with PARTNER 3 data [19] as used here.

Our analysis is important from several perspectives. Patients prefer a minimally invasive treatment option with lower risk of complications and/or rehospitalisation along with improved recovery rate and quality of life gains. For the Italian healthcare provider, efficient use of limited healthcare resources is preferable. With lower risk of infection, fewer complications and shorter hospital stays, TAVI with SAPIEN 3 offers a reduced impact on organisational aspects and resources (e.g., lower general anaesthesia) compared with SAVR whilst also improving patients' quality of life. Our analysis is valuable for decision making specifically considering the recent ESC/EACTS guidelines that recommend TAVI in all patients >75 years regardless of the degree of surgical risk [12]. Also, Italy has the largest proportion of elderly (≥65 years) citizens in Europe [34]; consequently, an increase in demand for TAVI is to be expected in Italy in the near future. This increased demand is likely to be seen among elderly patients with a low surgical risk profile. To sustainably meet the demand, TAVI probably needs to prove favourable in this population from a health-economics perspective. Our cost-effectiveness analysis provides a first step in that direction.

Finally, policy makers may consider the benefits of TAVI over SAVR in an overall societal–medical perspective; instead of considering procedure costs, rehabilitation costs and budget separately. Our findings may help to inform a holistic consideration when making policy decisions for the management of sSAS. While further investigations into the societal impact/benefit of TAVI versus SAVR may be warranted, the results of this analysis suggest that TAVI with SAPIEN 3 may be clinically beneficial and cost-effective for sSAS patients at low risk of surgical mortality in Italy.

4.1. Limitations

This study has certain limitations. First, there are inherent limitations of a cost-effectiveness analysis owing to: 1) assumptions made in the presence of 'best fit' data or paucity of data; 2) extrapolations into time horizons modelled beyond the scope of existing input data; 3) under- and over-estimations potentially caused by differences in healthcare systems, or by the criteria for intervention and treatment selection within a specific system. In this model, hospitalisation data were based on 1- and 2-year data from the PARTNER 3 trial. A simplifying assumption was used whereby this rate remained constant over the time horizon of the model after 2 years; the impact of this assumption is unknown because individuals in both treatment arms in the model are at risk of hospitalisation. Furthermore, due to a lack of long-term data, the rate of reinterventions was assumed to remain constant after 22 years; the impact of this assumption on modelled outcomes was considered to be minimal based on an expectation that only around 11% of patients would still be alive in the model after this time point, with limited need for reintervention. Nevertheless, uncertainty regarding the longer-term durability of the TAVI device and consequent reintervention rates in younger patients cannot be disregarded. Estimates based on historical studies suggest a structural valve deterioration rate of 7% at 5 years, although this can be expected to improve with improvements in TAVI valve construction and deployment techniques [35]. Finally, disutilities were not included for any intercurrent events because this risks them being counted twice with the health state utilities being applied to patients in the 'treated AF' and 'disabling stroke' states. This was a conservative assumption because, apart from pacemaker complications, rates of intercurrent events are generally lower for TAVI with SAPIEN 3 compared with SAVR [5].

A second limitation pertains to the generalisability of the conclusions. The results of this study cannot be generalised to the overall population with aortic stenosis because patients with some high-risk

features, such as annular calcification and unfavourable coronary anatomy, were excluded from the PARTNER 3 trial. Equal care also needs to be taken when generalising any findings from this model to populations outside of Italy and to other transcatheter heart valves than SAPIEN 3.

5. Conclusions

Data from PARTNER 3 suggested that the use of TAVI with SAPIEN 3 is likely to represent a more favourable clinical option than SAVR in sSAS patients at low risk of surgical mortality. The results of this cost-effectiveness analysis indicate that, in Italy, TAVI with SAPIEN 3 could provide a compelling value-based, cost-effective option over SAVR for this patient population, with an estimated ICER/QALY value well below the typical national threshold. The model seemed robust, with uncertainty addressed through a range of scenarios and sensitivity analyses. Thereby, results from this study can support Italian policy makers and healthcare budget holders in optimising management of patients with sSAS.

Funding/Support

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Data availability statement

All input data used in the model is reported in the manuscript and the appendix. Only exception is costs data used in two scenario analyses that was provided by three co-authors and can be shared on reasonable request to the corresponding author.

