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ORIGINAL RESEARCH

A Systematic Review and Statistical Analysis of Factors Influencing the Cost-Effectiveness of Transcatheter Aortic Valve Implantation for Symptomatic Severe Aortic Stenosis

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Objective: Transcatheter aortic valve implantation (TAVI) is a disruptive technology recommended for patients with symptomatic severe aortic stenosis (sSAS). Despite being available for over 15 years in Europe, with an extensive volume of clinical and economic evaluations across all surgical risk groups, there is little evidence on the identification of the key drivers of TAVI's cost-effectiveness. This study sought to identify these factors and quantify their role.

Methods: A systematic literature review was conducted to identify published economic evaluations of TAVI. This was supplemented by health technology assessment reports. The primary outcome was the likelihood of TAVI being found cost-effective. Secondary outcomes of TAVI being dominant, and the incremental health benefits of TAVI were also explored.

Results: Forty-two studies, reporting 65 unique analyses, were identified. TAVI was found to be cost-effective and dominant in 74% and 20% of analyses, respectively. The latest generation balloon-expandable TAVI device (SAPIEN 3) was more likely to be found cost-effective, as was TAVI use in low-risk populations and when performed via transfemoral access route. There was heterogeneity in the approach taken to economic modelling, which may also influence estimates of cost-effectiveness. Analyses that found TAVI to be dominant always compared it to surgery and usually considered the latest generation balloon-expandable TAVI device. Largest health benefits were observed for the inoperable risk group.

Conclusion: For patients with sSAS, TAVI is typically a cost-effective treatment option. There are important differences by device generation, risk group and access route. It is crucial to consider these differences when appraising the health economic evidence-base for TAVI.

Keywords: transcatheter aortic valve implantation, cost-effectiveness, severe aortic stenosis, statistical analysis, systematic review

Keypoints

Decision-makers should consider differences in device type, risk group, and access route when considering the health economic evidence on TAVI.

Inappropriately combining evidence from different devices, risk groups and access routes may lead to underestimating the economic benefit of TAVI using the most recent generation of devices.

Introduction

Symptomatic severe aortic stenosis (sSAS) is pathological narrowing of the aortic valve, obstructing flow of oxygenated blood from the left side of the heart to the organs and tissues that necessitates valve replacement in most patients.[1,2] It is most commonly caused by age-related calcification[3] and represents a growing burden of disease in the Western world,

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wherein it is the most common valvular heart disease among its ageing population.[1] Left untreated sSAS can lead to heart failure and death, with fatality following rapidly after the onset of symptoms.[4,5]

Fifteen years ago, there was only one active treatment option for patients with sSAS: surgical aortic valve replacement requiring an open-heart surgery (SAVR),[6,7] with medical management (MM) offered to patients who were unsuitable for surgery.[8] In 2007, transcatheter aortic valve implantation (TAVI) became a new treatment option.[9,10] In this intervention, a replacement valve device is inserted via a catheter and positioned inside the patient's damaged aortic valve, with no need for cardiopulmonary bypass.[11] The most common TAVI access route is transfemoral (TF-TAVI), which is the preferred and less invasive approach.[12,13] More invasive access routes, such as transapical TAVI, may be used in the case of poor vascular access.[14] For any access route, the TAVI device used can be either self-expandable or balloon-expandable (whereby a balloon catheter is inserted into the device and inflated to expand and situate the new valve).[11]

Originally, TAVI was only available for patients who either received MM due to being unsuitable for surgery, or who received SAVR and were at high surgical risk.[15–20] However, accumulating evidence on the clinical advantages of TAVI over SAVR led to its subsequent expansion into both intermediate and low surgical risk sSAS patients. The clinical safety and efficacy of TAVI in these different patient populations was assessed and demonstrated in a series of large multinational randomised control trials (RCTs).[15,16,18,19,21–26] Indication expansion of TAVI was accompanied by introduction of new generations of device that were designed to reduce the rate of complications observed with early models.[9,27–29] In light of a robust body of clinical evidence, TF-TAVI is now recommended as a treatment option for all sSAS patients in the American College of Cardiology/American Heart Association guidelines[30] and as the treatment of choice (class IA recommendation) for patients ≥75 years old whatever the surgical risk score in the European Society of Cardiology (ESC)/European Association for Cardio-Thoracic Surgery (EACTS) guidelines.[31]

There is a considerable volume of evidence covering not only the clinical effectiveness but also the cost-effectiveness of TAVI, and it is internationally recommended by a number of health technology assessment (HTA) agencies.[32–37] With respect to the economic evaluations, existing reviews have narratively identified some of the clinical factors that influence the cost-effectiveness of TAVI, but they have not quantified the impact of these factors and the evidence has progressed since the reviews were conducted.[38–40] Furthermore, there has been limited assessment of the impact of heterogenous health economic modelling methods on estimates of cost-effectiveness. This study sought to fill these evidence gaps and had two aims. The first was to systematically review the extant cost-effectiveness evidence of TAVI published in peer-reviewed journals and HTA reports. The second was to use statistical methods to quantify the impact of the identified key factors on the likelihood of TAVI being found cost-effective as a primary outcome, and TAVI being found dominant (providing increased clinical benefits and a lower overall cost than its comparator) and yielding incremental health gains (measured using quality-adjusted life years (QALYs)) as secondary outcomes.

Methodology

Systematic Literature Review

A systematic search of the literature was conducted in September 2021. The objective of this search was to identify published studies evaluating the cost-effectiveness of TAVI for patients with sSAS. The search was conducted in Medline, Embase, Econlit, NHS EED, and the Tufts cost-effectiveness analysis registry. Search terms relating to TAVI (and synonyms) were combined with a pragmatic cost-effectiveness search filter (developed in-house). A combination of subject headings (where available) and free-text search terms was used. Full details of the development of the search strategy and the search terms used are provided in the Supplementary Materials. This search was supplemented by two additional searches. The first was of the grey literature (HTA agency reports; see Supplementary Materials for details). The second was a manual search of key journals in December 2021 to identify any additional publications.

