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Transcatheter Aortic Valve Implantation for Patients With Severe Symptomatic Aortic Stenosis

Rapid Review

CADTH

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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Abbreviations

AMSTAR 2	A MeaSurement Tool to Assess systematic Reviews 2
EQ-5D	EuroQol 5-Dimensions questionnaire
HTA	health technology assessment
ICER	incremental cost-effectiveness ratios
NYHA	New York Heart Association
PARTNER	Placement of AoRTic TraNscathetER Valve
QALY	quality-adjusted life-years
SAVR	surgical aortic valve replacement
TAVI	transcatheter aortic valve implantation

Key Messages

- The cost-effectiveness of transcatheter aortic valve implantation (TAVI) compared to surgical aortic valve replacement was examined in patients with severe symptomatic aortic stenosis at high, intermediate, and low surgical risk, and the findings were mixed. When compared to surgical aortic valve replacement, some studies suggest that TAVI is cost-effective (less costly and/or more effective) and some studies suggest that TAVI is not cost-effective.
- Factors such as the type of TAVI system used, the cost of treatment-associated expenses (such as post-operative follow-up costs and hospitalization costs), and the characteristics of patients selected for treatment likely impact the cost-effectiveness of TAVI for patients with severe symptomatic aortic stenosis.

Context and Policy Issues

Aortic stenosis is a narrowing of the aortic valve that interferes with the flow of blood from the left ventricle of the heart to the aorta. This progressive valvular disorder affects approximately 2% of the population aged 65 years or older[1] and 5% of those older than 75 years of age.[2] People who are affected by aortic stenosis typically remain asymptomatic for many years and the condition may not measurably impact their health; however, patients who become symptomatic generally have a poor prognosis.[3,4] Symptoms of aortic stenosis — such as decreased capacity for exercise, heart murmur, chest pain or tightness, heart palpitations, shortness of breath, and feeling faint or dizzy with physical activity — tend to gradually develop as the condition worsens.[5] Serious complications of aortic stenosis include heart failure, stroke, blood clots, endocarditis, and sudden death.[3,6]

Treatment options for severe aortic stenosis include medical therapy (e.g., statin therapy, non-statin lipid-lowering therapy, antihypertensive therapy, and therapies that target or prevent aortic valve calcification) or various surgical procedures, such as aortic valvuloplasty, open-heart surgical aortic valve replacement (SAVR), or TAVI (also known as transcatheter aortic replacement).[7] Aortic valvuloplasty may be offered to some patients as a bridge therapy or to provide temporary palliation and symptomatic relief;[8] however, aortic valve replacement using SAVR or TAVI is considered the definitive treatment for severe symptomatic aortic stenosis.[7,9] TAVI is a minimally invasive procedure, where a prosthetic valve that functionally replaces the damaged aortic valve is implanted through a catheter inserted through the blood vessels. The replacement valve is typically delivered via the femoral artery in the groin,[10] but other access routes such as the subclavian artery, the common carotid artery, the femoral vein, or a route that enters directly into the ascending aorta may be considered as alternatives in some patients.[11-13]

CADTH has previously reviewed evidence regarding the clinical effectiveness of TAVI for the treatment of patients with severe aortic stenosis[14-16] or with degenerated mitral or tricuspid valve bioprostheses.[17] Additionally, 2 rapid qualitative reviews[18,19] conducted by CADTH have examined how people with aortic stenosis experience TAVI. While these previous reviews have summarized some of the literature on TAVI, the cost-effectiveness of this procedure is unclear. The objective of this report is to evaluate the cost-effectiveness of TAVI to support decisions involving the use of this therapy for the treatment of patients with severe symptomatic aortic stenosis.

Research Question

What is the cost-effectiveness of transcatheter aortic valve implantation or replacement in low-risk, intermediate-risk, and high-risk patients with severe symptomatic aortic stenosis undergoing this procedure?

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including MEDLINE, the Cochrane Database of Systematic Reviews, the international HTA database, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were transcatheter aortic valve implementation and aortic valve stenosis. CADTH-developed search filters were applied to limit retrieval to health technology assessments (HTAs), systematic reviews, meta-analyses, or network meta-analyses; and economic studies. Where possible, retrieval was limited to the human population. The search was also limited to English-language documents published between January 1, 2016 and June 2, 2021.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Criteria	Description
Population	Patients with severe symptomatic aortic stenosis at: • High surgical risk (STS-PROM > 8% at 30 days, or as estimated by a surgeon or cardiac team) • Intermediate or moderate surgical risk (STS-PROM ≥ 4%, or as estimated by a surgeon or cardiac team) • Low surgical risk (STS-PROM < 4%, or as estimated by a surgeon or cardiac team)
Intervention	TAVI or TAVR
Comparator	Open-heart SAVR
Outcomes	Cost-effectiveness (e.g., quality-adjusted life-years, incremental cost-effectiveness ratios)
Study designs	Health technology assessments, systematic reviews, and economic evaluations

SAVR = surgical aortic valve replacement; STS-PROM = Society of Thoracic Surgeons predicted risk of mortality; TAVI = transcatheter aortic valve implantation; TAVR = transcatheter aortic valve replacement.

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published before 2018. Systematic reviews in which all relevant studies were captured in other more recent or more comprehensive systematic reviews were excluded. Economic evaluations retrieved by the search were excluded if they were captured in 1 or more included systematic reviews.

Critical Appraisal of Individual Studies

The included publications were critically appraised by 1 reviewer using the following tools as a guide: A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2)[20] for systematic reviews and the Drummond checklist[21] for economic evaluations. Summary scores were not calculated for the included studies; rather, the strengths and limitations of each included publication were described narratively.

Quantity of Research Available

A total of 608 citations were identified in the literature search. Following the screening of titles and abstracts, 569 citations were excluded and 39 potentially relevant reports from the electronic search were retrieved for full-text review. Five potentially relevant publications were retrieved from the grey literature search for full-text review. Of these 44 potentially relevant articles, 33 publications were excluded for various reasons and 11 publications met the inclusion criteria and were included in this report. These comprised 3 HTAs (each included a systematic review[22-24]; 2 included primary economic evaluations[22,24]), 2 systematic reviews,[25,26] and 6 economic evaluations.[27-32] Appendix 1 presents the PRISMA[33] flow chart of the study selection. Additional references of potential interest are provided in Appendix 6.

Summary of Study Characteristics

Three relevant HTAs (which included 3 systematic reviews[22-24] and 2 de novo economic evaluations[22,24]), 2 systematic reviews,[25,26] and 6 economic evaluations[27-32] were included in this review. The components of the identified HTAs that are relevant to this report (i.e., 3 systematic reviews and 2 economic evaluations) will be described individually, as much of the other information contained in these HTAs is beyond the scope of the current report. Detailed study characteristics are available in Appendix 2, Table 6, and Table 7.

One included systematic review[26] had objectives and inclusion criteria that were wider in scope than the present review. Specifically, Gialama et al. (2018)[26] examined the cost-effectiveness of any interventions for the treatment of valvular heart disease. Only the characteristics and results of the subset of relevant studies will be described in this report.

Study Design

The systematic review by Health Technology Wales (2020)[22] included a systematic review of cost-utility analyses published up to September 8, 2020. Two previously completed HTAs were used as an initial source of published evidence, which were supplemented by additional literature searches. There were 10 eligible studies included in the systematic review,[22] all of which were relevant to the current report. The systematic review of cost-effectiveness literature conducted by Ontario Health (2020)[23] designated cost-benefit analyses, cost-effectiveness analyses, and cost-utility analyses as relevant study designs. Eligible studies were identified from a 2016 Ontario Health HTA that evaluated TAVI for patients with severe

aortic stenosis and through economic literature searches to identify studies published from January 1, 2015 to July 12, 2019. One relevant cost-utility analysis was included in the review.[23] The authors of the Health Information and Quality Authority SR[24] searched for economic evaluations (e.g., cost-utility analyses or cost-effectiveness analyses) published between January 1, 2013 and June 28, 2019. Six cost-utility analyses and 1 cost-effectiveness analysis were included in their review[24] (all were relevant to the current report). The systematic review by Azraai et al. (2020)[25] included cost-effectiveness studies published between January 2010 and November 2019. Eight economic evaluations were included in the review.[25] The authors of the Gialama et al. (2018)[26] systematic review included economic evaluations published up to June 2017. A total of 27 articles were included in the systematic review[26] (11 were relevant to the current report). In total, the 5 systematic reviews[22-26] included 24 unique economic evaluations relevant to the current report. The relevant primary study overlap between these systematic reviews is summarized in Appendix 5, Table 12.

In addition to those identified in the systematic reviews, 8 relevant economic evaluations[22,24,27-32] were identified. All 8 economic evaluations[22,24,27-32] were conducted as cost-utility analyses and incorporated Markov models that included between 2[31] and 9[24,28,29] health states. The time horizons were 8 years,[32] 15 years,[24,27-29] and lifetime.[22,30,31]

The analysis by Himmels et al. (2021)[27] employed a 3-state Markov model with 1-month cycle lengths from the Norwegian health care perspective, using a 15-year time horizon. The 3 health states were: alive and well, post major complications, and dead. Model inputs were derived from the Placement of AoRTic TraNscathetER Valve (PARTNER) 3 and PARTNER 2 trials, from Norwegian activity-based payment system, and from various sources of literature.

The model used in the study by Lorenzoni et al. (2021)[28] was constructed using a 15-year time horizon from the perspective of the Italian national health system. The model was structured as a Markov model with a 1-month cycle length, comprising 9 different health states and categorized using New York Heart Association (NYHA) functional classifications: NYHA I, NYHA I with a history of stroke, NYHA II, NYHA II with a history of stroke, NYHA III, NYHA III with a history of stroke, NYHA IV, NYHA IV with a history of stroke, and death. Effectiveness inputs, transition probabilities, and utility values were extrapolated from the PARTNER trials and other key clinical studies. Cost inputs were derived from Italian national tariffs and various sources of published literature.

Pinar et al. (2021)[29] conducted their analysis using a Markov model with a 1-month cycle length, comprising 9 different health states: NYHA I, NYHA I with a history of stroke, NYHA II, NYHA II with a history of stroke, NYHA III, NYHA III with a history of stroke, NYHA IV, NYHA IV with a history of stroke, and death. The analysis used a 15-year horizon from the perspective of the Spanish national health system. Transition probabilities and health state utilities were derived from key clinical studies, including the PARTNER trials. Costs were estimated using published literature, information provided by the accounts service at a Spanish hospital, and expert opinion.

The cost-utility analysis by Zhou et al. (2021)[30] was conducted from the perspective of the Australian health care system, using a lifetime horizon. Cost-effectiveness was estimated using a decision-analytic Markov model with 30-day cycles. The model included 4 health states: procedure, alive and well, alive with previous stroke, and dead. Key clinical data inputs, including utility values, were drawn from the PARTNER trials and the Evolut Low-Risk trial. Additional clinical inputs were derived from Australian life tables and other sources of clinical

literature. Cost inputs were retrieved from the Australian Medicare Benefits Schedule and published costs associated with the provision of TAVI and SAVR.

The economic evaluation by Health Technology Wales (2020)[22] used a Markov model with a 1-month cycle length from the perspective of the UK NHS–National Health Service and personal social services with a lifetime horizon, comprising 3 main health states: alive with no complications, disabling stroke, and dead. Mortality and complication rates were obtained from the PARTNER 2 study, cost inputs were obtained from NHS reference costs 2018-2019 and clinical expert opinion, and utility values were derived from EuroQol 5-Dimensions questionnaire (EQ-5D) scores measured in the PARTNER 2 study.

The cost-utility analysis by Inoue et al. (2020)[31] used a decision tree model for the initial 2 years of analysis that fed into a Markov model with 1-year cycles with 2 states: alive and dead. The model was from the perspective of public health care payers and used a lifetime horizon. Clinical inputs for were retrieved using a systematic review of the literature. Costs associated with treatments were calculated using a medical claims database. Utility values after TAVI were extrapolated from the PARTNER trials, whereas utility values from other health states were taken from a previously published economic evaluation.

Kuntjoro et al. (2020)[32] used a 2-phase economic model that had a decision tree model for the initial 30 days, followed by a long-term Markov model with 1-year cycles. The analysis was conducted using an 8-year horizon from the perspective of the National University Health System in Singapore. Clinical parameters, such as post-operative mortality rates and risk for complications, were derived from the PARTNER studies and Singapore life tables. Cost inputs were retrieved from a national database and published literature. Health utility values were taken from the Singapore population norm for EQ-5D scores using local preference weights.

The Health Information and Quality Authority (2019)[24] analysis used a 9-state Markov model that simulated patient outcomes in 1-month cycles. The health states included: alive and well, major complications, post major complications, re-hospitalization, and death. The major complications and post major complication each included 3 health states (i.e., acute kidney injury, disabling stroke, and myocardial infarction) to reflect the different risks of mortality associated with each complication. The analysis was conducted using a 15-year time horizon from the perspective of the publicly funded health and social care system in Ireland. Clinical inputs, including utility estimates, were derived from the PARTNER trials following a systematic review of the literature and from national life tables for Ireland from 2015. Cost estimates were retrieved from relevant Diagnostic Related Group codes in Ireland or from previously published HTAs.

Country of Origin

The included systematic reviews were conducted by groups in Australia,[25] Canada,[23] Greece,[26] Ireland,[24] and Wales.[22]

The economic evaluations were by authors in Australia,[30] Japan,[31] Ireland,[24] Italy,[28] Norway,[27] Singapore,[32] Spain,[29] and Wales.[22]

Patient Population

The systematic review by Health Technology Wales (2020)[22] was specific to adults with symptomatic aortic stenosis who were considered to be at intermediate surgical risk. The Ontario Health (2020)[23] systematic review included studies of adults with severe aortic valve

stenosis and low surgical risk. Two systematic reviews[24,25] included studies of patients with aortic stenosis at low or intermediate risk of surgical complications. The systematic review by Gialama et al. (2018)[26] included studies of people with valvular heart disease, regardless of their surgical risk; however, only primary studies of patients with aortic stenosis were considered relevant to the current report.

The study populations in all 8 included economic evaluations comprised patients with severe aortic stenosis. One study[31] was specific to high-risk patients, 1 study[22] was specific to intermediate-risk patients, 2 studies[27,30] were specific to low-risk patients, and 4 studies[24,28,29,32] considered patients at varying levels of surgical risk.

While the included studies[22-32] referenced various methods to determine the surgical risk of patients, such as the Society of Thoracic Surgeons predicted risk of mortality calculator and the logistic European System for Cardiac Operative Risk Evaluation (versions I and II), standardized criteria for categorizing patients were not detailed and applied consistently throughout. This reflects the absence of an ideal risk model and emphasizes the importance of assessment by multidisciplinary heart teams.[24]

Interventions and Comparators

The 5 systematic reviews[22-26] included economic evaluations that examined the cost-effectiveness of TAVI devices compared to SAVR. In all cases, there were no restrictions on the types of TAVI devices (e.g., self-expanding or balloon-expandable) or on the routes of access (e.g., transfemoral, subclavian, transapical) that were eligible for inclusion.

Of the 8 included economic evaluations, 3 studies reported the brand name of the TAVI system (i.e., SAPIEN, manufactured by Edwards Lifesciences): 1 study[29] was specific to TAVI performed using the balloon-expandable SAPIEN 3 system, 1 study[31] was specific to TAVI performed using the balloon-expandable SAPIEN XT system, 1 study[32] was specific to balloon-expandable SAPIEN systems; and 5 studies[22,24,27,28,30] were not specific to a particular type of TAVI. Consistent with the inclusion criteria for the current report, all 8 economic evaluations[22,24,27-32] used SAVR as a comparator.

Outcomes

The included systematic reviews[22-26] reported on various measures of costs and benefits, such as projected treatment-associated costs, quality-adjusted life-years (QALYs), incremental cost-effectiveness ratios (ICERs), and probabilities of cost-effectiveness at specified willingness-to-pay thresholds. ICERs were generally reported as costs per QALY gained; however, some primary studies reported costs per life-year gained or costs per life saved.