Declaration of Competing Interest

Francesco Saverio Mennini reports advisor/speaker/research grants from Abbvie, MSD, Gilead, BMS and Edwards Lifesciences. Francesco Meucci reports speech and consultant fees from Medtronic, Edwards Lifesciences and Boston Scientific. Gabriele Pesarini reports speech and consultant fees for Edwards Lifesciences and Boston Scientific. Pietro Vandoni reports fees for participation on Advisory Boards for Edwards Lifesciences. Maddalena Lettino reports receiving fees for lectures, manuscript writings or educational events by BMS, Pfizer, Sanofi, Boehringer, Daiichi Sankyo, and Edwards Lifesciences; participation on Advisory Boards for Boehringer and Edwards Lifesciences. Archita Sarmah reports employee and stock options holder of Edwards Lifesciences. Judith Shore reports consultancy fees paid to the employer for development of the economic model.Michelle Green reports consultancy fees paid to the employer for development of the economic model. Stefano Giardina reports employee and stock options holder of Edwards Lifesciences.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2022.03.034.

References

[1] A. Cribier, Development of transcatheter aortic valve implantation (TAVI): a 20-year odyssey, Arch. Cardiovasc. Dis. 105 (2012) 146–152.
[2] S.J. Baron, S.V. Arnold, K. Wang, E.A. Magnuson, K. Chinnakondepali, R. Makkar, H.C. Herrmann, S. Kodali, V.H. Thourani, S. Kapadia, L. Svensson, D.L. Brown, M. J. Mack, C.R. Smith, M.B. Leon, D.J. Cohen, PARTNER 2 investigators, health status benefits of transcatheter vs surgical aortic valve replacement in patients with severe aortic stenosis at intermediate surgical risk: results from the PARTNER 2 randomized clinical trial, J. Am. Med. Assoc. Cardiol. 2 (2017) 837–845.
[3] A. ElGuindy, PARTNER 2A & SAPIEN 3: TAVI for intermediate risk patients, Glob. Cardiol. Sci. Pract. 4 (2016), e201633.
[4] M.B. Leon, C.R. Smith, M.J. Mack, R.R. Makkar, L.G. Svensson, S.K. Kodali, V. H. Thourani, E.M. Tuzcu, D.C. Miller, H.C. Herrmann, D. Doshi, D.J. Cohen, A. D. Pichard, S. Kapadia, T. Dewey, V. Babaliaros, W.Y. Szeto, M.R. Williams, D. Kereiakes, A. Zajarias, K.L. Greason, B.K. Whisenant, R.W. Hodson, J.W. Moses, A. Trento, D.L. Brown, W.F. Fearon, P. Pibarot, R.T. Hahn, W.A. Jaber, W. N. Anderson, M.C. Alu, J.G. Webb, PARTNER 2 Investigators, Transcatheter or surgical aortic-valve replacement in intermediate-risk patients, N. Engl. J. Med. 374 (2016) 1609–1620.
[5] M.J. Mack, M.B. Leon, V.H. Thourani VH, R.R. Makkar, S.K. Kodali, M. Russo, S. R. Kapadia, S.C. Malaisrie, D.J. Cohen, P. Pibarot, J. Leipsic, R.T. Hahn, P. Blanke, M.R. Williams, J.M. McCabe, D.L. Brown, V. Babaliaros, S. Goldman, W.Y. Szeto, P. Genereux, A. Pershad, S.J. Pocock, M.C. Alu, J.G. Webb, C.R. Smith, PARTNER 3 Investigators, Transcatheter aortic-valve replacement with a balloon-expandable valve in low-risk patients, N. Engl. J. Med. 380 (2019) 1695–1705.
[6] R.R. Makkar, V.H. Thourani, M.J. Mack, S.K. Kodali, S. Kapadia, J.G. Webb, S. H. Yoon, A. Trento, L.G. Svensson, H.C. Herrmann, W.Y. Szeto, D.C. Miller, L. Satler, D.J. Cohen, T.M. Dewey, V. Babaliaros, M.R. Williams, D.J. Kereiakes, A. Zajarias, K.L. Greason, B.K. Whisenant, R.W. Hodson, D.L. Brown, W.F. Fearon, M.J. Russo, P. Pibarot, R.T. Hahn, W.A. Jaber, E. Rogers, K. Xu, J. Wheeler, M. C. Alu, C.R. Smith, M.B. Leon, PARTNER 2 Investigators, Five-year outcomes of transcatheter or surgical aortic-valve replacement, N. Engl. J. Med. 382 (2020) 799–809.