Studies were retained if they reported the results of a cost-utility analysis which included TAVI and the patient population was sSAS. Full inclusion and exclusion criteria are reported in Table S1. For each study, data were extracted on all the following relevant characteristics: author, year, study type, country, patient and device characteristics, modelling framework, details on the health economic model, costs, utilities, cost-effectiveness results. Cost-

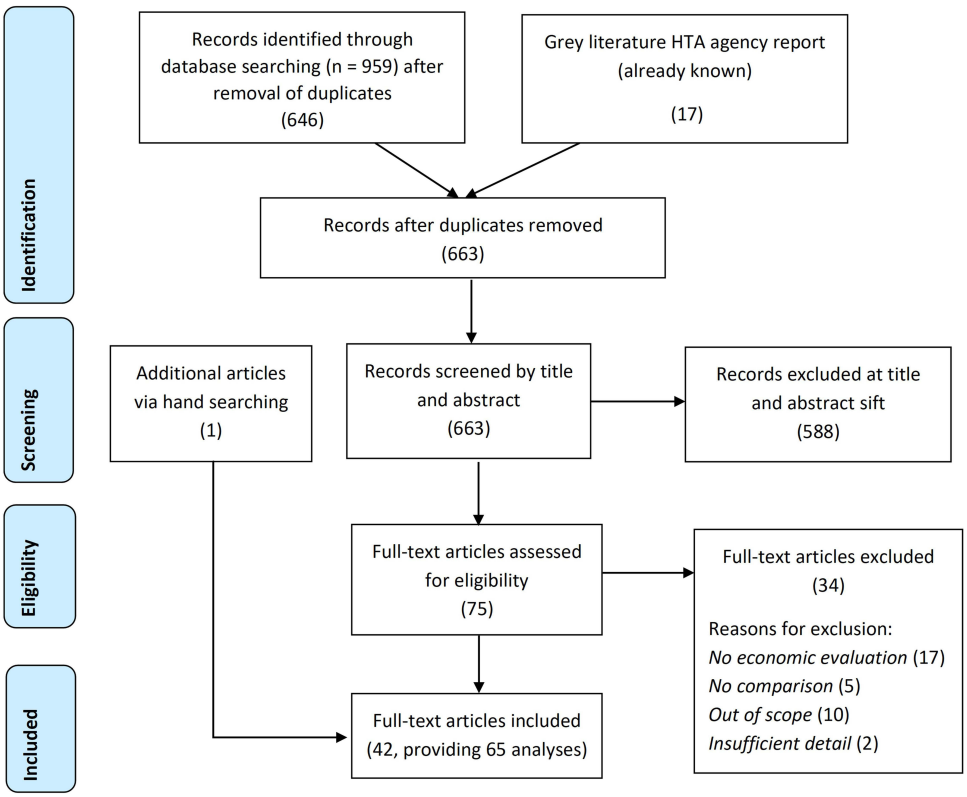

Figure 1 PRSIMA flow chart (HTA: Health Technology Assessment).

effectiveness was based on the authors' reported willingness-to-pay thresholds or on published thresholds for the country of origin (eg NICE guidelines for UK studies). Where neither were available, the study was excluded from analysis. Where data were not reported in the article, reference was made to the original source for effectiveness evidence, or other cited sources. For device type, we extracted data on the device manufacturer and model. To examine the effect of recent developments in device design, we compared data on the most recent generation of devices from each manufacturer with previous generations.

The results of the literature search are provided in Figure 1, with a detailed breakdown by database provided in Table S2. A total of 42 studies were identified, with full references provided in the Supplementary Materials. Some studies reported more than one cost-effectiveness analysis using multiple comparators; each analysis was extracted separately, giving 65 total evaluations. Unless otherwise stated, all subsequent analyses are based on the extracted final 65 evaluations.

Follow-Up Quantitative Analysis: Analytical Approach

After consideration of the extracted evidence, eight factors were identified that could both potentially influence study estimates of cost-effectiveness and be included within formal quantitative analyses. The key extracted variables were broadly grouped into procedural variables (those which described features of how TAVI is performed) and methodological variables (those which relate to the modelling methods chosen by the authors). These variables are summarised in Table 1, with additional information in the Supplementary Materials.

Of note, Table 1 does not include comparator (MM or SAVR). This is because MM is only available for the inoperable risk group, whilst SAVR is only available for the remaining risk groups. Hence, the inclusion of risk group meant there was no need to also include comparator. In addition, neither region (which was derived from the extracted characteristic "country") nor study type was included in quantitative analyses. This is because differences in health economic outcomes by these variables are likely to be explained by differences in the other variables in Table 1. In addition, we did not include information on device cost. The reasons for this are two-fold. First, differences in cost

Table 1 Variables Included in Quantitative Analyses

Procedural	Methodological
1) Risk group (inoperable, high, intermediate, low)	4) Time horizon (Less than two years, two to ten years, lifetime)
2) Access route (percent transfemoral. For descriptive statistics this is categorised into 0% transfemoral, 70–85% transfemoral, 85–99% transfemoral and 100% transfemoral. For quantitative analyses it is a continuous variable)	5) Discount rate: costs
3) Device type (latest generation vs older generations; balloon-expandable vs self-expandable)	6) Discount rate: benefits
	7) Model type (if a health economic model was used or not) 8) If base-case results are derived from a deterministic or a probabilistic analysis

outcomes between countries are difficult to interpret and there are recognised challenges in mapping them to comparable scales.[41] Secondly, this information was frequently not reported, which would have made it difficult to incorporate in quantitative analyses.