Similarly, model outputs from the 8 economic evaluations[22,24,27-32] included treatment costs (reported in local currencies), life-years gained, QALYs gained, ICERs (expressed as cost per QALY gained or cost per life-year gained), and incremental net monetary benefits. In some cases, the analyses also included cost-effectiveness acceptability curves that showed the probability of each treatment being cost-effective over a range of willingness-to-pay thresholds.

Summary of Critical Appraisal

Additional details regarding the strengths and limitations of the included publications are provided in Appendix 3, Table 8 and Table 9.

Systematic Reviews

The 5 systematic reviews[22-26] were considered to be of variable methodological quality based on the assessments using AMSTAR 2.[20] The authors of all included systematic reviews clearly defined their objectives and primary study eligibility criteria, conducted literature searches in multiple databases, provided a description of key search terms and restrictions (e.g., on language or date of publication), and included a flow chart that illustrated study selection. These methodological strengths increase the reproducibility of the systematic reviews. Additionally, the authors of all 5 systematic reviews justified their selection of study designs eligible for inclusion in the reviews and summarized the included studies in adequate detail. The quality of included primary studies was assessed using satisfactory techniques in 4 systematic reviews[22-24,26] and the authors of 3 systematic reviews[22,24,26] reported the sources of funding for the included primary studies.

As for methodological limitations, none of the included systematic reviews contained an explicit statement that the review methods were established before conducting the review (and did not reference a published protocol) or a list of studies excluded after full-text review. These limitations increase the risk for reporting bias and decrease the overall transparency of the review process. Additionally, sources of grey literature were not searched in 2 systematic reviews,[22,25] increasing the risk for missing relevant, non-indexed studies. In 4 systematic reviews, the methods for article selection and data extraction were poorly documented[22,25,26] or were conducted using a single reviewer,[23] increasing the likelihood for inaccuracies in these processes. Similarly, it was unclear how many reviewers were involved in the quality assessment process in 3 systematic reviews[22,23,26] and there was no quality assessment of included studies performed in the systematic review by Azraai et al.[25] Finally, the authors of 3 systematic reviews[22,23,25] did not state their potential conflicts of interest and the sources of funding for 2 reviews[25,26] were unclear.

Economic Evaluations

In all 8 economic evaluations,[22,24,27-32] the authors clearly stated their research questions, the economic importance of the research questions, described the interventions and comparators in detail, provided rationale for choosing alternative interventions, justified their selection of the form of economic evaluations, and explained model structures using figures. The selected time horizons, which were 8 years,[32] 15 years,[24,27-29] and lifetime,[22,30,31] were appropriate given the nature of severe aortic stenosis, TAVI, and SAVR. Additional methodological strengths common to all 8 economic evaluations[22,24,27-32] included:

- the perspectives of the analyses were clearly stated and justified
- the sources of clinical, cost, and utility data were appropriately referenced
- the approaches to sensitivity analyses and the choice of variables for sensitivity analyses were justified
- outcome measures for the economic evaluation were clearly stated
- currency and price data were recorded
- incremental analyses were reported
- the conclusions made by study authors followed the reported data and were accompanied by appropriate caveats.

As for methodological limitations, descriptions of the methods used for currency price adjustments for inflation were not included in 6 studies,[22,24,27-29,32] the authors of 3 studies[22,24,32] did not disclose their potential conflicts of interest, 3 studies[28,29,31] were industry-funded

(increasing the risk for sponsorship bias), and 2 studies[28,29] provided limited information on the characteristics of patient populations from whom model inputs were obtained. While various discount rates ranging between 2% and 5% were applied to costs and benefits in each of the included studies, the authors of 5 studies[27-29,31,32] did not provide a justification for their selected discount rates, making it unclear if the selected discount rates accurately represent the views and preferences of patients and payers. In some cases, advice from clinical experts or the extrapolation of results from key clinical trials to extend beyond the available follow-up periods was necessary to inform the economic models.[22,24,27-32] While the parameters that were estimated from expert clinical advice and the techniques used for extrapolation appeared to be reasonable, these inputs add additional uncertainty to the economic models.

Summary of Findings

The overall findings of the included studies are highlighted here, categorized by the surgical risk level of patients included in the studies. A consistent definition to categorize patients by their levels of surgical risk was not applied across all studies. Instead, studies were categorized based on the description of the patient population by study authors. There was overlap in the primary studies included in the systematic reviews, as described in Appendix 5, Table 12. The data from primary studies described in multiple systematic reviews are only presented once. Detailed summaries of the main findings and authors' conclusions are available in Appendix 4, Table 10 and Table 11.

Cost-Effectiveness of TAVI

High Surgical Risk Populations

Evidence regarding the cost-effectiveness of TAVI for the treatment of severe symptomatic aortic stenosis in patients at high surgical risk was available from 7 economic evaluations summarized in 1 included systematic review[26] and 3 additional economic evaluations.[28,29,31] These findings are described by primary study and presented in Table 2.

There was substantial variation in the cost-effectiveness results from studies in high-risk patients. The findings from 1 study suggested that TAVI was dominant versus SAVR (i.e., treatment with TAVI resulted in more QALYs and less costs),[26] 5 studies suggested TAVI was cost-effective versus SAVR at their specified willingness-to-pay thresholds,[26,28,29,31] 3 studies suggested that TAVI was not cost-effective or was dominated by SAVR (i.e., treatment with TAVI resulted in less QALYs and more costs),[26] and 1 study suggested that the cost-effectiveness of TAVI versus SAVR depended on the type of TAVI procedure (i.e., transfemoral TAVI was cost-effective, transapical TAVI was not cost-effective).[26]

Intermediate Surgical Risk Populations

The cost-effectiveness of TAVI for the treatment of severe symptomatic aortic stenosis in patients at intermediate surgical risk was examined in 8 economic evaluations summarized in 4 included systematic reviews[22,24-26] and 4 additional economic evaluations.[22,24,28,29] Findings are described by primary study; Table 3 summarizes the cost-effectiveness findings in intermediate-risk patients by primary study, including the country that the study was conducted in, ICERs, and the willingness-to-pay threshold that was referenced in the study.

Of the 12 economic evaluations that provided results specific to intermediate-risk patients, 4 studies suggested that TAVI was dominant compared to SAVR,[22,24,25] 5 studies (including 3 studies that were conducted from Canadian perspectives) suggested that TAVI was cost-effective versus SAVR at their specified willingness-to-pay thresholds,[22,24,25,28,29] and 3 studies

suggested that TAVI was not cost-effective.[22,24-26] None of the identified studies indicated that TAVI was dominated by SAVR for the treatment of aortic stenosis in intermediate-risk patients.

Low Surgical Risk Populations

Evidence regarding the cost-effectiveness of TAVI for the treatment of severe symptomatic aortic stenosis in patients at low surgical risk was available from 4 economic evaluations summarized in 3 included systematic reviews[23,25,26] and 2 additional economic evaluations.[27,30] These findings are described by primary study and summarized in Table 4.

The authors of these economic evaluations concluded that TAVI was dominant (1 study),[27] cost-effective at their specified willingness-to-pay thresholds (2 studies, including 1 conducted in Canada),[23,25] cost-ineffective (1 study),[26] or that the cost-effectiveness of TAVI depended on the type of TAVI procedure (i.e., self-expanding TAVI was dominant, balloon-expanding TAVI was cost-effective, transapical TAVI was not cost-effective; 1 study).[30] The findings of 1 economic evaluation in low-risk patients were not summarized in detail in the systematic review that included it.[25]

Table 2: Cost-Effectiveness Findings for TAVI Versus SAVR in Patients With Severe Aortic Stenosis at High Surgical Risk

Primary study citation	Country	ICER (vs. SAVR)	Specified WTP threshold(s)
Fairbairn TA, et al. Heart. 2013;99(13):914-920. [26]	UK	Dominant	£20,000 to £30,000 per QALY
Gada H, et al. Am J Cardiol. 2012;109(9):1326-1333.[26]	US	US$52,773 per QALY	US$100,000 per QALY
Gada H, et al. Ann Cardiothorac Surg. 2012;1(2):145-155.[26]	US	Dominated by SAVR	US$100,000 per QALY
Inoue et al. Value Health Reg Issues. 2020 May;21(5):82-90.[31]	Japan	¥1,337,525 per QALY	¥5,000,000 per QALY
Lorenzoni et al. Eur J Health Econ. 2021 May;21(5):21.[28]	Italy	€11,209 per QALY; €9,474 per LYG	€25,000 to €40,000 per QALY
Neyt M, et al. BMJ Open. 2012;2(3):e001032 [26]	Belgium	€750,000 per QALY	€47,141 per QALY
Orlando R, et al. Health Technol Assess. 2013;17(33):1-86.	UK	Dominated by SAVR	£20,000 to £30,000 per QALY
Pinar et al. Rev Esp Cardiol (Engl). 2021 May;17(5):17.[29]	Spain	€5,471 per QALY; €5,329 per LYG	€30,000 per QALY
Reynolds MR, et al. J Am Coll Cardiol. 2016;67(1):29-38.[26]	US	US$55,090 per QALY; US$43,114 per LYG	US$50,000 per QALY and US$150,000 per QALY
Reynolds MR, et al. J Am Coll Cardiol. 2012;60(25):2683-2692.[26]	US	TF-TA TAVI: US$76,877 per QALY TF TAVI: Dominant TA TAVI: Dominated by SAVR	US$50,000 per QALY

ICER = incremental cost-effectiveness ratio; LYG = life-year gained; QALY = quality-adjusted life-year; SAVR = surgical aortic valve replacement; TA = transapical; TAVI = transcatheter aortic valve implantation; TF = transfemoral; vs. = versus; WTP = willingness-to-pay; ¥ = Japanese yen.

Note: Citations in square brackets refer to the systematic reviews that were used as the sources of data for the primary study summarized in the table.

Populations With Mixed or Unclear Risk of Surgical Complications

Evidence regarding the cost-effectiveness of TAVI for the treatment of severe symptomatic aortic stenosis in patient populations with mixed or unclear levels of surgical risk was available from 3 economic evaluations summarized in 2 included systematic reviews[24,26] and 1 additional economic evaluation.[32] These findings are described by primary study and presented in Table 5.

The findings from these economic evaluations were inconsistent. The authors of 1 study suggested that TAVI was cost-effective versus SAVR at their specified willingness-to-pay threshold.[32] The findings from 2 studies, including 1 conducted in Canada, indicated that TAVI was not cost-effective or was dominated by SAVR.[26] The fourth economic evaluation reported

Table 3: Cost-Effectiveness Findings for TAVI Versus SAVR in Patients With Severe Aortic Stenosis at Intermediate Surgical Risk

Primary study citation	Country	ICER (vs. SAVR)	Specified WTP threshold(s)
Baron SJ, et al. Circulation. 2019;139(7):877-888.[22,24,25]	US	XT TAVI: Dominant S3 TAVI: Dominant	US$50,000 per QALY
Goodall G, et al. J Med Econ. 2019;22(4):289-296.[22,24,25]	France	Dominant	€15,000 per QALY
HIQA (2019)[24]	Ireland	Dominant	€20,000 per QALY
Kodera S, et al. J Cardiol. 2017;71(3):223-229.[22,24]	Japan	¥7,523,821 per QALY	¥5,000,000 per QALY
Lorenzoni et al. Eur J Health Econ. 2021 May;21(5):21.[28]	Italy	€8,338 per QALY; €8,035 per LYG	€25,000 to €40,000 per QALY
Osnabrugge RLJ, et al. Ann Thorac Surg. 2012;94(6):1954-1960.[25,26]	The Netherlands	€150,000 per QALY	€30,000 per QALY
Pinar et al. Rev Esp Cardiol (Engl). 2021 May;17(5):17.[29]	Spain	€8,119/QALY; €7,910 per LYG	€30,000 per QALY
Tam DY, et al. Ann Thorac Surg. 2018;106(3):676-684.[22,24,25]	Canada	CA$76,736 per QALY	CA$100,000 per QALY
Tam DY, et al. J Thorac Cardiovasc Surg. 2018;155(5):1978-1988.e1.[22,24,25]	Canada	CA$46,083 per QALY	CA$50,000 per QALY
Tarride JE, et al. Clinicoecon Outcomes Res. 2019;11:477-486.[22]	Canada	CA$28,154 per QALY	CA$50,000 per QALY
Evidence Appraisal Report 024. Cardiff (UK): Health Technology Wales; 2020.[22]	Wales	£94,512 per QALY	£20,000 per QALY
Zhou J, et al. Int J Cardiol. 2019;294:17-22.[22,24,25]	Australia	Dominant	AU$50,000 per QALY

ICER = incremental cost-effectiveness ratio; HIQA = Health Information and Quality Authority; ICER = incremental cost-effectiveness ratio; LYG = life-year gained; QALY = quality-adjusted life-year; S3 = SAPIEN 3 valve; SAVR = surgical aortic valve replacement; TAVI = transcatheter aortic valve implantation; vs. = versus; WTP = willingness-to-pay; XT = SAPIEN XT valve; ¥ = Japanese yen.

Note: Citations in square brackets refer to the systematic reviews that were used as the sources of data for the primary study summarized in the table.

an incremental cost of €1,486,118 per life saved, but the authors' specified willingness-to-pay threshold was not reported in the systematic review that included this study.[24]

Table 4: Cost-Effectiveness Findings for TAVI Versus SAVR in Patients With Severe Aortic Stenosis at Low Surgical Risk

Primary study citation	Country	ICER (vs. SAVR)	Specified WTP threshold(s)
Geisler BP, et al. EuroIntervention. 2019;15(11):e959-e967.[25]	Denmark	DKK 696,264 per QALY	DKK 1,130,000 per QALY
Himmels et al. Oslo (NO): Norwegian Institute of Public Health; 2021.[27]	Norway	Dominant	NOK 0 to NOK 825,000
Evidence Development Pilot Project. Edinburgh (UK): Scottish Health Technologies Group; 2010.[26]	Scotland	£87,293 per QALY	£20,000 to £30,000 per QALY
Tam DY, et al. Eur Heart J Qual Care Clin Outcomes. 2020;0:1-8.[23]	Canada	BE TAVI: CA$27,196 per QALY SE TAVI: CA$59,641 per QALY	CA$50,000 per QALY and CA$100,000 per QALY
Zhou et al. Heart Lung Circ. 2021 Apr;30(4):547-554.[30]	Australia	BE TAVI: AU$3,521 per QALY; AU$4,521 per LYG SE TAVI: Dominant (for both per QALY and per LYG results)	AU$50,000 per QALY and AU$100,000 per QALY
Zhou J, et al. Circulation. 2019;140:A14484-A.[25]	Australia	NR	NR

AU = Australian dollar; BE = balloon-expandable; DKK = Danish krone; ICER = incremental cost-effectiveness ratio; LYG = life-year gained; NOK = Norwegian krone; NR = not reported; QALY = quality-adjusted life-year; SAVR = surgical aortic valve replacement; SE = self-expanding; TAVI = transcatheter aortic valve implantation; vs. = versus; WTP = willingness-to-pay.

Note: Citations in square brackets refer to the systematic reviews that were used as the sources of data for the primary study summarized in the table.