[7] M.J. Reardon, N.M. Van Mieghem, J.J. Popma, N.S. Kleiman, L. Søndergaard, M. Mumtaz, D.H. Adams, G.M. Deeb, B. Maini, H. Gada, S. Chetcuti, T. Gleason, J. Heiser, R. Lange, W. Merhi, J.K. Oh, P.S. Olsen, N. Piazza, M. Williams, S. Windecker, S.J. Yakubov, E. Grube, R. Makkar, J.S. Lee, J. Conte, E. Vang, H. Nguyen, Y. Chang, A.S. Mugglin, P.W. Serruys, A.P. Kappetein, SURTAVI Investigators, Surgical or transcatheter aortic-valve replacement in intermediate-risk patients, N. Engl. J. Med. 376 (2017) 1321–1331.
[8] M.B. Leon, M.J. Mack, R.T. Hahn, V.H. Thourani, R. Makkar, S.K. Kodali, M.C. Alu, M.V. Madhavan, K.H. Chau, M. Russo, S.R. Kapadia, S.C. Malaisrie, D.J. Cohen, P. Blanke, J.A. Leipsic, M.R. Williams, J.M. McCabe, D.L. Brown, V. Babaliaros, S. Goldman, H.C. Herrmann, W.Y. Szeto, P. Genereux, A. Pershad, M. Lu, J. G. Webb, C.R. Smith, P. Pibarot, PARTNER 3 Investigators, Outcomes 2 years after transcatheter aortic valve replacement in patients at low surgical risk, J. Am. Coll. Cardiol. 77 (2021) 1149–1161.
[9] M.B. Leon, C.R. Smith, M. Mack, D.C. Miller, J.W. Moses, L.G. Svensson, E. M. Tuzcu, J.G. Webb, G.P. Fontana, R.R. Makkar, D.L. Brown, P.C. Block, R. A. Guyton, A.D. Pichard, J.E. Bavaria, H.C. Herrmann, P.S. Douglas, J.L. Petersen, J.J. Akin, W.N. Anderson, D. Wang, S. Pocock, PARTNER Trial Investigators, Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery, N. Engl. J. Med. 363 (2010) 1597–1607.
[10] C.R. Smith, M.B. Leon, M.J. Mack, D.C. Miller, J.W. Moses, L.G. Svensson, E. M. Tuzcu, J.G. Webb, G.P. Fontana, R.R. Makkar, M. Williams, T. Dewey, S. Kapadia, V. Babaliaros, V.H. Thourani, P. Corso, A.D. Pichard, J.E. Bavaria, H. C. Herrmann, J.J. Akin, W.N. Anderson, D. Wang, S.J. Pocock, PARTNER Trial Investigators, Transcatheter versus surgical aortic-valve replacement in high-risk patients, N. Engl. J. Med. 364 (2011) 2187–2198.
[11] C.M. Otto, R.A. Nishimura, R.O. Bonow, B.A. Carabello, J.P. Erwin 3rd, F. Gentile, H. Jneid, E.V. Krieger, M. Mack, C. McLeod, P.T. O'Gara, V.H. Rigolin, T. M. Sundt 3rd, A. Thompson, C. Toly, ACC/AHA guideline for the management of patients with valvular heart disease, J. Am. Coll. Cardiol. 77 (2021) (2020) 450–500.
[12] A. Vahanian, F. Beyersdorf, F. Praz, M. Milojevic, S. Baldus, J. Bauersachs, D. Capodanno, L. Conradi, M. De Bonis, R. De Paulis, V. Delgado, N. Freemantle, M. Gilard, K.H. Haugaa, A. Jeppsson, P. Jüni, L. Pierard, B.D. Prendergast, J. R. Sádaba, C. Tribouilloy, W. Wojakowski, ESC/EACTS Scientific Document Group, ESC/EACTS Guidelines for the management of valvular heart disease, Eur. J. Cardiothorac. Surg. 60 (2021) (2021) 727–800.
[13] G. Tarantini, G. Esposito, G. Musumeci, C. Fraccaro, A. Franzone, B. Castiglioni, A. La Manna, U. Limbruno, A. Marchese, C. Mauro, S. Rigattieri, F. Tarantino, C. Gandolfo, G. Santoro, R. Violini, F. Airoldi, R. Albiero, M. Balbi, G. Baralis, A. Luca Bartorelli, F. Bedogni, A. Benassi, A. Berni, G. Bonzani, A.S. Bortone, G. Braito, C. Briguori, E. Brscic, P. Calabrò, I. Calchera, M.C. Bigazzi, F. Caprioglio, F. Castriota, C. Cernetti, C. Cicala, P. Cioffi, A. Colombo, V. Colombo, G. Contegiacomo, A. Cremonesi, M. D'Amico, M. De Benedictis, A. De Leo, M. Di Biasi, D. Di Girolamo, E. Di Lorenzo, C. Di Mario, M. Dominici, F. Ettori, M. Ferrario, M. Fioranelli, D. Fischetti, G. Gabrielli, A. Giordano, P. Giudice, C. Greco, C. Indolfi, O. Leonzi, C. Lettieri, B. Loi, N. Maddestra, N. Marchionni, C. Marrozzini, M. Medda, B. Missiroli, L. My, J.A. Oreglia, C. Palmieri, P. Pantaleo, S.R. Paparoni, G. Parodi, A.S. Petronio, L. Piatti, E. Piccaluga, C. Pierli, A. Perkan, A. Pitì, A. Poli, A.B. Ramondo, M.A. Reale, B. Reimers, F.L. Ribichini, R. Rosso, S. Saccà, C. Sacra, A. Santarelli, G. Sardella, G. Satullo, F. Scalise, M. Siviglia, L. Spedicato, A. Stabile, C. Tamburino, T.N.M. Tesorio, S. Tolaro, F. Tomai,