Due to the relatively small sample size for quantitative analysis and correlations between predictors, additional approaches to reducing the number of variables were explored. For each possible combination of the variables in Table 1, cross-tabulations were generated along with chi-squared statistics to evaluate the correlation between the variables. There were strong correlations between the procedural variables, which reflects the evolution of TAVI devices. First-generation TAVI devices were generally performed on inoperable and high-risk patients using a variety of access routes. For intermediate risk patients, second-generation devices were used with increased use of TF-TAVI, and low-risk patients used the latest generation of TAVI device with exclusive TF-TAVI. There were also strong correlations between methodological variables (see Tables S3 and S4), likely reflecting clustering of analyses within a single article, the practices of individual research groups, and/or the standard conventions of each region or country. Hence, based on these correlations and the initial results of univariate analyses, the five methodological variables were combined into a single variable. This captured information on if a health economic model was used, the time horizon, and for time horizons greater than two years, the cost discount rate used. This "consolidated" methodological indicator had seven levels, as may be seen in Table S5. This single methods variable was strongly associated with the probability of TAVI being cost-effective (Table S4), which illustrates the importance of controlling for these factors. However, some of the variation in outcomes by methods were due to their reporting as opposed to genuine differences in approach. For example, analyses that did not state the discount rate used were less likely to find TAVI to be cost-effective or dominant. In addition, small numbers for some of the methodological categories (such as the number of analyses with a short-time horizon or that did not use an economic model) coupled with strong correlations between variables meant that interpretation of the single methodological variables was challenging. As such, the consolidated methodological variable was included within quantitative analyses, but interpretation focused on the procedural variables.

As the primary outcome (if TAVI is found cost-effective) is categorical, the original approach was to use logistic regression to estimate both univariate and multivariate associations, along with their statistical significance. However, for some factors TAVI was always found cost-effective. Logistic regression is unreliable when the outcome is 100% for some factors (causing "perfect separation"). Thereby, cross-tabulations were used for univariate associations, and penalised logistic regression, was used for multivariate associations.[42] This method incorporates shrinkage of a variable's coefficients, which allows for stable estimates of parameter effects when perfect separation occurs. For some variables, their coefficients are shrunk to zero. This implies that they are not significantly associated with the outcome. As estimates of statistical significance cannot be obtained for penalised logistic regression, instead the relative importance of the variables was estimated and displayed visually. Due to difficulties in interpreting the methodological variables, these are included in tabular presentations but omitted from graphical displays. For the probability that TAVI is

found dominant, the outcome numbers were too small to allow for statistical modelling. Instead, univariate cross-tabulations were supplemented by a narrative synthesis of the results. The impact of the identified factors on the incremental QALYs due to TAVI was analysed using linear regression (as incremental values can be positive or negative), with both univariate and multivariate models included and no variable selection.

Results

Descriptive Statistics

An overview of the 65 published analyses is provided in Table 2. The descriptive statistics of the published analyses that were reviewed are reported in Table 3.

The majority of the analyses were based in Europe or the UK (n = 30, 46%), with the remaining analyses equally split between the US, Canada, and the rest of the world. The most frequently assessed risk group was high risk (n = 18, 28%), followed by the inoperable and intermediate risk groups, with 16 analyses each (25%). Balloon-expandable (Edwards) TAVI valves were considered in 82% of analyses and the remaining 18% considered self-expandable (Medtronic) valves, whilst SAVR was the comparator in 46 analyses (71%) and MM the comparator in 19 analyses (29%). In 30 analyses (46%) TF-TAVI was evaluated, with a similar number considering a mixture of access approaches (n = 29, 45%).

There were nine trial-based analyses (14%) from four studies.[45,67,78,79] Of the remaining analyses, 50 used a Markov Model (77%, 18 of which also included an upfront decision tree). Discount rates varied from 1.5% to 5% and the most reported discount rate was 3% for both costs and benefits, used in 21 analyses (32%). A lifetime horizon was employed in the majority of analyses (n = 47, 72%). The lowest reported time horizon was one-year in 3 analyses (5%). Estimates of if TAVI was cost-effective were based on the mean of a probabilistic analysis in 22 analyses (34%) and a deterministic analysis in 32 analyses (49%).

Quantitative Analysis: Primary Outcome

Univariate Analyses of the Probability That TAVI is Cost-Effective

Overall, 48 (74%) of analyses found TAVI to be cost-effective. Univariate associations between the variables and the primary outcome (probability of TAVI being cost-effective) are provided in Table 3.

TAVI was found to be cost-effective in all the analyses of the low surgical risk group. The analyses with mixed risk groups also always found TAVI to be cost-effective but these were based on small numbers, so this should be interpreted with caution. Analyses reporting on TF-TAVI were more likely to find TAVI to be cost-effective than other approaches. For example, TF-TAVI was found cost-effective in 90% of the analyses, whereas transapical TAVI was only found cost-effective in 40% of analyses. All the evaluations of the latest generation balloon-expandable devices found TAVI to be cost-effective, whilst balloon expandable devices as a whole were found cost-effective in three-quarters of analyses. In contrast, self-expandable devices were found to be cost-effective in two-thirds of analyses; all the analyses considering the latest generation valves found them cost-effective, however this was a much smaller number of studies (n = 2 vs n = 18 for BE devices).

With respect to the methodological predictors, studies using a decision analytic model were more likely to find TAVI cost-effective than those that did not. There were no differences in the likelihood of a finding of cost-effectiveness between studies that based estimates of cost-effectiveness on deterministic or probabilistic analyses, or between discount rates. Studies with a time-horizon of less than two-years were less likely to find TAVI to be cost-effective (33%) when compared to studies with a longer time horizon (80% for two to ten years, 74% for a lifetime horizon). However, there were only three studies with a time-horizon of less than two-years.