Table 5: Cost-Effectiveness Findings for TAVI Versus SAVR in Patients With Aortic Stenosis at Mixed or Unclear Surgical Risk

Primary study citation	Country	ICER (vs. SAVR)	Specified WTP threshold(s)
Doble B, et al. J Thorac Cardiovasc Surg. 2013;146(1):52-60.e3.[26]	Canada	Dominated by SAVR	CA$50,000 per QALY
Kaier K, et al. Eur J Health Econ. 2019;20(4):625-632.[24]	Germany	€1,486,118 per life saved	NR
Kuntjoro et al. Ann Acad Med Singapore. 2020 Jul; 49(7):423-433.[32]	Singapore	SGD$33,833 per QALY	SGD$73,167 per QALY
Ribera A, et al. Int J Cardiol. 2015;182:321-328.[26]	Spain	BE TAVI: Dominated SE TAVI: €148,535 per QALY	€30,000 per QALY

BE = balloon-expandable; ICER = incremental cost-effectiveness ratio; NR = not reported; QALY = quality-adjusted life-year; SAVR = surgical aortic valve replacement; SE = self-expanding; SGD = Singapore dollar; TAVI = transcatheter aortic valve implantation; vs. = versus; WTP = willingness-to-pay.

Note: Citations in square brackets refer to the systematic reviews that were used as the sources of data for the primary study summarized in the table.

Limitations

There were some concerns relating to the generalizability of the findings from the included economic evaluations to Canadian settings, as these analyses were conducted using effectiveness and cost inputs from Australia,[30] Ireland,[24] Italy,[28] Japan,[31] Norway,[27] Singapore,[32] Spain,[29] and Wales.[22] Any differences in the expected clinical effectiveness or costs associated with TAVI and SAVR between Canadian health care systems and the systems of these Asian, European, and Oceanian countries would affect the applicability of the cost-effectiveness findings.

The 8 economic evaluations[22,24,27-32] used PARTNER trials as sources of clinical inputs for their analyses; however, it was not always clearly reported which of the PARTNER trials were used (e.g., PARTNER 1, PARTNER 2, or PARTNER 3) and the degree of overlap in clinical inputs from the PARTNER trials was unclear. Similarly, detailed descriptions of the clinical inputs used in the economic evaluations summarized in the included systematic reviews[22-26] were often unavailable. As a result, it is unclear how variations in the clinical inputs extrapolated from the PARTNER trials have impacted the cost-effectiveness findings summarized in this report.

Several of the included economic evaluations incorporated data from studies on first- or early-generation TAVI devices (e.g., Edwards Lifesciences SAPIEN, Medtronic CoreValve) into their economic models. Data from these first-generation devices may not precisely reflect the clinical and cost-effectiveness of newer systems (e.g., Edwards Lifesciences SAPIEN 3 valve, Medtronic Evolut R).[34]

The included literature stratified the cost-effectiveness of TAVI devices across patient populations with various levels of surgical risk; however, it is unclear how other patient characteristics — such as age, gender, body mass index, ethnicity, or comorbidities — may impact the cost-effectiveness of TAVI.

There was heterogeneity in the way that surgical risk was determined across included studies, often involving clinical assessment by a cardiac team or using various risk algorithms, such as the Society of Thoracic Surgeons Predicted Risk of Mortality and the logistic European System for Cardiac Operative Risk Evaluation (versions I or II). It was unclear how applying different criteria to assess surgical risk may impact the cost-effectiveness findings summarized in this review.

While the volume of cost-effectiveness evidence summarized in this report is substantial (i.e., 32 unique economic evaluations), only 5 economic evaluations (summarized in the included systematic reviews[22-26]) were conducted using Canadian perspectives, none of which were conducted in populations with high surgical risk. The cost-effectiveness of TAVI is expected to be context-specific and to be influenced by many factors (e.g., local costs of the procedure and associated costs, patient characteristics). Therefore, the applicability of cost-effectiveness findings from studies conducted outside of Canada should be considered when interpreting the results summarized in this report.

Conclusions and Implications for Decision- or Policy-Making

This review comprised 5 systematic reviews[22-26] (3 conducted as part of HTAs[22-24]) and 8 primary economic evaluations[22,24,27-32] (2 conducted as part of HTAs[22,24]) regarding the cost-effectiveness of TAVI for the treatment of severe aortic stenosis.

The evidence summarized in this review provided inconsistent findings regarding the cost-effectiveness of TAVI compared to SAVR across the 3 categories of surgical risk. While the authors of many included studies concluded that TAVI was dominant[22,24-27,30] (i.e., cost-saving and generated more QALYs) or that TAVI was cost-effective at commonly cited willingness-to-pay thresholds versus SAVR,[22-26,28-32] the findings of other studies[22,24,26] suggested that TAVI was not cost-effective for treating patients with severe symptomatic aortic stenosis compared to SAVR. Of the 10 economic evaluations[22,24,26] that suggested TAVI was not cost-effective or was dominated by SAVR, 8 were published before 2014. On the other hand, 17 of the 18 studies[22-32] published since 2018 suggested that TAVI was cost-effective or dominant versus SAVR. This observation may indicate that the cost-effectiveness of TAVI has improved over time.

The cost-effectiveness of TAVI is likely to be sensitive to the access route, the costs of the procedure and related expenses, and the characteristics of patients selected for treatment. Despite the mixed conclusions provided by authors of identified economic evaluations, 4 of the 5 studies[22-26] conducted between 2018 and 2020 from Canadian perspectives indicated that TAVI was cost-effective compared to SAVR in patients at intermediate to low surgical risk. It is likely that the findings from these analyses have the highest generalizability to Canadian settings and may be most useful to Canadian decision-makers. The remaining Canadian study, which was on patients with unclear surgical risk (as summarized in the review by Gialama et al.[26]), suggested that TAVI was dominated by SAVR; however, this study was conducted in 2013, indicating that the results of more recent clinical trials on TAVI devices were unavailable for incorporation into the analysis and that the costs associated with providing TAVI may not accurately reflect the current landscape in Canada. It's worth noting that, while these 5 economic evaluations[22-26] were conducted from Canadian perspectives (and thus incorporate Canadian-specific cost data), the clinical inputs used in these models were not derived entirely from patients treated with TAVI or SAVR in Canada.

The limitations of the included literature[22-32] (e.g., uncertainty in the economic models) should be considered when interpreting the findings of this report. Future economic evaluations conducted from Canadian perspectives may be useful to further inform clinical and policy decisions, especially those that integrate real-world data collected in Canada regarding the clinical effectiveness of TAVI and the costs associated with the provision of TAVI or those that include patients considered to be of high surgical risk.

References

1. Czarny MJ, Resar JR. Diagnosis and management of valvular aortic stenosis. *Clin Med Insights Cardiol.* 2014;8(Suppl 1):15-24. PubMed
2. Badran AA, Vohra HA, Livesey SA. Unoperated severe aortic stenosis: decision making in an adult UK-based population. *Ann R Coll Surg Engl.* 2012;94(6):416-421. PubMed
3. Pujari SH, Agasthi P. *Aortic Stenosis. StatPearls.* Treasure Island (FL): StatPearls Publishing LLC; 2021.
4. Grimard BH, Safford RE, Burns EL. Aortic Stenosis: Diagnosis and Treatment. *Am Fam Physician.* 2016;93(5):371-378. PubMed
5. Harris C, Croce B, Phan K. Aortic stenosis. *Ann Cardiothorac Surg.* 2015;4(1):99-99. PubMed
6. Spitzer E, Hahn RT, Pibarot P, et al. Aortic Stenosis and Heart Failure: Disease Ascertainment and Statistical Considerations for Clinical Trials. *Card Fail Rev.* 2019;5(2):99-105. PubMed
7. Marquis-Gravel G, Redfors B, Leon MB, Généreux P. Medical Treatment of Aortic Stenosis. *Circulation.* 2016;134(22):1766-1784. PubMed
8. Baber U, Kini AS, Moreno PR, Sharma SK. Aortic Stenosis: Role of Balloon Aortic Valvuloplasty. *Cardiol Clin.* 2013;31(3):327-336. PubMed
9. Szerlip M, Arsalan M, Mack MC, et al. Usefulness of Balloon Aortic Valvuloplasty in the Management of Patients With Aortic Stenosis. *Am J Cardiol.* 2017;120(8):1366-1372. PubMed
10. Biasco L, Ferrari E, Pedrazzini G, et al. Access Sites for TAVI: Patient Selection Criteria, Technical Aspects, and Outcomes. *Front Cardiovasc Med.* 2018;5:88-88. PubMed
11. Lederman RJ, Babaliaros VC, Greenbaum AB. How to perform transcaval access and closure for transcatheter aortic valve implantation. *Catheter Cardiovasc Interv.* 2015;86(7):1242-1254. PubMed
12. Pascual I, Carro A, Avanzas P, et al. Vascular approaches for transcatheter aortic valve implantation. *J Thorac Dis.* 2017;9(Suppl 6):S478-S487. PubMed
13. Ramlawi B, Anaya-Ayala JE, Reardon MJ. Transcatheter aortic valve replacement (TAVR): access planning and strategies. *Methodist Debakey Cardiovasc J.* 2012;8(2):22-25. PubMed
14. Transcatheter Aortic Valve Implantation for Aortic Stenosis: A Review of the Clinical Effectiveness and Guidelines. *Summary with critical appraisal*. Ottawa (ON): CADTH; 2011: https://cadth.ca/sites/default/files/pdf/htis/oct-2011/RC0303-000%20Tavi%20final.pdf. Accessed 2021 Jun 7.
15. Ho C, Argáez C. Transcatheter Aortic Valve Implantation for Patients with Severe Aortic Stenosis at Various Levels of Surgical Risk: A Review of Clinical Effectiveness. *Peer reviewed summary with critical appraisal*. Ottawa (ON): CADTH; 2018: https://www.cadth.ca/sites/default/files/pdf/htis/2018/RD0043%20TAVI%20and%20Surgical%20Risk%20Final.pdf. Accessed 2021 Jun 7.
16. Ho C, Cimon K, Rabb D. Transcatheter Aortic Valve Replacement in Severe Aortic Stenosis: A Review of Comparative Durability and Clinical Effectiveness Beyond 12 Months. *Peer reviewed summary with critical appraisal*. Ottawa (ON): CADTH; 2013: https://cadth.ca/sites/default/files/pdf/RD0029_TAVR_e.pdf. Accessed 2021 Jun 7.
17. Thompson W, McCormack S. Transcatheter Aortic Valve Implantation for Degenerated Mitral or Tricuspid Bioprostheses: A Review of Clinical Effectiveness and Cost-Effectiveness Ottawa (ON): CADTH; 2020: https://www.cadth.ca/sites/default/files/pdf/htis/2020/RD0057%20TAVI%202%20Final.pdf. Accessed 2021 Jun 28.
18. Smith A, Argáez C. Experiences and Perspectives of Treatments for Heart Valve Disease: A Rapid Qualitative Review. *Summary with critical appraisal*. Ottawa (ON): CADTH; 2020: https://cadth.ca/sites/default/files/pdf/htis/2020/RC1289%20Treatment%20of%20Heart%20Valve%20Disease%20Qual__Final.pdf. Accessed 2021 Jun 7.
19. Smith A, Argáez C. Transcatheter Aortic Valve Implantation for Aortic Stenosis: A Rapid Qualitative Review. *Summary with critical appraisal*. Ottawa (ON): CADTH; 2019: https://cadth.ca/sites/default/files/pdf/htis/2019/RC1180%20TAVI%20Final.pdf. Accessed 2021 Jun 7.
20. Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *Bmj.* 2017;358:j4008. PubMed
21. Higgins JPT, Green S, editors. Figure 15.5.a: Drummond checklist (Drummond 1996). *Cochrane handbook for systematic reviews of interventions*. London (GB): The Cochrane Collaboration; 2011: http://handbook-5-1.cochrane.org/chapter_15/figure_15_5_a_drummond_checklist_drummond_1996.htm. Accessed 2021 Jun 28.
22. Transcatheter Aortic Valve implantation to treat people with severe symptomatic aortic stenosis, who are at intermediate surgical risk. *Evidence Appraisal Report.* Vol EAR024. Cardiff (UK): Health Technology Wales; 2020: https://www.healthtechnology.wales/wp-content/uploads/2020/07/EAR024-Transcatheter-Aortic-Valve-implantation-1.pdf. Accessed 2021 Jun 28.
23. Ontario H. Transcatheter Aortic Valve Implantation in Patients With Severe Aortic Valve Stenosis at Low Surgical Risk: A Health Technology Assessment. *Ont Health Technol Assess Ser.* 2020;20(14):1-148. PubMed
24. Health Technology Assessment of transcatheter aortic valve implantation (TAVI) in patients with severe symptomatic aortic stenosis at low and intermediate risk of surgical complications. Dublin (IE): Health Information and Quality Authority; 2019: https://www.hiqa.ie/sites/default/files/2019-12/TAVI_HTA.pdf. Accessed 2021 Jun 28.
25. Azraai M, Gao L, Ajani AE. Cost-Effectiveness of Transcatheter Aortic Valve Intervention (TAVI) Compared to Surgical Aortic Valve Replacement (SAVR) in Low- to Intermediate-Surgical-Risk Patients. *Cardiovasc Revasc Med.* 2020;21(9):1164-1168. PubMed

26. Gialama F, Prezerakos P, Apostolopoulos V, Maniadakis N. Systematic review of the cost-effectiveness of transcatheter interventions for valvular heart disease. *Eur Heart J Qual Care Clin Outcomes.* 2018;4(2):81-90. PubMed

27. Himmels J, Flottorp S, Stoinska-Schneider A, Kvist B, Robberstad B. Transcatheter aortic valve implantation (TAVI) versus surgical aortic valve replacement (SAVR) for patients with severe aortic stenosis and low surgical risk and across surgical risk groups: a health technology assessment. Oslo (NO): Norwegian Institute of Public Health; 2021: https://www.fhi.no/globalassets/dokumenterfiler/rapporter/2021/tavi-vs-savr-for-patients-with-severe-aortic-stenosis-and-low-surgical-risk-and-across-surgical-risk-groups-hta-report-2021.pdf. Accessed 2021 Jun 28.