C. Trani, R. Valenti, O. Valsecchi, G. Valva, F. Varbella, C. Vigna, L. Vignali, S. Berti, Updated SICI-GISE position paper on institutional and operator requirements for transcatheter aortic valve implantation, G. Ital. Cardiol. 19 (2018) 519–529.
[14] G. Tarantini, G. Musumeci, G. Esposito, C. Mauro, A.G. La Manna, U. Limbruno, F. F. Tarantino, B. Castiglioni, S. Rigattieri, M. Longoni, A. Marchese, G. Masiero, A. Mattesini, S. Berti, F. Saia, A strategic roadmap of the Italian Society of Interventional Cardiology (SICI-GISE) to ensure patient's access to appropriate treatment, G. Ital. Cardiol. 20 (2019) 4s–19s.
[15] GISE Italia, Dati di Attivita, Available from: https://gise.it/notizie/ordinaria/0/0/319, 2020 (Accessed November 2021).
[16] A.P. Durko, R.L. Osnabrugge, N.M. Van Mieghem, M. Milojevic, D. Mylotte, V. T. Nkomo, A.P. Kappetein, Annual number of candidates for transcatheter aortic valve implantation per country: current estimates and future projections, Eur. Heart J. 39 (2018) 2635–2642.
[17] V. Lorenzoni, G. Barbieri, F. Saia, F. Meucci, G.L. Martinelli, A.G. Cerillo, S. Berti, P. Candolfi, G. Turchetti, The cost-effectiveness of transcatheter aortic valve implantation: exploring the Italian National Health System perspective and different patient risk groups, Eur. J. Health Econ. 22 (2021) 1349–1363.
[18] G. Fattore, Proposta di linee guida per la valutazione economica degli interventi sanitari in Italia, PharmacoEcon. Ital. Res. Artic. 11 (2009) 83–93.
[19] M. Gilard, H. Eltchaninoff, B. Iung, T. Lefèvre, C. Spaulding, N. Dumonteil, P. Mutuon, C. Roussel, P. Candolfi, G. de Pouvourville, M. Green, J. Shore, Cost-effectiveness analysis of SAPIEN 3 transcatheter aortic valve implantation procedure compared with surgery in patients with severe aortic stenosis at low risk of surgical mortality in France, Value Health (2021), https://doi.org/10.1016/j.jval.2021.10.003 (In press).
[20] L. Pradelli, M. Calandriello, V.R. Di, M. Bellone, M. Tubaro, Comparative pharmacoeconomic assessment of apixaban vs. standard of care for the prevention of stroke in Italian atrial fibrillation patients, Farmeconomia Health Econ. Ther. Pathways 15 (2014) 15–25.
[21] A. Szende, B. Janssen, J. Cabases, Self-reported Population Health: An International Perspective Based on EQ-5D, Springer, Dordrecht, NL, 2014.
[22] Stroke Alliance for Europe (SAFE), The Burden of Stroke in Italy, Available from: https://www.safestroke.eu/wp-content/uploads/2017/12/SAFE_STROKE_ITALY.pdf, 2017 (Accessed November 2021).
[23] A. Odutayo, C.X. Wong, A.J. Hsiao, S. Hopewell, D.G. Altman, C.A. Emdin, Atrial fibrillation and risks of cardiovascular disease, renal disease, and death: systematic review and meta-analysis, Br. Med. J. 354 (2016), i4482.
[24] T. Bourguignon, A.L. Bouquiaux-Stablo, P. Candolfi, A. Mirza, C. Loardi, M.A. May, R. El-Khoury, M. Marchand, M. Aupart, Very long-term outcomes of the Carpentier-Edwards perimount valve in aortic position, Ann. Thorac. Surg. 99 (2015) 831–837.