An overview of correlations between the study characteristics is provided in Tables S3 and S4, which demonstrates the importance of accounting for correlations amongst the methodological variables. When using the individual methodological variables, none of these were significantly associated with a finding of cost-effectiveness. When using the combined methodological variable, this was strongly associated ($p < 0.01$). Of the procedural variables, device type was significantly associated with a finding of cost-effectiveness ($p = 0.034$). Risk group was significantly associated with both device type and access route; this is likely due to clusters of studies drawing data from the same clinical trials.

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Table 2 Overview of Included Analyses

Author, Year	Study Type	Country	Pop-ulation	Key Evidence Source(s)	Inter-vention	Comp-arator	Access route	Time Horizon (Years)	Discount Rate (QALYs, Costs)	Model Type	Inc. Costs	Inc. QALYs	ICER
Watt 2012 [43]	EM	UK	Inop.	PARTNER 1B	Older BE	MM	TF	10	0.035, 0.035	Markov	£25,200	1.56	£16,200
HQO 2012 [44]	HTA	CAN	Inop.	PARTNER 1B	Older BE	MM	TF	20	NR, 0.05	DT + Markov	$31,203	0.638	$48,912
Reynolds 2012a [45]	TE	USA	Inop.	PARTNER 1B	Older BE	MM	TF	2.5	0.03, 0.03	No model	$79,837	1.59	$50,212
Doble 2013 [46]	EM	CAN	Inop.	PARTNER 1A, PARTNER 1B	Older BE	MM	TF	20	NR, 0.05	DT + Markov	$31,028	0.6	$51,324
Hancock-Howard 2013 [47]	EM	CAN	Inop.	PARTNER 1B	Older BE	MM	TF	3	0.05, 0.05	DT	$15,687	0.488	$32,170
Murphy 2013 [48]	EM	UK	Inop.	PARTNER 1B	Older BE	MM	TF	Lifetime	NR, NR	DT + Markov	£15,885	0.44	£35,956
Simons 2013 [49]	EM	USA	Inop.	PARTNER 1B	Older BE	MM	TF	Lifetime	0.03, 0.03	Markov	$85,600	0.7	$116,500
Brecker 2014 [50]	EM	UK	Inop.	PARTNER 1B, ADVANCE	Older SE	MM	TF, direct, SC	5	0.035, 0.035	Markov	£22,009	1.24	£17,718
Brecker 2014 [50]	EM	UK	Inop.	PARTNER 1B, ADVANCE	Older SE	MM	TF, direct, SC	5	0.035, 0.035	Markov	£21,038	1.51	£13,943
MSAC 2016 [36]	HTA	AUS	Inop.	PARTNER 1B	Older BE	MM	TF	5	NR, NR	NR	$8,777	0.75	$11,708
HAS 2017 [51]	EM	FRA	Inop.	FRANCE 2 registry	Older SE	MM	TF	5	0.04, 0.04	DT + Markov	€21,207	1.023	€20,738
HAS 2021 [35]	EM	FRA	Inop.	FRANCE 2 registry	Older BE	MM	TF	5	0.04, 0.04	DT + Markov	€18,090	0.163	€15,552
Kodera 2018 [52]	EM	JPN	Inop.	PARTNER 2A	Older BE	MM	TF, TA	10	0.02, 0.02	Markov	¥6,375,062	1.75	¥3,918,808
Inoue 2020 [53]	EM	JPN	Inop.	Literature review	Older BE	MM	TF	Lifetime	0.02, 0.02	DT + Markov	¥1,556,749	1.16	¥1,337,525
Lorenzoni 2021 [54]	EM	IT	Inop.	PARTNER 2A	Latest BE	MM	NR	15	0.03, 0.03	Markov	€11,920	1.18	€10,133
Pinar 2021 [55]	EM	SPN	Inop.	PARTNER 1B	Latest BE	MM	TF	15	0.03, 0.03	Markov	€12,967	1.31	€9,748
HQO 2012 [44]	HTA	CAN	High	PARTNER 1A	Older BE	SAVR	TF, TA	20	NR, 0.05	DT + Markov	$11,153	−0.102	TAVI dominated
Gada 2012a [56]	EM	USA	High	Registry data (not named)	Older BE	SAVR	NR	Lifetime	0.05, 0.05	Markov	$3164	0.06	$52,773.00
Gada 2012b [57]	EM	USA	High	Registry data (not named)	Older BE	SAVR	TA	Lifetime	0.05, 0.05	Markov	$100	−0.04	TAVI dominated
Reynolds 2012b [45]	TE	USA	High	PARTNER 1A	Older BE	SAVR	TF	1	0.03, 0.03	No model	-$1250	0.068	TAVI dominant