28. Lorenzoni V, Barbieri G, Saia F, et al. The cost-effectiveness of transcatheter aortic valve implantation: exploring the Italian National Health System perspective and different patient risk groups. *Eur J Health Econ.* 2021;21:21. PubMed

29. Pinar E, Garcia de Lara J, Hurtado J, et al. Cost-effectiveness analysis of the SAPIEN 3 transcatheter aortic valve implant in patients with symptomatic severe aortic stenosis. *Rev Esp Cardiol (Engl).* 2021;17:17. PubMed

30. Zhou JY, Liew D, Duffy SJ, Walton A, Htun N, Stub D. Cost-Effectiveness of Transcatheter Versus Surgical Aortic Valve Replacement in Low-Risk Patients With Severe Aortic Stenosis. *Heart Lung Circ.* 2021;30(4):547-554. PubMed

31. Inoue S, Nakao K, Hanyu M, et al. Cost-Effectiveness of Transcatheter Aortic Valve Implantation Using a Balloon-Expandable Valve in Japan: Experience From the Japanese Pilot Health Technology Assessment. *Value Health Reg Issues.* 2020;21:82-90. PubMed

32. Kuntjoro I, Tay E, Hon J, et al. Cost-Effectiveness of Transcatheter Aortic Valve Implantation in Intermediate and Low Risk Severe Aortic Stenosis Patients in Singapore. *Ann Acad Med Singapore.* 2020;49(7):423-433. PubMed

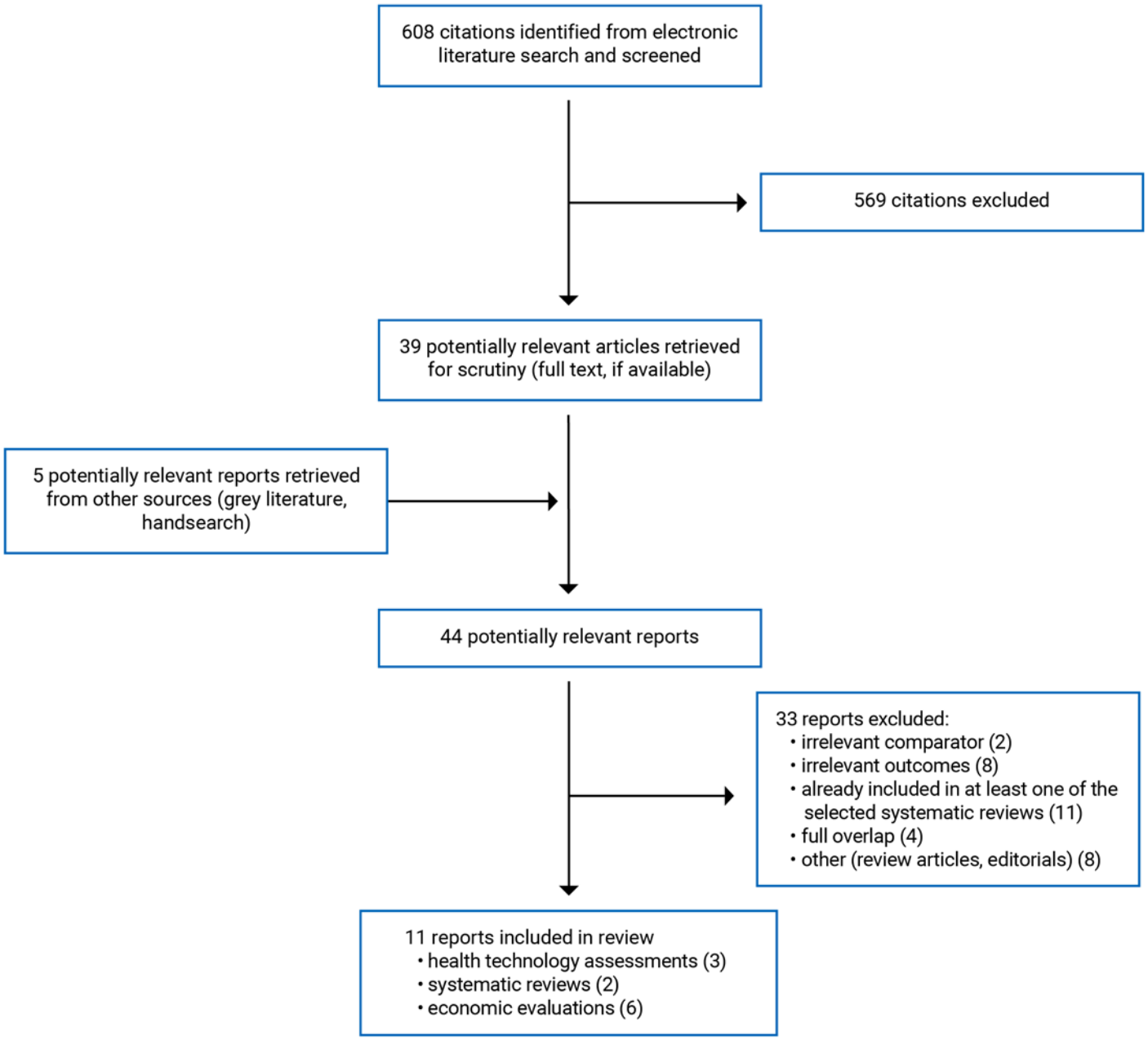
33. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol.* 2009;62(10):e1-e34. PubMed

34. Pilgrim T, Lee JKT, O'Sullivan CJ, et al. Early versus newer generation devices for transcatheter aortic valve implantation in routine clinical practice: a propensity score matched analysis. *Open Heart.* 2018;5(1):e000695. PubMed

Appendix 1: Selection of Included Studies

Note that this appendix has been formatted for accessibility but has not been copy-edited.

Figure 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Note that this appendix has been formatted for accessibility but has not been copy-edited.

Table 6: Characteristics of Included Health Technology Assessments and Systematic Reviews

Study citation, country, funding source	Study designs and numbers of primary studies included	Population characteristics	Intervention and comparator(s)	Economic outcomes
Health technology assessments				
Health Technology Wales (2020)[22] Wales **Funding source**: Health Technology Wales is funded by the Welsh government.	**Study design**: A systematic review of cost-utility analyses. In addition to the review of cost-effectiveness evidence, the HTA included a de novo economic evaluation, which is described in Appendix 2, Table 7. Outside of the scope of the current report, the HTA also included a systematic review of clinical effectiveness and reviews of organizational and patient issues. **Literature search strategy:** The systematic review incorporated evidence from 2 previous HTA reports. Additional literature searches were performed in MEDLINE, Embase, the Cochrane Library, and clinical trials registries on September 8, 2020, to identify evidence published since the previous HTAs. **Number of included studies**: A total of 10 cost-utility analyses were included in the systematic review of cost-effectiveness (all were relevant to the current report).	Adults with severe symptomatic aortic stenosis who were assessed as being operable but at intermediate surgical risk. Studies of patients at other levels of surgical risk (i.e., low, high, inoperable) were excluded.	**Intervention**: TAVI devices. **Comparator**: SAVR.	**Economic outcomes:** • Costs • QALYs • ICERs (i.e., cost per QALY)

Study citation, country, funding source	Study designs and numbers of primary studies included	Population characteristics	Intervention and comparator(s)	Economic outcomes
Ontario Health (2020)[23] Canada **Funding source**: Ontario Health is funded by the Ontario government.	**Study design**: A systematic review of cost-benefit analyses, cost-effectiveness analyses, and cost-utility analyses. The HTA also included a systematic review of clinical evidence, a budget impact analysis, and a review of the experiences, preferences, and values of people with severe aortic valve stenosis at low surgical risk, all of which were outside the scope of the current report. **Literature search strategy**: Eligible studies were identified from a 2016 Ontario Health HTA that evaluated TAVI for patients with severe aortic stenosis and through an economic literature search performed on July 12, 2019. The search was conducted in Ovid MEDLINE, Embase, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, CRD Health Technology Assessment Database, and the NHS Economic Evaluation Database to identify studies published since January 1, 2015. Additionally, a targeted grey literature search of HTA agency websites, clinical trial and systematic review registries, and the Tufts Cost-Effectiveness Analysis Registry was performed. **Number of included studies**: 1 cost-utility analysis was included in the review (it was relevant to the current report)	Adults with severe aortic valve stenosis and low surgical risk, as assessed by multidisciplinary heart teams using STS- PROM scores.	**Intervention**: TAVI devices (either self-expanding or balloon-expandable, using any implantation route). **Comparator**: SAVR.	**Economic outcomes:** • Costs • Health outcomes (e.g., QALYS) • Incremental costs • Incremental effectiveness • ICERs

Study citation, country, funding source	Study designs and numbers of primary studies included	Population characteristics	Intervention and comparator(s)	Economic outcomes
HIQA (2019)[24] Ireland **Funding source**: HIQA is funded by the Irish government.	**Study design**: A systematic review of economic evaluations (e.g., cost-utility analyses or cost-effectiveness analyses). In addition to the review of economic evaluations, the HTA included a de novo primary economic evaluation, which was relevant to the current report and is described in Appendix 2, Table 7. Outside of the scope of the current report, the authors conducted a systematic review of clinical effectiveness and safety and reviews of social, organizational, and ethical issues. **Literature search strategy**: Electronic searches were conducted in PubMed, Embase, the Cochrane Library, and the University of York CRD database for economic evaluations published between January 1, 2013 and June 28, 2019. In addition, a grey literature search and a search in Scopus were conducted. **Number of included studies**: A total of 7 economic evaluations, including 6 cost-utility analyses and 1 cost-effectiveness analysis, were included in the systematic review of cost-effectiveness (all were relevant to the current report).	Patients with aortic stenosis at low or intermediate risk of surgical complications	**Intervention**: TAVI. **Comparator**: SAVR.	**Economic outcomes:** • Any measures of costs and benefits (e.g., costs, QALYs, ICERs)

Study citation, country, funding source	Study designs and numbers of primary studies included	Population characteristics	Intervention and comparator(s)	Economic outcomes
Systematic reviews				
Azraai et al. (2020)[25] Australia **Funding source**: NR.	**Study design**: Systematic review of cost-effectiveness studies. **Literature search strategy**: Electronic searches were performed using Ovid MEDLINE, PubMed, Embase, and the Cochrane Database of Systematic Reviews for articles published between January 2010 and November 2019. **Number of included studies**: A total of 8 cost-effectiveness studies were included in the systematic review (all were relevant to the current report).	Studies of people with severe aortic stenosis considered to be at low or intermediate surgical risk were included.	**Intervention**: TAVI. **Comparator**: SAVR.	**Economic outcomes:** • Costs • QALYs • ICERs • Probabilities of cost-effectiveness
Gialama et al. (2018)[26] Greece **Funding source**: NR.	**Study design**: Systematic review of economic evaluations. **Literature search strategy**: Studies were identified through electronic searches in PubMed and Cochrane conducted in June 2017. There were no search restrictions on publication dates. **Number of included studies**: A total of 27 articles were included in the systematic review (11 were relevant to the current report).	Studies of people with valvular heart disease (i.e., disease of the mitral, aortic, tricuspid, or pulmonary valves) were included. Only studies of people with severe aortic stenosis were considered relevant to the current report.	**Intervention**: Any interventions for the treatment of valvular heart disease. Only primary studies that examined TAVI devices were considered relevant to the current report. **Comparators**: Any alternative interventions for the treatment of valvular heart disease were eligible for the systematic review. Only economic evaluations that used SAVR as the comparator were considered relevant to the current report.	**Economic outcomes:** • Costs • QALYs • Life-years gained • ICERs

CRD = Centre for Reviews and Dissemination; HIQA = Health Information and Quality Authority; HTA = health technology assessment; ICER = incremental cost-effectiveness ratio; NHS = National Health Service; NR = not reported. QALY = quality-adjusted life-year; TAVI = transcatheter aortic valve implantation; SAVR = surgical aortic valve replacement; STS-PROM = Society of Thoracic Surgeons predicted risk of mortality.

Table 7: Characteristics of Included Economic Evaluations

Study citation, country, funding source	Type of analysis, time horizon, perspective	Population characteristics	Intervention and comparator	Approach	Source of clinical, cost, and utility data used in analysis	Main assumptions
Himmels et al. (2021)[27] Norway **Funding source**: NIPH is funded by the Norwegian government.	**Analysis**: Cost-utility analysis conducted as part of an HTA. **Time horizon**: 15 years (scenario analyses considered a 1-year time horizon). **Perspective**: The Norwegian health care perspective.	A hypothetical cohort of patients with severe calcific aortic stenosis considered to be at low surgical risk. Patients entered the model at the age of 73 years (based on the PARTNER 3 trial).	**Intervention**: TAVI. **Comparator**: SAVR.	A 3-state Markov model with 1-month cycle lengths was analyzed. The 3 health states included: 1) alive and well, 2) post major complications, and 3) dead. Major complications were stroke, acute kidney injury, and myocardial infarction.	Transition probabilities were derived using clinical outcomes at 30-days and 1-year from the PARTNER 3 RCT. Mortality risks for patients following major complications were retrieved from the literature. The costs associated with the valve replacement procedures were obtained from Norwegian activity-based payment system. Utility values were derived from EuroQol 5-dimensional scores measured in the PARTNER 2 trial.	Patients who experienced a major complication could not recover to the "alive and well" health state Patients who experienced a minor complication would recover to the "alive and well" health state after 1 cycle The risk of mortality in patients treated with TAVI or SAVR were not available beyond 1-year; therefore, mortality rates were extrapolated from the available trial data using various methods. The long-term medical management costs between those treated with TAVI and those treatment with SAVR were assumed equivalent Uncertainty surrounding cost parameters were assumed to have a gamma distribution

Study citation, country, funding source	Type of analysis, time horizon, perspective	Population characteristics	Intervention and comparator	Approach	Source of clinical, cost, and utility data used in analysis	Main assumptions
Lorenzoni et al. (2021)[28] Italy **Funding source**: Scuola Superiore Sant'Anna and a research grant from Edwards Lifesciences Italia.	**Analysis**: Cost-utility analysis. **Time horizon**: 15 years. **Perspective**: The Italian National Health System.	Patients with aortic stenosis considered to be of various levels of surgical risk, including intermediate, high, or inoperable.	**Intervention**: TAVI. **Comparator**: SAVR (in high- or intermediate-risk patients) or medical treatment (in inoperable patients). Only the analysis that compared TAVI to SAVR was considered relevant to the current report.	The analysis used a Markov model with a 1-month cycle length, comprising 9 different health states. The 9 health states included: NYHA I, NYHA I with a history of stroke, NYHA II, NYHA II with a history of stroke, NYHA III, NYHA III with a history of stroke, NYHA IV, NYHA IV with a history of stroke, and death.	Effectiveness inputs, transition probabilities, and utility values for TAVI- and SAVR-treated groups were extrapolated from the PARTNER trials and other key clinical studies. Cost inputs were derived from Italian national tariffs. Data from the literature was used to complement cost information not available from the national tariffs.	Linear extrapolation was used to extend mortality data to the 15-year time horizon Complication rates were assumed constant beyond the follow-up period observed in key clinical trials Cost inputs were assumed to have a normal distribution Beta distributions were applied for the incidence of adverse events and utilities

Study citation, country, funding source	Type of analysis, time horizon, perspective	Population characteristics	Intervention and comparator	Approach	Source of clinical, cost, and utility data used in analysis	Main assumptions
Pinar et al. (2021)[29] Spain **Funding source**: Edwards Lifesciences SL.	**Analysis**: Cost-utility analysis. **Time horizon**: 15 years. **Perspective**: The Spanish National Health System.	Patients with severe symptomatic aortic stenosis considered to be of various levels of surgical risk, including intermediate, high, or inoperable.	**Intervention**: TAVI using the SAPIEN 3 system. **Comparator**: SAVR (in high- or intermediate-risk patients) or conservative medical treatment (in inoperable patients). Only the analysis that compared TAVI to SAVR was considered relevant to the current report.	The analysis used a Markov model with a 1-month cycle length, comprising 9 different health states. The 9 health states included: NYHA I, NYHA I with a history of stroke, NYHA II, NYHA II with a history of stroke, NYHA III, NYHA III with a history of stroke, NYHA IV, NYHA IV with a history of stroke, and death.	Transition parameters and probabilities were derived from key clinical studies, including the PARTNER trials. Costs were estimated using published literature, information provided by the accounts service at Hospital Clínico Universitario Virgen de la Arrixaca, checks of diagnosis-related groups, and expert opinion. The utility values assigned to each health state were extracted from the PARTNER 2 trial, where health-related quality of life was measured using EQ-5D scores. Utilities were adjusted to weight for the Spanish population.	Mortality rates were extrapolated from 1 year in TAVI-treated patients and 2 years in SAVR-treated patients to the 15-year horizon used in the analysis using various functions Cost inputs were assumed to have a gamma distribution Beta distributions were applied for utility values

Study citation, country, funding source	Type of analysis, time horizon, perspective	Population characteristics	Intervention and comparator	Approach	Source of clinical, cost, and utility data used in analysis	Main assumptions
Zhou et al. (2021)[30] Australia **Funding source**: The National Heart Foundation of Australia Fellowship, the Viertel Charitable Foundation Award, a National Health and Medical Research Council of Australia grant, and the Edwards Fellowship	**Analysis**: Cost-utility analysis. **Time horizon**: A lifetime horizon. **Perspective**: Australian health care system.	A hypothetical cohort of patients with severe aortic stenosis considered to be at low surgical risk. Patients entered the model at the age of 73 or 74 years.	**Intervention**: Balloon-expandable TAVI or self-expanding TAVI. **Comparator**: SAVR.	A decision-analytic Markov model with 30-day cycles. The model included 4 health states: procedure, alive and well, alive with previous stroke, and dead.	Key clinical data inputs were drawn from the PARTNER 3 trial for balloon-expandable TAVI and the Evolut Low-Risk trial for self-expanding TAVI. Additional clinical inputs were derived from Australian life tables and other sources of clinical literature. Cost inputs were retrieved from the Australian Medicare Benefits Schedule and published costs associated with the provision of TAVI and SAVR. Utility values were estimated using EQ-5D values reported following treatment with TAVI or SAVR in the PARTNER S3i intermediate-risk study.	Risk of stroke beyond 1 year was assumed to be equal in those treated with TAVI and those treated with SAVR A hazard ratio for mortality of 1.0 was assumed for those who received TAVI compared to those who received SAVR Procedural costs for the health care system were assumed to equal to the amount reimbursed by Medicare When standard errors were unavailable to define probability distributions for costs the standard error was assumed to be 1-third of the mean