[25] M. Ruggeri, M. Basile, A. Zini, S. Mangiafico, E.C. Agostoni, K. Lobotesis, J. Saver, S. Coretti, C. Drago, A. Cicchetti, Cost-effectiveness analysis of mechanical thrombectomy with stent retriever in the treatment of acute ischemic stroke in Italy, J. Med. Econ. 21 (2018) 902–911.
[26] L. Scalone, P.A. Cortesi, R. Ciampichini, A. Belisari, L.S. D'Angiolella, G. Cesana, L. G. Mantovani, Italian population-based values of EQ-5D health states, Value Health 16 (2013) 814–822.
[27] M. Kelly-Hayes, Influence of age and health behaviors on stroke risk: lessons from longitudinal studies, J. Am. Geriatr. Soc. 58 (Suppl. 2) (2010) S325–S328.
[28] T.H. Jørgensen, J.B. Thygesen, H.G. Thyregod, J.H. Svendsen, L. Søndergaard, New-onset atrial fibrillation after surgical aortic valve replacement and transcatheter aortic valve implantation: a concise review, J. Invasive Cardiol. 27 (2015) 41–47.
[29] D.Y. Tam, P.M. Azizi, S.E. Fremes, J. Chikwe, M. Gaudino, H.C. Wijeysundera, The cost-effectiveness of transcatheter aortic valve replacement in low surgical risk patients with severe aortic stenosis, Eur. Heart J. Qual. Care Clin. Outcomes 7 (2021) 556–563.
[30] J.Y. Zhou, D. Liew, S.J. Duffy, A. Walton, N. Htun, D. Stub, Cost-effectiveness of transcatheter versus surgical aortic valve replacement in low-risk patients with severe aortic stenosis, Heart Lung Circ. 30 (2021) 547–554.
[31] Health Information, Quality Authority, Health Technology Assessment of Transcatheter Aortic Valve Implantation (TAVI) in Patients With Severe Symptomatic Aortic Stenosis at Low and Intermediate Risk of Surgical Complications, Available from: https://www.hiqa.ie/sites/default/files/2020-06/HIQA-Annual-Report-2019.pdf, 2019 (Accessed November 2021).
[32] Haute Autorité de Santé, SAPIEN 3 Modèle 9600 TFX Bioprothese Valvulaire Aortique Avec Systeme de Mise en Place Edwards Commander, Available from: https://www.has-sante.fr/jcms/p_3244168/fr/sapien-3-modele-9600-tfx-bioprothese-valvulaire-aortique-avec-systeme-de-mise-en-place-edwards-commander#analyseEco, 2021 (Accessed November 2021).
[33] Norweigan Institute of Public Health, Health Technology Assessment: Transcatether Aortic Valve Implantation (TAVI) as Treatment of Patients With Severe Aortic Stenosis and Intermediate Surgical Risk – Part 2. Health Economic Evaluation, Available from: https://nyemetoder.no/Documents/Rapporter/ID2016_076%20TAVI_cost-effectiveness.pdf, 2019 (Accessed November 2021).
[34] P. Mazzola, S.M. Rimoldi, P. Rossi, M. Noale, F. Rea, C. Facchini, S. Maggi, G. Corrao, G. Annoni, Aging in Italy: the need for new welfare strategies in an old country, Gerontologist 56 (2016) 383–390.
[35] A. Kataruka, C.M. Otto, Valve durability after transcatheter aortic valve implantation, J. Thorac. Dis. 10 (Suppl. 30) (2018) S3629–S3636.