Reynolds 2012b [45]	TE	USA	High	PARTNER 1A	Older BE	SAVR	TA	1	0.03, 0.03	No model	$9906	−0.07	TAVI dominated
Reynolds 2012b [45]	TE	USA	High	PARTNER 1A	Older BE	SAVR	TF, TA	1	0.03, 0.03	No model	$2070	0.027	$76,877
Doble 2013 [46]	EM	CAN	High	PARTNER 1A, PARTNER 1B	Older BE	SAVR	TF, TA	20	NR, 0.05	DT + Markov	$11,153	−0.102	TAVI dominated
Fairbairn 2013 [58]	EM	UK	High	PARTNER 1A	Older BE	SAVR	TF, TA	10	0.035, 0.035	DT + Markov	-£1350	0.063	TAVI dominant
Osteba 2014 [59]	EM	SPN	High	PARTNER 1A	Older BE	SAVR	TF, TA	Lifetime	0.03, 0.03	DT + Markov	€9,072	0.08	€119,575
HTA Ontario 2016 [33]	HTA	CAN	High	CoreValve High Risk Trial	Older SE	SAVR	All	5	0.05, 0.05	Markov	$9,412	0.181	$51,988
MSAC 2016 [36]	HTA	AUS	High	PARTNER 1A	Older BE	SAVR	TF	5	NR, NR	NR	$3,987	0.26	$15,541
Reynolds 2016 [60]	TE	USA	High	CoreValve High Risk Trial	Older SE	SAVR	TF, AX, direct	Lifetime	0.03, 0.03	No model	$17,849	0.324	$55,090
Geisler 2017 [61]	EM	NL	High	CoreValve High Risk Trial	Older SE	SAVR	TA	Lifetime	0.04, 0.015	DT + Markov	€9,048	0.41	€21,946
HAS 2017 [51]	EM	FRA	High	CoreValve High Risk Trial	Older SE	SAVR	TF, AX, direct	5	0.04, 0.04	DT + Markov	€7,823	0.146	€53,754
Tarride 2019 [62]	EM	CAN	High	PARTNER 2A	Latest BE	SAVR	TF, TA, direct	15	0.015, 0.015	Markov	$7,362	0.43	$17,237.00
Inoue 2020 [53]	EM	JPN	High	Literature review	Older BE	SAVR	TF	Lifetime	0.02, 0.02	DT + Markov	¥6,837,595	1.98	¥3,460,810
Lorenzoni 2021[54]	EM	IT	High	PARTNER 2A	Latest BE	SAVR	Not reported	15	0.03, 0.03	Markov	€3,831	0.34	€11,209
Pinar 2021[55]	EM	SPN	High	PARTNER 1A	Latest BE	SAVR	TF, TA	15	0.03, 0.03	Markov	€2,155	0.39	€4,796
Ferreira-González 2013 [63]	EM	SPN	High or inop.	SOURCE Registry	Older BE	MM	TA	3	0.03, 0.03	DT	€14,208	0.5	€28,003
Ferreira-González 2013 [63]	EM	SPN	High or inop.	SOURCE Registry	Older BE	MM	TF	3	0.03, 0.03	DT	€12,586	0.64	€19,499
HTA UK 2013 [64]	HTA	UK	High or inop.	PARTNER 1	Older BE	MM*	TF	25	0.035, 0.035	DT	£22,528	1.62	£13,900
Kodera 2018 [52]	EM	JPN	Int.	PARTNER 1B	Older BE	SAVR	TF	10	0.02, 0.02	Markov	¥1,723,516	0.22	¥7,523,821
Tam 2018a [65]	EM	CAN	Int.	PARTNER 2A	Older BE	SAVR	TF, TA, direct	Lifetime	0.015, 0.015	Markov	$10,548	0.23	$46,083
Tam 2018b [66]	EM	CAN	Int.	SURTAVI	Older SE, latest SE	SAVR	TF, direct, SC	Lifetime	0.015, 0.015	Markov	$11,305	0.15	$76,736

(Continued)

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Table 2 (Continued).

Author, Year	Study Type	Country	Pop-ulation	Key Evidence Source(s)	Inter-vention	Comp-arator	Access route	Time Horizon (Years)	Discount Rate (QALYs, Costs)	Model Type	Inc. Costs	Inc. QALYs	ICER
Baron 2019 [67]	TE	USA	Int.	PARTNER 2A	Older BE	SAVR	TF, TA, direct	Lifetime	0.03, 0.03	No model	-$7949	0.15	TAVI dominant
Baron 2019 [67]	TE	USA	Int.	PARTNER 2 S3	Latest BE	SAVR	TF, TA, direct	Lifetime	0.03, 0.03	No model	-$9692	0.27	TAVI dominant
Baron 2019[67]	TE	USA	Int.	PARTNER 2A	Older BE	SAVR	TF	Lifetime	0.03, 0.03	No model	-$11,738	0.3	TAVI dominant
Baron 2019[67]	TE	USA	Int.	PARTNER 2A	Older BE	SAVR	TA	Lifetime	0.03, 0.03	No model	$4,489	−0.35	TAVI dominated
Goodall 2019 [68]	EM	FRA	Int.	PARTNER 2 S3	Latest BE	SAVR	TF, TA, direct	15	0.04, 0.04	Markov	-€439	0.41	TAVI dominant
HIQA 2019 [32]	HTA	ROI	Int.	PARTNER 2A	Older BE	SAVR	TF, TA, direct	15	0.04, 0.04	Markov	Not reported	Not reported	TAVI dominant
HIS 2019 [34]	HTA	SCO	Int.	PARTNER 2A	Older BE	SAVR	TF, TA, direct	Lifetime	0.035, 0.035	Markov	£12,944	0.13	£98,965
NIPH 2019 [69]	HTA	NOR	Int.	PARTNER 2A	Older BE	SAVR	TF, TA, direct	2	0.04, 0.04	Markov	NOK 71,000	0.07	NOK 1,040,000
Tarride 2019 [62]	EM	CAN	Int.	PARTNER 2A	Latest BE	SAVR	TF, TA, direct	15	0.015, 0.015	Markov	$13,473	0.48	$28,154
Zhou 2019 [70]	EM	AUS	Int.	PARTNER 2 S3	Latest BE	SAVR	All	Lifetime	0.05, 0.05	Markov	-$9,629	0.31	TAVI dominant
HTW 2020 [71]	HTA	WAL	Int.	PARTNER 2A	Older BE	SAVR	TF, TA, direct	Lifetime	0.035, 0.035	Markov	£9,145	0.1	£94,512
Lorenzoni 2021 [54]	EM	IT	Int.	PARTNER 2 S3	Latest BE	SAVR	NR	15	0.03, 0.03	Markov	€3,593	0.43	€8,338
Pinar 2021[55]	EM	SPN	Int.	PARTNER 2 S3	Latest BE	SAVR	TF, TA	15	0.03, 0.03	Markov	€3,537	0.44	€,7497
Geisler 2019 [72]	EM	DK	Low	NOTION	Older SE	SAVR	TF, SC	Lifetime	0.04, 0.015	DT + Markov	DKK 64,561	0.09	DKK 696,664
HIQA 2019 [32]	HTA	ROI	Low	PARTNER 3	Latest BE	SAVR	TF	15	0.04, 0.04	Markov	Not reported	Not reported	TAVI dominant
Tam 2020 [73]	EM	CAN	Low	PARTNER 3	Latest BE	SAVR	TF	Lifetime	0.015, 0.015	Markov	$5,077	0.085	$59,641
Tam 2020 [73]	EM	CAN	Low	Evolut low-risk	Latest SE	SAVR	TF	Lifetime	0.015, 0.015	Markov	$2,747	0.099	$27,196
Gilard 2021 [74]	EM	FRA	Low	PARTNER 3	Latest BE	SAVR	TF	Lifetime	0.025, 0.025	DT + Markov	-€12,742	0.89	TAVI dominant
HAS 2021 [75]	EM	FRA	Low	Evolut low-risk	Latest SE	SAVR	TF	15	0.025, 0.025	Markov	€708	0.12	€5,893