Study citation, country, funding source	Type of analysis, time horizon, perspective	Population characteristics	Intervention and comparator	Approach	Source of clinical, cost, and utility data used in analysis	Main assumptions
Health Technology Wales (2020)[22] Wales **Funding source**: Health Technology Wales is funded by the Welsh government.	**Analysis**: Cost-utility analysis conducted as part of an HTA. **Time horizon**: A lifetime horizon. **Perspective**: The UK National Health Service and personal social services.	People with severe symptomatic aortic stenosis at intermediate surgical risk. Patients entered the model at the age of 81.6 years and were 55% male (based on the PARTNER 2 trial).	**Intervention:** TAVI. **Comparator**: SAVR.	The analysis used a Markov model with a 1-month cycle length, comprising 3 main health states and 1 complications health state. The main health states were: 1) alive with no complications, 2) disabling stroke, and 3) dead. The complications health state could be transitioned to for 1 cycle before returning to the alive with no complications state.	Mortality and complication rates were obtained from the PARTNER 2 study. Costs of the valve replacement procedure and associated costs were obtained from National Health Service Reference costs 2018/19. Costs of managing complications were National Health Service Reference costs and clinical expert opinion. Utility values were derived from EQ-5D scores measured in the PARTNER 2 study.	Risk of complications from both procedures was assumed to be 0 after 2 years Mortality rates beyond 2 years were calculated from general population mortality multiplied by a hazard ratio of 1.15, regardless of treatment received (i.e., TAVI and SAVR were assumed equivalent) Quality of life 2 years post-procedure was assumed equivalent between TAVI and SAVR patient groups

Study citation, country, funding source	Type of analysis, time horizon, perspective	Population characteristics	Intervention and comparator	Approach	Source of clinical, cost, and utility data used in analysis	Main assumptions
Inoue et al. (2020)[31] Japan **Funding source**: Edwards Lifesciences Limited.	**Analysis**: Cost-utility analysis. **Time horizon**: A lifetime horizon. **Perspective**: Public health care payers.	High surgical risk and inoperable patients with severe aortic stenosis. High-risk patients entered the model at the age of 81; inoperable patients entered at the age of 83.	**Intervention**: Transfemoral TAVI using the SAPIEN XT system. **Comparator**: SAVR (in high-risk patients) or supportive pharmacotherapy (in inoperable patients). Only the analysis that compared TAVI to SAVR was considered relevant to the current report.	A 2-phase economic model that used a decision tree model for the initial 2 years of analysis followed by a Markov model with 1-year cycles. The decision tree modelled the incidence of myocardial infarction, stroke, renal failure, new pacemaker implantation, new atrial fibrillation, heart failure hospitalization and death at 6, 12, and 24 months. The Markov model included 2 health states: alive and dead.	Clinical inputs for TAVI and comparators were retrieved using a systematic review of the literature. Costs associated with treatments were calculated using a medical claims database provided by Medical Data Vision Co, Ltd. Utility values after TAVI were extracted from the PARTNER trial, whereas utility values from other health states were taken from a previously published economic evaluation.	The cost of post-operative follow-up in years 3 and beyond was assumed to be the same as year 2 The probabilistic sensitivity analysis assumed a beta distribution for transition probabilities and utility values and a gamma distribution for costs

Study citation, country, funding source	Type of analysis, time horizon, perspective	Population characteristics	Intervention and comparator	Approach	Source of clinical, cost, and utility data used in analysis	Main assumptions
Kuntjoro et al. (2020)[32] Singapore **Funding source**: The Singapore Ministry of Health (through a National Medical Research Council research grant)	**Analysis**: Cost-utility analysis. **Time horizon**: 8-year horizon (scenario analyses considered a 5-year time horizon) **Perspective**: The National University Health System in Singapore.	A hypothetical cohort of patients with severe aortic stenosis considered to be at intermediate or low surgical risk. Patients entered the model at the age of 82 years.	**Intervention**: Transfemoral TAVI using balloon-expandable SAPIEN systems. **Comparator**: SAVR.	A 2-phase economic model that used a decision tree model for the initial 30 days after the procedure followed by a long-term Markov model with 1-year cycles.	Clinical parameters, such as post-operative mortality rates and risk for complications, were derived from the PARTNER 2A RCT, the PARTNER 2 S3 observational trial, and Singapore life tables. Cost inputs were retrieved from the National University Health System database, data published by the National Kidney Foundation, or from other published sources. Health utility values were taken from the Singapore population norm for EQ-5D using local preference weights.	The risk for chronic complications was equivalent between patients treated with TAVI and SAVR after 2 years (based on clinical literature that suggested there is no difference within the first 2 years) Annual mortality rates were derived from 5-year mortality rates and assumed a linear increase in mortality over time Patients who developed chronic complications (e.g., stroke, acute kidney injury, myocardial infarction) were assumed to stay in those health states until they died Paravalvular leak was not considered as a potential complication in the long-term model due to data unavailability

Study citation, country, funding source	Type of analysis, time horizon, perspective	Population characteristics	Intervention and comparator	Approach	Source of clinical, cost, and utility data used in analysis	Main assumptions
HIQA (2019)[24] Ireland **Funding source**: HIQA is funded by the Irish government.	**Analysis**: Cost-utility analysis conducted as part of an HTA. **Time horizon**: 15 years (scenario analyses considered lifetime and 5-year time horizons). **Perspective**: The publicly funded health and social care system in Ireland.	Patients with severe symptomatic aortic stenosis at low (e.g., STS-PROM < 4%) or intermediate risk (e.g., STS-PROM ≥ 4 and < 8%) of surgical complications. At model entry patients were 76 years of age and 55% were male.	**Intervention**: TAVI. **Comparator**: SAVR.	A decision-analytic model that comprised a 9 state Markov model that simulated patient outcomes in 1-month cycles. The health states included "alive and well," "major complications," "post major complications," "re-hospitalization," and "death." The "major complications" and "post major complications" each included 3 health states (i.e., acute kidney injury, disabling stroke, and myocardial infarction) to reflect the different risk of mortality associated with each complication.	Clinical effectiveness inputs for intermediate-risk patients were derived from the PARTNER 2 trial. This study was chosen following a systematic review of the literature, and the data from these patients was deemed most appropriate to use in the model. Similarly, data from the PARTNER 3 trial was used to model clinical effectiveness in low-risk patients following a systematic review of the literature. All-cause mortality data beyond 2 years in intermediate-risk patients and 1 year in low-risk patients were calculated from national life tables for Ireland from 2015, after applying a higher relative risk from published literature. Cost estimates were derived from relevant Diagnostic	There was no difference in rates of clinical events in both arms beyond the observed trial data (i.e., 2 years in intermediate-risk patients, 1 year in low-risk patients) due to a lack of evidence Beta distributions were assumed for all probabilities in the probabilistic analysis Lognormal distributions were assumed for all relative risks All cost inputs assumed lognormal distributions in the probabilistic analysis Health utilities of patients treated with TAVI considered to be at low-risk were assumed to be the same as those at intermediate-risk

Study citation, country, funding source	Type of analysis, time horizon, perspective	Population characteristics	Intervention and comparator	Approach	Source of clinical, cost, and utility data used in analysis	Main assumptions
					Related Group codes in Ireland or from previously published HTAs. Utility estimates were obtained from the PARTNER 2 RCT, where patients' health-related quality of life was measuring using the 3-level EQ-5D questionnaire.	

HIQA = Health Information and Quality Authority; HTA = health technology assessment; NIPH = Norwegian Institute of Public Health; NYHA = New York Heart Association; PARTNER = Placement of AoRTic TraNscathetER Valve; TAVI = transcatheter aortic valve implantation; RCT = randomized controlled trial. SAVR = surgical aortic valve replacement; STS-PROM = Society of Thoracic Surgeons predicted risk of mortality.

Appendix 3: Critical Appraisal of Included Publications

Note that this appendix has been formatted for accessibility but has not been copy-edited.

Table 8: Strengths and Limitations of Systematic Reviews Using AMSTAR 2[20]

Strengths	Limitations
Azraai et al. (2020)[25]	
The objectives and inclusion criteria were clearly stated and included components of population, intervention, comparator, and outcomes The choice of included study designs (i.e., any studies presenting cost-effectiveness data) was explained Multiple databases were searched (Ovid MEDLINE, PubMed, Embase, and the Cochrane Database of Systematic Reviews). Additionally, reference lists from identified studies were further screened for any other eligible studies Key search terms and search restrictions were provided (e.g., studies published in English between January 2010 and November 2019 were eligible) A flow chart of study selection was provided The review authors described the included studies in adequate detail	It was unclear whether the review methods were established before conducting the review (no mention of a protocol) A grey literature search was not completed It was unclear if study selection and data extraction were conducted in duplicate The quality of included studies was not assessed A list of studies excluded after full-text review was not provided (although the reasons for exclusion were) Review authors did not report on sources of funding for the included primary studies Review authors did not state their potential conflicts of interest The source of funding for the review was not disclosed

Strengths	Limitations
Health Technology Wales (2020)[22]	
The objectives and inclusion criteria were clearly stated and included components of population, intervention, comparator, and outcomes The choice of included study designs (i.e., economic evaluations) was explained Evidence from 2 previously published HTA reports was included in the analysis. Additionally, literature searches were performed in multiple databases (MEDLINE, Embase, the Cochrane Library, and clinical trials registries) to identify evidence published since the HTAs Key search terms and search restrictions were provided (e.g., studies published in English were eligible) A flow chart of study selection was provided The review authors described the included studies in adequate detail The quality of included primary studies was assessed using a satisfactory technique Review authors reported on sources of funding for the included primary studies Sources of funding were disclosed and were unlikely to have had an effect on the findings of the review	It was unclear whether the review methods were established before conducting the review (no mention of a protocol) A grey literature search was not completed It was unclear if study selection, data extraction, and quality assessment were conducted in duplicate A list of studies excluded after full-text review was not provided (although the reasons for exclusion were) Review authors did not state their potential conflicts of interest

Strengths	Limitations
Ontario Health (2020)[23]	
The objectives and inclusion criteria were clearly stated and included components of population, intervention, comparator, and outcomes The choice of included study designs (i.e., cost-benefit analyses, cost-effectiveness analyses, or cost-utility analyses) was explained Evidence from a previously published HTA report was included in the analysis. Additionally, literature searches were performed in multiple databases (Ovid MEDLINE, Embase, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, CRD Health Technology Assessment Database, and the NHS Economic Evaluation Database) to identify evidence published since the HTAs and a targeted grey literature search of HTA agency websites, clinical trial and systematic review registries, and the Tufts Cost-Effectiveness Analysis Registry was performed Key search terms and search restrictions were provided (e.g., studies published in English between January 1, 2011, and July 12, 2019 were eligible) A flow chart of study selection was provided The review authors described the included studies in adequate detail The quality of included primary studies was assessed using a satisfactory technique (i.e., a modified quality appraisal checklist for economic evaluations originally developed by NICE) Sources of funding were disclosed and were unlikely to have had an effect on the findings of the review	It was unclear whether the review methods were established before conducting the review (no mention of a protocol) Study selection was performed by a single reviewer It was unclear if data extraction and quality assessment were conducted in duplicate A list of studies excluded after full-text review was not provided (although the reasons for exclusion were) Review authors did not report on sources of funding for the included primary studies Review authors did not state their potential conflicts of interest

Strengths	Limitations
HIQA (2019)[24]	
The objectives and inclusion criteria were clearly stated and included components of population, intervention, comparator, and outcomes The choice of included study designs (i.e., economic evaluations) was explained Multiple databases were searched (PubMed, Embase, the Cochrane Library, and the University of York CRD database for economic evaluations). In addition, a grey literature search and a search in Scopus were conducted Key search terms and search restrictions were provided (e.g., studies published in any language between January 1, 2013 and June 28, 2019 were eligible) A flow chart of study selection was provided Full-text screening was conducted by 2 reviewers Data extraction and quality assessment were conducted by 2 independent reviewers (disagreements were resolved through discussion, or by a third reviewer) The review authors described the included studies in adequate detail The quality of included primary studies was assessed using a satisfactory technique (i.e., the Consensus on Health Economic Criteria list) Review authors reported on sources of funding for the included primary studies Review authors stated that they had no conflicts of interest related to this review Sources of funding were disclosed and were unlikely to have had an effect on the findings of the review	It was unclear whether the review methods were established before conducting the review (no mention of a protocol) The first level of screening (i.e., title and abstracts) was performed by a single reviewer A list of studies excluded after full-text review was not provided (although the reasons for exclusion were)

Strengths	Limitations
Gialama et al. (2018)[26]	
The objectives and inclusion criteria were clearly stated and included components of population, intervention, comparator, and outcomes The choice of included study designs (i.e., economic evaluations) was explained Multiple databases were searched (PubMed and Cochrane databases). Additionally, the search was supplemented using internet search engines and reference lists from identified studies were further screened for any other eligible studies Key search terms and search restrictions were provided (e.g., studies published before June 2017 in English were eligible) A flow chart of study selection was provided The review authors described the included studies in adequate detail The quality of included primary studies was assessed using a satisfactory technique (i.e., 35-item British Medical Journal checklist to economic evaluations) Review authors reported on sources of funding for the included primary studies Review authors stated that they had no conflicts of interest related to this review	It was unclear whether the review methods were established before conducting the review (no mention of a protocol) It was unclear if study selection, data extraction, and quality assessment were conducted in duplicate A list of studies excluded after full-text review was not provided (although the reasons for exclusion were) The source of funding for the review was not disclosed

AMSTAR 2 = A MeaSurement Tool to Assess systematic Reviews 2; CRD = Centre for Reviews and Dissemination; HIQA = Health Information and Quality Authority; HTA = health technology assessment; NICE = National Institute for Health and Care Excellence.

Table 9: Strengths and Limitations of Economic Evaluations Using the Drummond Checklist[21]

Strengths	Limitations
Himmels et al. (2021)[27]	
Study design • The research question, economic importance of the research question, and rationale for choosing alternative interventions compared were clearly stated • The treatment strategies being compared were clearly described • The form of economic evaluation used was stated • The viewpoint/perspective of the analysis was clearly stated and justified • The choice of form of economic evaluation was justified in relation to the questions addressed **Data collection** • The sources of effectiveness estimates and treatment costs were provided • The designs and results of effectiveness studies from which assumptions were drawn were provided • The primary outcome measures for the economic evaluation were clearly stated • Methods to value benefits were stated • Details of the subjects from whom valuations were obtained were given • Methods for the estimation of quantities and unit costs were described • Currency and price data were recorded (2020 Norwegian kroner) • The structure of the model was clearly described using figures **Analysis and interpretation of results** • Time horizon of costs and benefits was stated (15-year horizon) • The discount rate for costs and benefits was stated (4% per year) • The approach to sensitivity analysis was given • The choice of variables for the sensitivity analysis was justified • Incremental analyses were reported • The answer to the study question was given • Conclusions followed from the data reported • Conclusions were accompanied by appropriate caveats **Miscellaneous** • Sources of funding were disclosed and were unlikely to have had an effect on the findings of the analysis • Authors stated that they had no conflicts of interest related to this study	Model inputs were taken from single trials, rather than a synthesis or meta-analysis of estimates from multiple sources No description of currency price adjustments for inflation was provided No justification for the selected discount rate was provided The findings of this Norway-based study may not be generalizable to the Canadian health system

Strengths	Limitations
Lorenzoni et al. (2021)[28]	
Study design • The research question, economic importance of the research question, and rationale for choosing alternative interventions compared were clearly stated • The treatment strategies being compared were clearly described • The form of economic evaluation used was stated • The viewpoint/perspective of the analysis was clearly stated and justified • The choice of form of economic evaluation was justified in relation to the questions addressed **Data collection** • The sources of effectiveness estimates and treatment costs were provided • The designs and results of effectiveness studies from which assumptions were drawn were provided • The primary outcome measures for the economic evaluation were clearly stated • Methods to value benefits were stated • Methods for the estimation of quantities and unit costs were described • Currency and price data were recorded (2019 euros) • The structure of the model was clearly described using figures **Analysis and interpretation of results** • Time horizon of costs and benefits was stated (15-year horizon) • The discount rate for costs and benefits was stated (3% per year) • The approach to sensitivity analysis was given • The choice of variables for the sensitivity analysis was justified • Incremental analyses were reported • The answer to the study question was given • Conclusions followed from the data reported • Conclusions were accompanied by appropriate caveats **Miscellaneous** • Study authors stated their potential conflicts of interest (5 authors stated they had no conflicts of interest to declare; 4 authors declared various ties to industry)	Limited information was provided on the characteristics of patient populations from whom model inputs were obtained Model inputs were taken from single trials, rather than a synthesis or meta-analysis of estimates from multiple sources No description of currency price adjustments for inflation was provided No justification for the selected discount rate was provided This work was funded by industry The findings of this Italy-based study may not be generalizable to the Canadian health system

Strengths	Limitations
Pinar et al. (2021)[29]	
Study design • The research question, economic importance of the research question, and rationale for choosing alternative interventions compared were clearly stated • The treatment strategies being compared were clearly described • The form of economic evaluation used was stated • The viewpoint/perspective of the analysis was clearly stated and justified • The choice of form of economic evaluation was justified in relation to the questions addressed **Data collection** • The sources of effectiveness estimates and treatment costs were provided • The results of effectiveness studies from which assumptions were drawn were provided • The primary outcome measures for the economic evaluation were clearly stated • Methods to value benefits were stated • Methods for the estimation of quantities and unit costs were described • Currency and price data were recorded (2019 euros) • The structure of the model was clearly described using figures **Analysis and interpretation of results** • Time horizon of costs and benefits was stated (15-year horizon) • The discount rate for costs and benefits was stated (3% per year) • The approach to sensitivity analysis was given • The choice of variables for the sensitivity analysis was justified • Incremental analyses were reported • The answer to the study question was given • Conclusions followed from the data reported • Conclusions were accompanied by appropriate caveats **Miscellaneous** • Study authors stated their potential conflicts of interest (4 authors declared various ties to industry)	The designs of effectiveness studies from which assumptions were drawn were not provided Limited information was provided on the characteristics of patient populations from whom model inputs were obtained Model inputs were taken from single trials, rather than a synthesis or meta-analysis of estimates from multiple sources No description of currency price adjustments for inflation was provided No justification for the selected discount rate was provided This work was funded by industry The findings of this Spain-based study may not be generalizable to the Canadian health system

Strengths	Limitations
Zhou et al. (2021)[30]	
Study design • The research question, economic importance of the research question, and rationale for choosing alternative interventions compared were clearly stated • The treatment strategies being compared were clearly described • The form of economic evaluation used was stated • The viewpoint/perspective of the analysis was clearly stated and justified • The choice of form of economic evaluation was justified in relation to the questions addressed **Data collection** • The sources of effectiveness estimates and treatment costs were provided • The designs and results of effectiveness studies from which assumptions were drawn were provided • The primary outcome measures for the economic evaluation were clearly stated • Methods to value benefits were stated • Details of the subjects from whom valuations were obtained were given • Methods for the estimation of quantities and unit costs were described • Currency and price data were recorded (2019 Australian dollars) • The details of currency price adjustments for inflation were given • The structure of the model was clearly described using figures **Analysis and interpretation of results** • Time horizon of costs and benefits was stated (lifetime horizon) • The discount rate for costs and benefits was stated and justified (5% per year) • The approach to sensitivity analysis was given • The choice of variables for the sensitivity analysis was justified • Incremental analyses were reported • The answer to the study question was given • Conclusions followed from the data reported • Conclusions were accompanied by appropriate caveats **Miscellaneous** • Sources of funding were disclosed and were unlikely to have had an effect on the findings of the analysis • Study authors stated their potential conflicts of interest (2 authors stated they had no conflicts of interest to declare; 4 authors declared various ties to industry)	Model inputs were taken from single trials, rather than a synthesis or meta-analysis of estimates from multiple sources The findings of this Australia-based study may not be generalizable to the Canadian health system

Strengths	Limitations
Health Technology Wales (2020)[22]	
Study design • The research question, economic importance of the research question, and rationale for choosing alternative interventions compared were clearly stated • The treatment strategies being compared were clearly described • The form of economic evaluation used was stated • The viewpoint/perspective of the analysis was clearly stated and justified • The choice of form of economic evaluation was justified in relation to the questions addressed **Data collection** • The sources of effectiveness estimates and treatment costs were provided • The designs and results of effectiveness studies from which assumptions were drawn were provided • The primary outcome measures for the economic evaluation were clearly stated • Methods to value benefits were stated • Details of the subjects from whom valuations were obtained were given • Methods for the estimation of quantities and unit costs were described • Currency and price data were recorded (2019 pound sterling) • The structure of the model was clearly described using figures **Analysis and interpretation of results** • Time horizon of costs and benefits was stated (lifetime horizon) • The discount rate for costs and benefits was stated and justified (3.5% per year) • The approach to sensitivity analysis was given • The choice of variables for the sensitivity analysis was justified • Incremental analyses were reported • The answer to the study question was given • Conclusions followed from the data reported • Conclusions were accompanied by appropriate caveats **Miscellaneous** • Sources of funding were disclosed and were unlikely to have had an effect on the findings of the analysis	Model inputs were taken from single trials, rather than a synthesis or meta-analysis of estimates from multiple sources No description of currency price adjustments for inflation was provided Study authors did not state their potential conflicts of interest The findings of this Wales-based study may not be generalizable to the Canadian health system

Strengths	Limitations
Inoue et al. (2020)[31]	
Study design • The research question, economic importance of the research question, and rationale for choosing alternative interventions compared were clearly stated • The treatment strategies being compared were clearly described • The form of economic evaluation used was stated • The viewpoint/perspective of the analysis was clearly stated and justified • The choice of form of economic evaluation was justified in relation to the questions addressed **Data collection** • The sources of effectiveness estimates and treatment costs were provided • The designs and results of effectiveness studies from which assumptions were drawn were provided • The clinical inputs for the model were derived from a systematic review of the literature • The primary outcome measures for the economic evaluation were clearly stated • Methods to value benefits were stated • Details of the subjects from whom valuations were obtained were given • Methods for the estimation of quantities and unit costs were described • Currency and price data were recorded (2016 Japanese yen) • The details of currency price adjustments for inflation were given • The structure of the model was clearly described using figures **Analysis and interpretation of results** • Time horizon of costs and benefits was stated (lifetime horizon) • The discount rate for costs and benefits was stated (2% per year) • The approach to sensitivity analysis was given • The choice of variables for the sensitivity analysis was justified • Incremental analyses were reported • The answer to the study question was given • Conclusions followed from the data reported • Conclusions were accompanied by appropriate caveats **Miscellaneous** • Authors stated that they had no conflicts of interest related to this study	No justification for the selected discount rate was provided This work was funded by industryThe findings of this Japan-based study may not be generalizable to the Canadian health system

Strengths	Limitations
Kuntjoro et al. (2020)[32]	
Study design • The research question, economic importance of the research question, and rationale for choosing alternative interventions compared were clearly stated • The treatment strategies being compared were clearly described • The form of economic evaluation used was stated • The viewpoint/perspective of the analysis was clearly stated and justified • The choice of form of economic evaluation was justified in relation to the questions addressed **Data collection** • The sources of effectiveness estimates and treatment costs were provided • The designs and results of effectiveness studies from which assumptions were drawn were provided • The primary outcome measures for the economic evaluation were clearly stated • Methods to value benefits were stated • Details of the subjects from whom valuations were obtained were given • Methods for the estimation of quantities and unit costs were described • Currency and price data were recorded (2017 Singapore dollars) • The structure of the model was clearly described using figures **Analysis and interpretation of results** • Time horizon of costs and benefits was stated (8-year horizon) • The discount rate for costs and benefits was stated (3% per year) • The approach to sensitivity analysis was given • The choice of variables for the sensitivity analysis was justified • Incremental analyses were reported • The answer to the study question was given • Conclusions followed from the data reported • Conclusions were accompanied by appropriate caveats **Miscellaneous** • Sources of funding were disclosed and were unlikely to have had an effect on the findings of the analysis	Model inputs were taken from single trials, rather than a synthesis or meta-analysis of estimates from multiple sources No description of currency price adjustments for inflation was provided No justification for the selected discount rate was providedStudy authors did not state their potential conflicts of interest The findings of this Singapore-based study may not be generalizable to the Canadian health system

Strengths	Limitations
HIQA (2019)[24]	
Study design • The research question, economic importance of the research question, and rationale for choosing alternative interventions compared were clearly stated • The treatment strategies being compared were clearly described • The form of economic evaluation used was stated • The viewpoint/perspective of the analysis was clearly stated and justified • The choice of form of economic evaluation was justified in relation to the questions addressed **Data collection** • The sources of effectiveness estimates and treatment costs were provided • The designs and results of effectiveness studies from which assumptions were drawn were provided • The clinical inputs for the model were derived from a systematic review of the literature • The primary outcome measures for the economic evaluation were clearly stated • Methods to value benefits were stated • Details of the subjects from whom valuations were obtained were given • Methods for the estimation of quantities and unit costs were described • Currency and price data were recorded (2019 euros) • The structure of the model was clearly described using figures **Analysis and interpretation of results** • Time horizon of costs and benefits was stated (15-year horizon) • The discount rate for costs and benefits was stated and justified (4% per year) • The approach to sensitivity analysis was given • The choice of variables for the sensitivity analysis was justified • Incremental analyses were reported • The answer to the study question was given • Conclusions followed from the data reported • Conclusions were accompanied by appropriate caveats **Miscellaneous** • Sources of funding were disclosed and were unlikely to have had an effect on the findings of the analysis • Authors stated that they had no conflicts of interest related to this study	No description of currency price adjustments for inflation was provided Study authors did not state their potential conflicts of interest The findings of this Ireland-based study may not be generalizable to the Canadian health system

Appendix 4: Main Study Findings and Authors' Conclusions

Note that this appendix has been formatted for accessibility but has not been copy-edited.

Summary of Findings Included Systematic Reviews

Azraai et al. (2020)[25]

Main study findings

Systematic review that evaluated the cost-effectiveness of TAVI for patients with aortic stenosis at low to intermediate surgical risk.

Relevant primary studies: A total of 8 cost-effectiveness studies were included in the systematic review, all of which were relevant to the current report. Relevant results are summarized individually by primary study.

Intermediate-risk patients

Baron et al. (2019)

- Total costs
  - SAVR: US$224,569; TAVI: US$214,282
- Incremental QALYs (versus SAVR)
  - TAVI: 0.27
- ICER (incremental costs/incremental QALYs; versus SAVR)
  - TAVI: Dominant (i.e., treatment resulted in more QALYs and less costs)
- Probability of cost-effectiveness
  - At a willingness-to-pay threshold of US$50,000 per QALY, TAVI had a 97% probability of being cost-effective

Goodall et al. (2019)

- Total costs
  - SAVR: €34,596; TAVI: €34,157
- Incremental QALYs (versus SAVR)
  - TAVI: 0.41
- ICER (incremental costs/incremental QALYs; versus SAVR)
  - TAVI: Dominant (i.e., treatment resulted in more QALYs and less costs)
- Probability of cost-effectiveness
  - At a willingness-to-pay threshold of €15,000 per QALY, TAVI had a 90% probability of being cost-effective

Osnabrugge et al. (2012)

- Total costs
  - SAVR: €35,511; TAVI: €46,217
- Incremental QALYs (versus SAVR)

    - TAVI: 0.068
- ICER (incremental costs/incremental QALYs; versus SAVR)
    - TAVI: €57,441/QALY
- Probability of cost-effectiveness
    - The willingness-to-pay threshold and probability of cost-effectiveness were not reported (NR)

Tam et al. (2018a)

- Total costs
    - SAVR: CA$29,856; TAVI: CA$40,274
- Incremental QALYs (versus SAVR)
    - TAVI: 0.23
- ICER (incremental costs/incremental QALYs; versus SAVR)
    - TAVI: CA$46,083/QALY
- Probability of cost-effectiveness
    - CA$50,000 per QALY was used as the willingness-to-pay threshold; however, the probability that TAVI was cost-effective at this threshold was NR

Tam et al. (2018b)

- Total costs
    - SAVR: CA$32,994; TAVI: CA$44,299
- Incremental QALYs (versus SAVR)
    - TAVI: 0.14
- ICER (incremental costs/incremental QALYs; versus SAVR)
    - TAVI: CA$76,736/QALY
- Probability of cost-effectiveness
    - CA$100,000 per QALY was used as the willingness-to-pay threshold; however, the probability that TAVI was cost-effective at this threshold was NR

Zhou et al. (2019a)

- Total costs
    - SAVR: AU$60,144; TAVI: AU$50,515
- Incremental QALYs (versus SAVR)
    - TAVI: 0.33
- ICER (incremental costs/incremental QALYs; versus SAVR)
    - TAVI: Dominant (i.e., treatment resulted in more QALYs and less costs)
- Probability of cost-effectiveness
    - At a willingness-to-pay threshold of AU$50,000 per QALY, TAVI had a 92% probability of being cost-effective

Low-risk patients

Geisler et al. (2019)

- Total costs

- SAVR: Danish krone (DKK) 211,581; TAVI: DKK 276,142
- Incremental QALYs (versus SAVR)
  - TAVI: 0.09
- ICER (incremental costs/incremental QALYs; versus SAVR)
  - TAVI: DKK 696,264/QALY
- Probability of cost-effectiveness
  - At a willingness-to-pay threshold of DKK 1,130,000 per QALY, TAVI had a 78% probability of being cost-effective

Zhou et al. (2019b)

- Total costs
  - SAVR: NR; TAVI: NR
- Incremental QALYs (versus SAVR)
  - TAVI: 0.15
- ICER (incremental costs/incremental QALYs; versus SAVR)
  - TAVI: NR
- Probability of cost-effectiveness
  - At an unspecified willingness-to-pay threshold, TAVI had a 85% probability of being cost-effective

Authors' conclusion

"The present systematic review showed that TAVI is potentially cost-effective alternative to SAVR in patients with intermediate surgical risk, possibly extending to those with low surgical risk. Although the raw costs of TAVI is greater, the procedure has been associated with a significant gain in QALY compared to SAVR (p. 1167)."[25]

Health Technology Wales (2020)[22]

Main study findings

Systematic review (conducted as part of an HTA) that summarized the evidence regarding the cost-effectiveness of TAVI for severe symptomatic aortic stenosis in adults at intermediate surgical risk.

Relevant primary studies: A total of 10 cost-utility analyses were included in the systematic review, all of which were relevant to the current report. Relevant results are summarized individually by primary study.