NIPH 2021 [37]	HTA	NOR	Low	PARTNER 3	Latest BE	SAVR	TF	15	0.04, 0.04	Markov	NOK −35,000	0.05	TAVI dominant
Zhou 2021 [76]	EM	AUS	Low	PARTNER 3	Latest BE	SAVR	TF	Lifetime	0.05, 0.05	Markov	$702.00	0.2	$3,521
Zhou 2021 [76]	EM	AUS	Low	Evolut low-risk	Latest SE	SAVR	TF	Lifetime	0.05, 0.05	Markov	-$507	0.08	TAVI dominant
HAS 2021 SAPIEN 3 [35]	EM	FRA	Low	PARTNER 3	Latest BE	SAVR	TF	15	0.025, 0.025	DT + Markov	-€7,737	0.64	TAVI dominant
Kuntjoro 2020 [77]	EM	SG	Int. or low	PARTNER 2A	Older BE	SAVR	TF	8	0.03, 0.03	DT + Markov	$5,852	0.21	$33,833
Kuntjoro 2020 [77]	EM	SG	Int. or low	PARTNER 2 S3	Latest BE	SAVR	TF	8	0.03, 0.03	DT + Markov	Not reported	Not reported	$21,732

Notes: *Actual comparator is "TAVI not available". Based on the description given, this appeared to be treated as medical management.

Abbreviations: AUS, Australia; AX, Axillary; BE, Balloon-Expandable; CAN, Canada; DK, Denmark; DT, Decision Tree; EM, Economic model; Inc., Incremental; Inop., Inoperable; Int., Intermediate; IT, Italy; JPN, Japan; MM, Medical management; NL, Netherlands; NOR, Norway; NR, Not reported; ROI, Republic of Ireland; SC, Subclavian; SCO, Scotland; SE, Self-Expandable; SG, Singapore; SPN, Spain; TE, Trial evaluation; TA, Transapical; TF, Transfemoral; UK, United Kingdom; US, United States; WAL, Wales.

Table 3 Univariate Associations Between Variables and the Probability That TAVI is Found Cost-Effective or Dominant

		Count of Analyses		TAVI Cost-Effective		TAVI Dominant	
		N	**% of All Studies**	**N**	**% of Row**	**N**	**% of Row**
Region	US	12	18%	6	50%	4	33%
	Canada	12	18%	8	67%	0	0%
	Europe	30	46%	24	80%	7	23%
	Rest of the world	11	17%	10	91%	2	18%
Population/Indication	Inoperable	16	25%	14	88%	0	0%
	High Risk	18	28%	9	50%	2	11%
	Intermediate Risk	16	25%	10	63%	6	38%
	Low Risk	10	15%	10	100%	5	50%
	Mixed	5	8%	5	100%	0	0%
Valve Type	Balloon Expandable	53	82%	40	75%	12	23%
	Older (SAPIEN / SAPIEN XT)	35	54%	22	63%	5	14%
	Latest (SAPIEN 3)	18	28%	18	100%	7	39%
	Self Expandable	12	18%	8	67%	1	8%
	Older (CoreValve)	8	12%	5	63%	0	0%
	Latest (Evolut)	2	3%	2	100%	1	50%
	Mixed	2	3%	1	50%	0	0%
TAVI approach	Transapical	5	8%	2	40%	0	0%
	Mixed (70% - 85% transfemoral)	20	31%	10	50%	3	15%
	Mixed (85% - 99% transfemoral)	9	14%	8	89%	3	33%
	Transfemoral	30	46%	27	90%	7	23%
	Not reported	1	2%	1	100%	0	0%
Study type	Economic model	44	68%	36	82%	6	14%
	HTA	12	18%	7	58%	3	25%
	Trial evaluation (no model)	9	14%	5	56%	4	44%
Model type	Markov model	32	49%	24	75%	6	19%
	Decision tree	4	6%	4	100%	0	0%
	Decision tree + Markov model	18	28%	13	72%	3	17%
	No model	9	14%	5	56%	4	44%
	Not reported	2	3%	2	100%	0	0%
Time Horizon	Lifetime	47	72%	35	74%	12	26%
	2–10 years	15	23%	12	80%	0	0%
	< 2 years	3	5%	1	33%	1	33%

(*Continued*)

Table 3 (Continued).