Baron et al. (2019)

- Total costs
  - SAVR: US$235,312; SAPIEN XT TAVI: US$227,363
  - SAVR: US$240,871; SAPIEN 3 TAVI: US$231,179
- Incremental costs (versus SAVR)
  - SAPIEN XT TAVI: −US$7,949
  - SAPIEN 3 TAVI: −US$9,692
- Incremental QALYs (versus SAVR)

    - SAPIEN XT TAVI: 0.15
    - SAPIEN 3 TAVI: 0.27
- ICER (incremental costs/incremental QALYs; versus SAVR)
    - SAPIEN XT TAVI: Dominant (i.e., treatment resulted in more QALYs and less costs)
    - SAPIEN 3 TAVI: Dominant (i.e., treatment resulted in more QALYs and less costs)
- Probability of cost-effectiveness
    - SAPIEN XT TAVI: NR
    - SAPIEN 3 TAVI: NR

Goodall et al. (2019)

- Total costs
    - SAVR: €34,596; TAVI: €34,157
- Incremental costs (versus SAVR)
    - TAVI: −£439
- Incremental QALYs (versus SAVR)
    - TAVI: 0.41
- ICER (incremental costs/incremental QALYs; versus SAVR)
    - TAVI: Dominant (i.e., treatment resulted in more QALYs and less costs)
- Probability of cost-effectiveness
    - At a willingness-to-pay threshold of €15,000 per QALY, TAVI had a 100% probability of being cost-effective

Health Information and Quality Authority (2019)

- Total costs
    - SAVR: €42,879; TAVI: €42,681
- Incremental costs (versus SAVR)
    - TAVI: −£198
- Incremental QALYs (versus SAVR)
    - TAVI: 0.06
- ICER (incremental costs/incremental QALYs; versus SAVR)
    - TAVI: Dominant (i.e., treatment resulted in more QALYs and less costs)
- Probability of cost-effectiveness
    - At a willingness-to-pay threshold of €20,000 per QALY, TAVI had a 61.8% probability of being cost-effective

Kodera et al. (2018)

- Total costs
    - SAVR: ¥6,316,178; TAVI: ¥8,039,694
- Incremental costs (versus SAVR)
    - TAVI: ¥1,723,516
- Incremental QALYs (versus SAVR)
    - TAVI: 0.22

- ICER (incremental costs/incremental QALYs; versus SAVR)
  - TAVI: ¥7,523,821/QALY
- Probability of cost-effectiveness
  - At a willingness-to-pay threshold of ¥5,000,000 per QALY, TAVI had a 46% probability of being cost-effective

Norwegian Institute of Public Health (2019)

- Total costs
  - SAVR: Norwegian krone (NOK) 343,607; TAVI: NOK 414,526
- Incremental costs (versus SAVR)
  - TAVI: NOK 70,920
- Incremental QALYs (versus SAVR)
  - TAVI: 0.07
- ICER (incremental costs/incremental QALYs; versus SAVR)
  - TAVI: NOK 1,037,083/QALY
- Probability of cost-effectiveness
  - Across willingness-to-pay thresholds between NOK 0 and NOK 825,000 per additional QALY, SAVR had a higher probability of being cost-effective

Scottish Health Technologies Group (2019)

- Total costs
  - SAVR: £22,051; TAVI: £34,995
- Incremental costs (versus SAVR)
  - TAVI: £12,945
- Incremental QALYs (versus SAVR)
  - TAVI: 0.13
- ICER (incremental costs/incremental QALYs; versus SAVR)
  - TAVI: £98,965/QALY
- Probability of cost-effectiveness
  - At a willingness-to-pay threshold of £20,000 per QALY, TAVI had a 26.9% probability of being cost-effective

Tam et al. (2018a)

- Total costs
  - SAVR: CA$36,356; TAVI: CA$46,904
- Incremental costs (versus SAVR)
  - TAVI: CA$10,547
- Incremental QALYs (versus SAVR)
  - TAVI: 0.23
- ICER (incremental costs/incremental QALYs; versus SAVR)
  - TAVI: CA$46,083/QALY
- Probability of cost-effectiveness

- At a willingness-to-pay threshold of CA$50,000 per QALY, TAVI had a 52.7% probability of being cost-effective

Tam et al. (2018b)

- Total costs
  - SAVR: CA$32,994; TAVI: CA$44,299
- Incremental costs (versus SAVR)
  - TAVI: CA$11,305
- Incremental QALYs (versus SAVR)
  - TAVI: 0.14
- ICER (incremental costs/incremental QALYs; versus SAVR)
  - TAVI: CA$76,736/QALY
- Probability of cost-effectiveness
  - At a willingness-to-pay threshold of CA$50,000 per QALY, TAVI had a 52.9% probability of being cost-effective

Tarride et al. (2019)

- Total costs
  - SAVR: CA$57,083; TAVI: CA$70,556
- Incremental costs (versus SAVR)
  - TAVI: CA$13,473
- Incremental QALYs (versus SAVR)
  - TAVI: 0.48
- ICER (incremental costs/incremental QALYs; versus SAVR)
  - TAVI: CA$28,154/QALY
- Probability of cost-effectiveness
  - At a willingness-to-pay threshold of CA$50,000 per QALY, TAVI had a 91% probability of being cost-effective

Zhou et al. (2019a)

- Total costs
  - SAVR: AU$60,144; TAVI: AU$50,515
- Incremental QALYs (versus SAVR)
  - TAVI: 0.31
- ICER (incremental costs/incremental QALYs; versus SAVR)
  - TAVI: Dominant (i.e., treatment resulted in more QALYs and less costs)
- Probability of cost-effectiveness
  - At a willingness-to-pay threshold of AU$50,000 per QALY, TAVI had a 92% probability of being cost-effective

Authors' conclusion

"The results of the economic analysis suggested that TAVI is more effective and more costly than SAVR but not cost-effective as the ICER exceeds the threshold of £20,000 per QALY. This result was consistent with the analysis by SHTG and other analyses in this area. However,

some of the analyses in other settings have found contrasting results, with TAVI found to be less costly and more effective than SAVR (i.e. dominant). The contrasting results primarily reflect differences in the procedure costs for TAVI and SAVR (p. 35)."[22]

Ontario Health (2020)[23]

Main study findings

Systematic review (conducted as part of an HTA) that evaluated the cost-effectiveness of TAVI for adults with severe aortic valve stenosis who are at low surgical risk.

Relevant primary studies: A total of 1 cost-utility analysis was included in the systematic review. This analysis was relevant to the current report.

Tam et al. (2020)

- Total costs
  - SAVR: CA$34,583; balloon-expandable TAVI: CA$37,330; self-expanding TAVI: CA$39,660
- QALYs
  - SAVR: 9.05; balloon-expandable TAVI: 9.15; self-expanding TAVI: 9.13
- ICER (incremental costs/incremental QALYs; versus SAVR)
  - Balloon-expandable TAVI: CA$27,196/QALY; self-expanding TAVI: CA$59,641/QALY
- Probability of cost-effectiveness
  - At a willingness-to-pay thresholds of CA$50,000 and CA$100,000 per QALY, balloon-expandable TAVI had 53% and 59% probabilities of being cost-effective, respectively
  - At a willingness-to-pay thresholds of CA$50,000 and CA$100,000 per QALY, self-expanding TAVI had < 5% and < 10% probabilities of being cost-effective, respectively

Authors' conclusion

"Our review of the literature identified one published cost-effectiveness analysis that compared TAVI with SAVR in adults with severe aortic valve stenosis who were at low surgical risk. The study was directly applicable and conducted from the perspective of the Ontario Ministry of Health. The TAVI procedure might be cost-effective for patients at low surgical risk; however, there is some uncertainty in this result (p. 56)."[23]

HIQA (2019)[24]

Main study findings

Systematic review (conducted as part of an HTA) that investigated the cost-effectiveness of TAVI compared to SAVR in patients with severe symptomatic aortic stenosis at low or intermediate risk of surgical complications.

Relevant primary studies: A total of 7 economic evaluations were included in the systematic review, all of which were relevant to the current report. Relevant results are summarized individually by primary study.

Baron et al. (2019)

- Total costs
  - SAVR: US$235,312; SAPIEN XT TAVI: US$227,363
  - SAVR: US$240,871; SAPIEN 3 TAVI: US$231,179

- QALYs
  - SAVR: 5.01; SAPIEN XT TAVI: 5.16; SAPIEN 3 TAVI: 5.29
- ICER (incremental costs/incremental QALYs; versus SAVR)
  - SAPIEN XT TAVI: Dominant (i.e., treatment resulted in more QALYs and less costs)
  - SAPIEN 3 TAVI: Dominant (i.e., treatment resulted in more QALYs and less costs)

Goodall et al. (2019)

- Total costs
  - SAVR: €34,596; TAVI: €34,157
- QALYs
  - SAVR: 3.65; TAVI: 4.06
- ICER (incremental costs/incremental QALYs; versus SAVR)
  - TAVI: Dominant (i.e., treatment resulted in more QALYs and less costs)

Kaier et al. (2019)

- Total costs
  - SAVR: €19,175; TAVI: €33,614
- Risk-adjusted in-hospital mortality
  - SAVR: 2.65%; TAVI: 2.07%
- ICER (versus SAVR)
  - TAVI: €1,486,118 per life saved

Kodera et al. (2018)

- Total costs
  - SAVR: ¥6,316,178; TAVI: ¥8,039,694
- QALYs
  - SAVR: 4.59; TAVI: 4.81
- ICER (incremental costs/incremental QALYs; versus SAVR)
  - TAVI: ¥7,523,821/QALY

Tam et al. (2018a)

- Total costs
  - SAVR: CA$36,356; TAVI: CA$46,904
- QALYs
  - SAVR: 5.40; TAVI: 5.63
- ICER (incremental costs/incremental QALYs; versus SAVR)
  - TAVI: CA$46,083/QALY

Tam et al. (2018b)

- Total costs
  - SAVR: CA$32,994; TAVI: CA$44,299
- QALYs
  - SAVR: 6.28; TAVI: 6.42

- ICER (incremental costs/incremental QALYs; versus SAVR)
  - TAVI: CA$76,736/QALY

Zhou et al. (2019a)

- Total costs
  - SAVR: AU$60,144; TAVI: AU$50,515
- QALYs
  - SAVR: 3.82; TAVI: 4.13
- ICER (incremental costs/incremental QALYs; versus SAVR)
  - TAVI: Dominant (i.e., treatment resulted in more QALYs and less costs)

Authors' conclusion

"This systematic review identified seven studies to date that evaluated the cost-effectiveness of TAVI versus SAVR in intermediate risk patients. The cost-effectiveness of the device was generally supported in these studies; however, a number of concerns regarding the quality and credibility of the economic evaluations were identified. These largely related to model structure (for example, many studies modelled implausible health state transitions) and choice of input parameters (for example, few studies comprehensively evaluated postoperative complications). The systematic review found no studies that considered the cost-effectiveness of the device in patients at low surgical risk (p. 82-83)."

Gialama et al. (2018)[26]

Main study findings

Systematic review that assessed the cost-effectiveness of interventions for valvular heart disease.

Relevant primary studies: The systematic review included 24 studies that investigated various transcatheter interventions for valvular heart disease; however, only primary studies that compared TAVI versus SAVR for the treatment of severe aortic stenosis were relevant to the current report (11 studies). Relevant results are summarized individually by primary study.

Doble et al. (2012)

- Total costs
  - SAVR: CA$74,602; TAVI: CA$85,755
- Incremental QALYs (versus SAVR)
  - TAVI: −0.102
- Incremental life-years gained (versus SAVR)
  - TAVI: 0.0128
- ICER (incremental costs/incremental QALYs; versus SAVR)
  - TAVI: Dominated (i.e., treatment resulted in less QALYs and more costs)
- Probability of cost-effectiveness
  - CA$50,000 per QALY was used as the willingness-to-pay threshold; however, the probability that TAVI was cost-effective at this threshold was NR

Fairbairn et al. (2013)

- Total costs

    - SAVR: £53,943.40; TAVI: £52,593.02
- QALYs
    - SAVR: 2.75; TAVI: 2.81
- Life-years gained
    - SAVR: 4.30; TAVI: 4.43
- ICER (incremental costs/incremental QALYs; versus SAVR)
    - TAVI: Dominant (i.e., treatment resulted in more QALYs and less costs)
- Probability of cost-effectiveness
    - £20,000 to £30,000 per QALY were used as the willingness-to-pay thresholds; however, the probability that TAVI was cost-effective at these thresholds was NR

Gada et al. (2012a)

- Total costs
    - SAVR: US$56,630; TAVI: US$56,730
- QALYs
    - SAVR: 1.70; TAVI: 1.66
- ICER (incremental costs/incremental QALYs; versus SAVR)
    - TAVI: Dominated (i.e., treatment resulted in less QALYs and more costs)
- Probability of cost-effectiveness
    - US$100,000 per QALY was used as the willingness-to-pay threshold; however, the probability that TAVI was cost-effective at this threshold was NR

Gada et al. (2012b)

- Total costs
    - SAVR: US$56,339; TAVI: US$59,503
- Incremental QALYs (versus SAVR)
    - TAVI: 0.06
- ICER (incremental costs/incremental QALYs; versus SAVR)
    - TAVI: US$52,773/QALY
- Probability of cost-effectiveness
    - US$100,000 per QALY was used as the willingness-to-pay threshold; however, the probability that TAVI was cost-effective at this threshold was NR

Neyt et al. (2012)

- Incremental costs (versus SAVR)
    - TAVI: €20,397
- Incremental QALYs (versus SAVR)
    - TAVI: 0.03
- ICER (incremental costs/incremental QALYs; versus SAVR)
    - TAVI: €750,000/QALY
- Probability of cost-effectiveness
    - €47,141 per QALY was used as the willingness-to-pay threshold; however, the probability that TAVI was cost-effective at this threshold was NR

Orlando et al. (2013)

- Total costs
  - SAVR: £19,871; TAVI: £27,833
- QALYs
  - SAVR: 3.46; TAVI: 2.85
- ICER (incremental costs/incremental QALYs; versus SAVR)
  - TAVI: Dominated (i.e., treatment resulted in less QALYs and more costs)
- Probability of cost-effectiveness
  - £20,000 to £30,000 per QALY were used as the willingness-to-pay thresholds; however, the probability that TAVI was cost-effective at these thresholds was NR

Osnabrugge et al. (2012)

- Total costs
  - SAVR: €35,511; TAVI: €46,217
- Incremental QALYs (versus SAVR)
  - TAVI: 0.068
- ICER (incremental costs/incremental QALYs; versus SAVR)
  - TAVI: €150,000/QALY
- Probability of cost-effectiveness
  - €30,000 per QALY was used as the willingness-to-pay threshold; however, the probability that TAVI was cost-effective at this threshold was NR

Reynolds et al. (2012)

- Total costs
  - SAVR: US$98,434; transfemoral-transapical TAVI: US$100,504
  - SAVR: US$97,992; transfemoral TAVI: US$96,743
  - SAVR: US$99,499; transapical TAVI: US$109,405
- QALYs
  - SAVR: 0.606; transfemoral-transapical TAVI: 0.633
  - SAVR: 0.591; transfemoral TAVI: 0.659
  - SAVR: 0.641; transapical TAVI: 0.570
- Life-years gained
  - SAVR: 0.817; transfemoral-transapical TAVI: 0.858
  - SAVR: 0.813; transfemoral TAVI: 0878
  - SAVR: 0.826; transapical TAVI: 0.811
- ICER (incremental costs/incremental QALYs; versus SAVR)
  - Transfemoral-transapical TAVI: US$76,877/QALY
  - Transfemoral TAVI: Dominant (i.e., treatment resulted in more QALYs and less costs)
  - Transapical TAVI: Dominated (i.e., treatment resulted in less QALYs and more costs)
- Probability of cost-effectiveness

- US$50,000 per QALY was used as the willingness-to-pay threshold; however, the probability that TAVI was cost-effective at this threshold was NR

Reynolds et al. (2016)

- Total costs
  - SAVR: US$189 629; TAVI: US$207,478
- QALYs
  - SAVR: 3.825; TAVI: 4.149
- Life-years gained
  - SAVR: 5.92; TAVI: 6.45
- ICER (incremental costs/incremental QALYs; versus SAVR)
  - TAVI: US$55,090/QALY
- ICER (incremental costs/incremental life-year gained; versus SAVR)
  - TAVI: US$43,114/LYG
- Probability of cost-effectiveness
  - US$50,000 and US$150,000 per QALY were used as the willingness-to-pay thresholds; however, the probability that TAVI was cost-effective at these thresholds was NR

Ribera et al. (2015)

- Total costs
  - SAVR: €23,288; Edwards SAPIEN self-expandable TAVI: €32,087; Medtronic CoreValve balloon-expandable TAVI: €32,111
- QALYs
  - SAVR: 0.644; Edwards SAPIEN self-expandable TAVI: 0.680; Medtronic CoreValve balloon-expandable TAVI: 0.633
- ICER (incremental costs/incremental QALYs; versus SAVR)
  - Edwards SAPIEN self-expandable TAVI: €148,535/QALY; Medtronic CoreValve balloon-expandable TAVI: Dominated (i.e., treatment resulted in less QALYs and more costs)
- Probability of cost-effectiveness
  - €30,000 per QALY was used as the willingness-to-pay threshold; however, the probability that TAVI was cost-effective at this threshold was NR

SHTG (2010)

- Total costs
  - SAVR: £31,516; TAVI: £36,375
- QALYs
  - SAVR: 3.65; TAVI: 3.71
- ICER (incremental costs/incremental QALYs; versus SAVR)
  - TAVI: £87,293/QALY
- Probability of cost-effectiveness
  - £20,000 to £30,000 per QALY were used as the willingness-to-pay thresholds; however, the probability that TAVI was cost-effective at these thresholds was NR

Authors' conclusion

"…the cost-effectiveness of TAVI compared with SAVR in high-risk operable patients, based on the current data, is uncertain. Some studies show it to dominate, others to be dominated, others to be cost-effective and other not. Hence, is not possible to reach any safe conclusions. The limited evidence available, supports that whether TAVI compared with SAVR is cost-effective may depend on the access route (transfemoral or transapical), the procedural cost, and the patients selected, since in general terms TAVI and SAVR have demonstrated similar survival and only small differences in benefit in terms of quality of life. More research is needed in this area (p. 89)."[26]

Summary of Findings of Included Economic Evaluations

Himmels et al. (2021)[27]

Main study findings

Cost-utility analysis (conducted as part of an HTA) that examined the cost-effectiveness of TAVI versus SAVR in patients with severe calcific aortic stenosis considered to be at low surgical risk from the Norwegian health care perspective.