		Count of Analyses		TAVI Cost-Effective		TAVI Dominant	
		N	% of All Studies	N	% of Row	N	% of Row
Discount Rate- Benefits	< 3%	15	23%	11	85%	2	15%
	≥ 3%	47	72%	33	73%	11	24%
	Not reported	3	5%	4	57%	0	0%
Discount Rate- Costs	< 3%	13	20%	2	13%	2	13%
	≥ 3%	45	69%	11	23%	11	23%
	Not reported	7	11%	4	6%	0	0%
Base case methods	Deterministic mean	32	49%	25	78%	6	19%
	Probabilistic mean	22	34%	16	73%	3	14%
	No model	9	14%	5	56%	4	44%
	Not reported	2	3%	2	100%	0	0%

Abbreviations: HTA, Health Technology Assessment; TAVI, Transcatheter Aortic Valve Implantation.

Multivariate Analyses of the Probability That TAVI is Cost-Effective

The relative importance of the clinical variables, derived from the penalized logistic regression analysis, is displayed in Figure 2, with full results in Table S5. Results of the multivariate analysis were similar to the univariate analysis. The most important factor associated with the finding of cost-effectiveness of TAVI is the use of the latest generation balloon-expandable device, followed by risk group. Low surgical risk population is associated with an increased probability of TAVI being found cost-effective, whilst both intermediate and high surgical risk populations are associated with TAVI being less likely to be found cost-effective than the inoperable population. Of note, access route was found not to be significant in the multivariate analysis. This may be due to strong correlations between access route and both risk group and device type (see Tables S3 and S4).

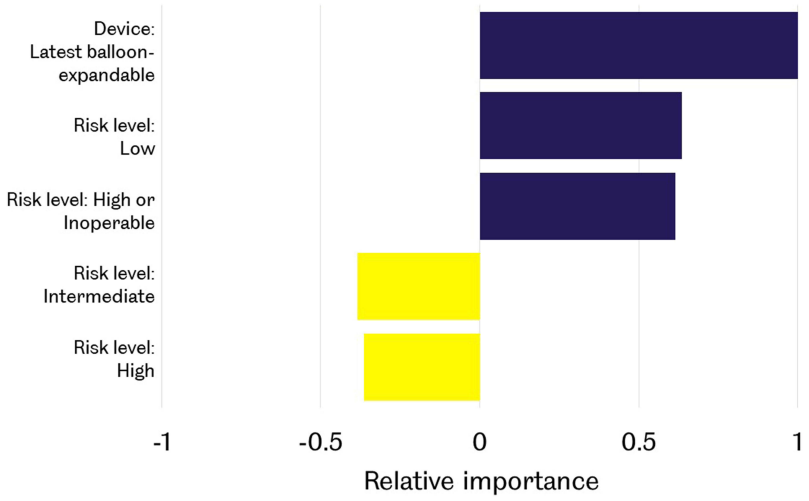

Figure 2 Relative importance of clinical variables (TAVI: transcatheter aortic valve implantation). Results are shown relative to the most important factor (indexed to 1). Positive values indicate more likely to be found cost-effective, negative values less likely.

Quantitative Analyses: Secondary Outcomes

i) Analyses of the Probability That TAVI is Dominant

Table 3 provides univariate associations between the variables and the secondary outcome of TAVI being found dominant. TAVI dominated its comparator in 13 analyses (20%). As with the primary outcome, studies of latest generation balloon-expandable devices or a low-risk population were more likely to report dominance, as were studies with a higher proportion of TF-TAVI. When TAVI was found to be dominant, it was always compared with SAVR, with the greater up-front cost of TAVI more than offset by cost-savings due to a shorter length of hospital stay and resource use. Two studies evaluated the impact of access route on outcomes, and found that transapical TAVI was dominated by SAVR, whilst TF-TAVI dominated SAVR.[41,78]

Trial-based evaluations had a higher proportion of dominant results (4/9; 44% compared with 9/56; 16% for economic models), although this was partly driven by one trial-based analysis reporting three separate analyses (varying device type and access route) which found TAVI to be dominant.[80] Studies with higher discount rates were more likely to find TAVI to be dominant. Due to the small number of model-based evaluations that found TAVI to be dominant (n = 9, 39%), it was not possible to identify any further patterns by methodological variable.

Analyses of the Impact on the Incremental QALYs Due to TAVI

Use of TAVI resulted in more QALYs than its comparator in 60 analyses (92%). The impact on incremental QALYs associated with the use of TAVI is reported in Table S6. There was significant variation by risk group, with the largest benefits observed by analyses in the inoperable risk group, which reflects the comparator for this group (MM). In both univariate and multivariate analyses, an increase in the proportion of TF-TAVI led to an increase in QALYs (transapical and transfemoral TAVI were associated with 0.09 and 0.64 incremental QALYs, respectively). There was no notable difference in QALYs gained by device generation, which is likely to be due to strong correlations with risk level (in univariate analyses, the latest generation balloon-expandable device had the largest QALY gains of all devices).

Discussion

This systematic review identified 42 studies, reporting the results of 65 economic evaluations of TAVI. TAVI was found to be cost-effective in 48 (74%) of the evaluations. Device generation, risk group, and access route were all individually found to be associated with the probability that TAVI was found cost-effective. Multivariate analysis demonstrated that device type had the strongest association with cost-effectiveness, with the latest generation balloon-expandable device most likely to be found cost-effective. This was followed by surgical risk, with the lowest probability of a finding of cost-effectiveness observed in the high and intermediate risk groups.

In general, findings for the secondary outcomes (TAVI being dominant, impact on incremental QALYs due to TAVI) were similar to those for the primary outcome of TAVI being cost-effective. An important exception is the comparator; TAVI was never found to dominate MM though it was found to be cost-effective 89% of the time when compared with MM. Furthermore, TAVI was found to generate approximately one extra QALY (per patient) than MM. This is likely to reflect the fact that MM has lowest costs of the treatment options considered and therefore the incremental costs of TAVI are much higher than when compared to SAVR. A multivariate analysis of QALYs gained showed that these were largest for the inoperable risk group and increased as the proportion of patients receiving TF-TAVI increased.

The majority of studies used economic models. There were often strong correlations between the modelling methods employed, but no clear picture about how these influenced estimates of cost-effectiveness. The results of this study illustrate the importance of good modelling practice. Key modelling information such as the discount rates used were not always reported, most evaluations did not base their conclusions on a probabilistic analysis, and a lifetime horizon was not always employed. It is important that future economic evaluations employ appropriate methods. This may however cause some evidential challenges. In particular, the requirement of a lifetime horizon (to accurately capture all mortality benefits) typically requires long follow-up data to provide reliable estimates. Newer generation devices are unlikely to have long follow-up, and this study has shown that evidence from older devices cannot be used interchangeably. Similarly, these results have demonstrated that the risk group, type of device, and access route must also be considered when assessing health

economic evidence for TAVI. As these factors impact on the likelihood that TAVI is found cost-effective, treating all TAVI procedures as similar creates a danger of underestimating the potential benefit of this procedure in certain settings.

The findings of this study complement and expand those of previous reviews. Gialama and colleagues[39] performed a review of economic evaluations of TAVI published up to June 2017. As with this study, TAVI was more likely to be found cost-effective when compared with MM (for the inoperable risk group), and also for TF-TAVI.[39] An older review by Eaton and colleagues focused on the inoperable risk group and also found TAVI to be cost-effective.[38] Since these reviews were conducted, TAVI use has expanded into intermediate and low-risk groups, with newer generation devices also available. This review has demonstrated that these are important factors associated with the cost-effectiveness of TAVI. A rapid review published in 2021 by the Canadian Agency for Drugs and Technologies in Health compared TAVI with SAVR, with results stratified by risk-group. Results were consistent with the findings of this review, with estimates of cost-effectiveness found to vary by risk-group, TAVI approach, and valve type.[81] Similarly, a systematic review conducted in May 2021 identified 29 cost-effectiveness analyses and found very similar results to those presented here, with TAVI being found cost-effective in all the studies of low-risk patients, the majority of inoperable or intermediate risk, and half of high-risk studies.[82] The analyses reported here present a more structured and systematic approach to quantifying the factors that may affect study estimates of cost-effectiveness and dominance.

A particular strength of this study is the relatively large number of evaluations that were identified (n = 65). This allowed for quantitative exploration of the drivers of heterogeneity in the cost-effectiveness of TAVI, including an exploration of the different approaches to health economic modelling. The consideration of multiple outcomes also provides a more nuanced description of where the health economic benefits of TAVI are observed. For example, TAVI generally provides more QALY benefits than MM, but is also typically more expensive. Hence, for the inoperable risk group, TAVI is often found cost-effective but never dominant. This review is also the first to employ advanced statistical methods to quantify the relative impact of each factor. The newest generation TAVI devices were found to have the largest impact on the probability of a finding of cost-effectiveness. This is consistent with the aim of developing new generation devices; to improve clinical outcomes and hence cost-effectiveness. This review also explored variation in results by the approach to health economic modelling; an area previously identified as requiring further research.[39]

This study comes with certain limitations. First, the use of penalised logistic regression (required due to "perfect separation" as some predictors had 100% probability of TAVI being cost-effective) precluded an assessment of uncertainty. Any future assessment of uncertainty should account for some parts of studies using the same evidence sources, which will induce correlations across studies. Hence, multivariate results for categories with small counts should be interpreted with caution. This is partly offset by using shrinkage, which sets some categories equal to zero. Second, whilst heterogeneity in the estimates for QALY gains was explored, this was not performed for incremental costs. This is due to established methodological challenges in comparing costs from different countries, contexts, and price years.[41] Third, only cost–utility studies were included. There may be additional useful information for cost-effectiveness studies using different outcomes (such as cost-per-life-year). This would be a useful area for future research. Fourth, we did not consider potential conflicts of interest when assessing the probability that TAVI is found cost-effective or dominant. This is because this is neither a procedural variable nor a modelling choice (such as the time horizon to use). In univariate analyses we noted that HTA studies, which are unlikely to have a conflict of interest, were the most likely to conclude that TAVI is dominant. This suggests that conflicts of interest are unlikely to be a key driver of results. Fifth, we decided to include cost-effectiveness as a binary variable (yes/no) based on the authors' reporting. This was a deliberate choice to avoid the established methodological limitations associated with converting ICERs between currencies and price years.[41] Moreover, comparing an ICER to a given threshold is based on the specific values and preferences of the population of that country, so comparing ICERs from different countries without reference to the differences in thresholds is not methodologically sound. However, this approach did mean that one Belgian study[83] that was otherwise eligible for inclusion was excluded. Lastly, strong correlations were observed amongst the methodological variables. This made modelling these methodological variables challenging, and the relationship between this and the health economic outcomes of TAVI was unclear. Some of these methodological clusters are likely to represent the practices of individual research groups or institutions, or the recommended reference case of each country or region. For example, health economic researchers in the UK are likely to base their methods from the NICE reference case. There currently exists no global "best practice" approach for health economic evaluations, therefore it was not

possible to compare these different approaches to a gold standard. Future research to explore the impact of methodological choices, potentially using case-studies, would be beneficial.

Conclusion

The results of this systematic review and quantitative analysis show that TAVI is generally found to be a cost-effective option for the treatment of patients with sSAS. Health economic results can be influenced by device generation, risk group, and access route. The largest impact was observed for the newer generation balloon-expandable TAVI device. There was also heterogeneity in the modelling approach taken. It is important that analysts clearly report the assumptions and inputs used, and also that decision makers consider the influence of these factors to avoid incorrectly pooling evidence across studies whilst making access and policy decisions.

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