Summary of findings

Base-case results

- Total costs
  - SAVR: NOK 428,070; TAVI: NOK 392,788
- QALYs
  - SAVR: 9.0079; AVI: 9.0617
- Incremental costs (versus SAVR)
  - TAVI: NOK −35 283
- Incremental QALYs (versus SAVR)
  - TAVI: 0.054
- ICER (incremental costs/incremental QALYs; versus SAVR)
  - TAVI: Dominant (i.e., treatment resulted in more QALYs and less costs)
- Probabilities of cost-effectiveness
  - Across willingness-to-pay thresholds between NOK 0 and NOK 825,000 per additional QALY, TAVI was approximately 70% likely to be cost-effective

Scenario analysis (minimal cost of SAVR procedures)

- Total costs
  - SAVR: NOK 369,900; TAVI: NOK 393,900
- QALYs
  - SAVR: 9.0026; TAVI: 9.0574
- Incremental costs (versus SAVR)
  - TAVI: NOK 24,000
- Incremental QALYs (versus SAVR)
  - TAVI: 0.0548

- ICER (incremental costs/incremental QALYs; versus SAVR)
  - TAVI: NOK 436,363/QALY
- Probability of cost-effectiveness
  - TAVI was cost-effective at a willingness-to-pay threshold over NOK 436,400
  - SAVR was cost-effective at a willingness-to-pay threshold under NOK 436,400

Scenario analysis (maximal cost of SAVR procedures)

- Total costs
  - SAVR: NOK 488,657; TAVI: NOK 394,084
- QALYs
  - SAVR: 9.0073; TAVI: 9.0629
- Incremental costs (versus SAVR)
  - TAVI: NOK −94,573
- Incremental QALYs (versus SAVR)
  - TAVI: 0.0556
- ICER (incremental costs/incremental QALYs; versus SAVR)
  - TAVI: Dominant (i.e., treatment resulted in more QALYs and less costs)
- Probabilities of cost-effectiveness
  - Across willingness-to-pay thresholds between NOK 0 and NOK 825,000 per additional QALY, TAVI was at least 80% likely to be cost-effective

Scenario analysis (time horizon 1 year)

- Total costs
  - SAVR: NOK 340,789; TAVI: NOK 344,118
- QALYs
  - SAVR: 0.6625; TAVI: 0.7610
- Incremental costs (versus SAVR)
  - TAVI: NOK 3,329
- Incremental QALYs (versus SAVR)
  - TAVI: 0.0985
- ICER (incremental costs/incremental QALYs; versus SAVR)
  - TAVI: NOK 33,800/QALY
- Probabilities of cost-effectiveness
  - The probability that TAVI was the cost-effective procedure ranged from approximately 50% to 85% across willingness-to-pay thresholds between NOK 0 and NOK 825,000 per additional QALY

Authors' conclusion

"The cost-utility analysis indicated that TAVI for patients at low surgical risk was marginally more effective (incremental effectiveness: 0.05 QALYs) and less costly (saving of NOK 35 000) than SAVR. The analysis is based on 1-year follow-up data from the PARTNER 3 study and long-term mortality and adverse events for TAVI and SAVR beyond this period remain unclear. The results are sensitive to variations in procedure costs (p. 66)."[27]

Lorenzoni et al. (2021)[28]

Main study findings

Cost-utility analysis that modelled the cost-effectiveness of TAVI versus SAVR (in high- or intermediate-risk patients) or medical treatment (in inoperable patients) in patients with severe symptomatic aortic stenosis. Findings from the analysis in inoperable patients were not summarized as they were not relevant to the current report.

Summary of findings

Base-case results in intermediate-risk patients

- Total costs
  - SAVR: €33,030; TAVI: €36,623
- QALYs
  - SAVR: 3.78; TAVI: 4.21
- Life-years gained
  - SAVR: 5.64; TAVI: 6.08
- Incremental costs (versus SAVR)
  - TAVI: €3,593
- Incremental QALYs (versus SAVR)
  - TAVI: 0.43
- Incremental life-years gained (versus SAVR)
  - TAVI: 0.45
- ICER (incremental costs/incremental QALYs)
  - TAVI: €8,338/QALY
- ICER (incremental costs/incremental life-year gained)
  - TAVI: €8,035/life-year gained

Base-case results in high-risk patients

- Total costs
  - SAVR: €33,358; TAVI: €37,189
- QALYs
  - SAVR: 2.49; TAVI: 2.83
- Life-years gained
  - SAVR: 4.08; TAVI: 4.49
- Incremental costs (versus SAVR)
  - TAVI: €3,831
- Incremental QALYs (versus SAVR)
  - TAVI: 0.34
- Incremental life-years gained (versus SAVR)
  - TAVI: 0.40
- ICER (incremental costs/incremental QALYs)
  - TAVI: €11,209/QALY

- ICER (incremental costs/incremental life-years gained)
  - TAVI: €9,474/life-year gained

Probabilities of cost-effectiveness

- "Cost-effectiveness acceptability curves, shown in Fig. 5, suggest that considering conventional thresholds defined at national level (typically comprised between €25,000–40,000/QALY), TAVI showed high probability (in the range of about 90–100%) of being cost-effective in all risk groups, both when considering the upper and lower limits of the range of value generally considered in Italy (p. 8)."[28]

Sensitivity analyses

- Sensitivity analyses suggested that mortality along the time horizon, major incidence of stroke in the short-term, and repeated hospitalizations for aortic stenosis were among the main drivers of base-case results.

Authors' conclusion

"The results of the cost-effectiveness analysis performed show that, considering the Italian National Health System perspective, TAVI would be considered highly cost-effective at frequently cited willingness to pay thresholds. Similar conclusions emerged over a range of analyses performed and also modelling a scenario considering micro-costing data. Indeed, the diverse of analyses performed offer the possible range defining the value for money of TAVI and offer important messages to clinicians and decision maker on both the overall value of TAVI, but also on the feasibility of considering the procedure over diverse risk groups, some of which were rarely considered as candidate for TAVI procedure both in view of the limited evidence related to both clinical and economic implications (p. 12)."[28]

Pinar et al. (2021)[29]

Main study findings

A cost-utility analysis that investigated the cost-effectiveness of TAVI using the SAPIEN 3 system versus SAVR (in high- or intermediate-risk patients) or conservative medical treatment (in inoperable patients) from the perspective of the Spanish National Health System. Only the analysis that compared TAVI to SAVR was considered relevant to the current report.

Summary of findings

Base-case results in intermediate-risk patients

- Total costs
  - SAVR: €47,413; TAVI: €50,950
- QALYs
  - SAVR: 4.15; TAVI: 4.59
- Life-years gained
  - SAVR: 5.64; TAVI: 6.08
- ICER (incremental costs/incremental QALYs)
  - TAVI: €8,119/QALY
- ICER (incremental costs/incremental life-years gained)
  - TAVI: €7,910/life-year gained

Base-case results in high-risk patients

- Total costs
  - SAVR: €47,191; TAVI: €49,346
- QALYs
  - SAVR: 2.74; TAVI: 3.13
- Life-years gained
  - SAVR: 4.08; TAVI: 4.49
- ICER (incremental costs/incremental QALYs)
  - TAVI: €5,471/QALY
- ICER (incremental costs/incremental life-years gained)
  - TAVI: €5,329/life-year gained

Probabilistic sensitivity analyses

- TAVI was the cost-effective option in 74.9% of simulations and dominant in 24.3% of simulations in intermediate-risk patients, based on a willingness-to-pay threshold of €30,000 per QALY gained
- TAVI was cost-effective in 87.8% of simulations and dominant in 12.2% of simulations in high-risk patients, based on a willingness-to-pay threshold of €30,000 per QALY gained

Authors' conclusion

"Treatment of aortic stenosis by S3 TAVI is an effective option for inoperable patients, patients at high surgical risk, and those at intermediate risk and is, moreover, highly likely to be the most cost-effective strategy. With the increasing health care demands linked to population aging, there is a growing need for technological innovations that permit less invasive interventions to simplify procedures while maintaining clinical standards and optimizing resource use (p. 7)."[29]

Zhou et al. (2021)[30]

Main study findings

Cost-utility analysis that examined the cost-effectiveness of balloon-expandable or self-expanding TAVI versus SAVR in patients with severe aortic stenosis considered to be at low surgical risk, from the perspective of the Australian health care system.

Summary of findings

Base-case results for balloon-expandable TAVI

- Total costs
  - SAVR: AU$60,557; balloon-expandable TAVI: AU$61,259
- Life-years gained
  - SAVR: 9.40; balloon-expandable TAVI: 9.57
- QALYs
  - SAVR: 7.20; balloon-expandable TAVI: 7.40
- Incremental costs (versus SAVR)
  - Balloon-expandable TAVI: AU$702

- Incremental life-years gained (versus SAVR)
  - Balloon-expandable TAVI: 0.17
- Incremental QALYs (versus SAVR)
  - Balloon-expandable TAVI: 0.20
- ICER (incremental costs/incremental life-years gained)
  - TAVI: AU$4,521/life-year gained
- ICER (incremental costs/incremental QALYs)
  - Balloon-expandable TAVI: AU$3,521 /QALY

Base-case results for self-expanding TAVI

- Total costs
  - SAVR: AU$65,093; self-expanding TAVI: AU$64,585
- Life-years gained
  - SAVR: 8.82; self-expanding TAVI: 8.88
- QALYs
  - SAVR: 6.53; self-expanding TAVI: 6.60
- Incremental costs (versus SAVR)
  - Self-expanding TAVI: −AU$507
- Incremental life-years gained (versus SAVR)
  - Self-expanding TAVI: 0.06
- Incremental QALYs (versus SAVR)
  - Self-expanding TAVI: 0.08
- ICER (incremental costs/incremental life-years gained)
  - Self-expanding TAVI: Dominant (i.e., treatment resulted in more life-years and less costs)
- ICER (incremental costs/incremental QALYs)
  - Self-expanding TAVI: Dominant (i.e., treatment resulted in more QALYs and less costs)

Probabilities of cost-effectiveness

- Probabilistic sensitivity analyses suggested that balloon-expandable TAVI was cost-effective in 78% of Monte Carlo iterations at a willingness-to-pay threshold of AU$50,000 per QALY gained. At a willingness-to-pay threshold of AU$100,000 per QALY gained balloon-expandable TAVI was cost-effective in 88% of iterations.
- Self-expanding TAVI was considered cost-effective in 70% and 80% of iterations when willingness-to-pay thresholds of AU$50,000 and AU$100,000 were applied, respectively

Sensitivity analyses

- "Balloon-expandable TAVI remained cost-effective compared to SAVR when most input parameters were varied across their 95% confidence intervals. The ICER only exceeded the willingness-to-pay threshold of AU$50,000 per QALY gained if the cost of the TAVI valve exceeded A$35,511 (versus A$26,250 in the base case) (p. 550)."
- "For self-expanding TAVI, findings were also robust to changes in most model inputs over plausible ranges. However, compared with the balloon-expandable TAVI analysis, results were more sensitive to key cost drivers such as the price of the transcatheter valve and length of intensive care unit stay. As shown in Figure 2B, self-expanding TAVI was no longer

cost-effective if the price of the TAVI valve exceeded AU$27,286 or if TAVI intensive care unit length of stay exceeded the base-case estimate of 2 days (p. 550)."

Authors' conclusion

"Among low-risk patients with severe symptomatic AS, both balloon-expandable and self-expanding TAVI are likely to be cost-effective compared with SAVR from the perspective of the Australian health care system (p. 553)."[30]

Health Technology Wales (2020)[22]

Main study findings

A cost-utility analysis (conducted as part of an HTA) that estimated the cost-effectiveness of TAVI compared to SAVR for people with severe symptomatic aortic stenosis at intermediate surgical risk. The analysis was conducted from the perspective of the UK National Health Service and personal social services.

Summary of findings

Base-case results

- Total costs
  - SAVR: £19,880; TAVI: £29,025
- QALYs
  - SAVR: 4.27; TAVI: 4.36
- Incremental costs (versus SAVR)
  - TAVI: £9,145
- Incremental QALYs (versus SAVR)
  - TAVI: 0.10
- ICER (incremental costs/incremental QALYs; versus SAVR)
  - TAVI: £94,512 per QALY

Probabilities of cost-effectiveness

- Using a willingness-to-pay threshold of £20,000 per QALY, TAVI had a 27% probability of being cost-effective using the base-case scenario

Sensitivity analyses

- Baseline age = 70 years
  - ICER (incremental costs/incremental QALYs; versus SAVR)
    - TAVI: £70,497 per QALY
- Baseline age = 75 years
  - ICER (incremental costs/incremental QALYs; versus SAVR)
    - TAVI: £78,266per QALY
- Baseline age = 80 years
  - ICER (incremental costs/incremental QALYs; versus SAVR)
    - TAVI: £89,996 per QALY
- Baseline age = 85 years
  - ICER (incremental costs/incremental QALYs; versus SAVR)

        - TAVI: £105,551 per QALY
- Only statistically significant differences in complications included
    - ICER (incremental costs/incremental QALYs; versus SAVR)
        - TAVI: £508,239 per QALY
- TAVI and SAVR costs based on HIQA estimates
    - ICER (incremental costs/incremental QALYs; versus SAVR)
        - TAVI: Dominant (i.e., treatment resulted in more life-years and less costs)

Additional sensitivity analyses are available in the publication.[22]

Authors' conclusion

"The results of the analysis show that TAVI was marginally more effective than SAVR but substantially more costly. The resulting ICER of £94,512 per QALY is substantially higher than the £20,000 per QALY threshold indicating that TAVI is not cost-effective (p. 72)."[22]

Inoue et al. (2020)[31]

Main study findings

Cost-utility analysis that investigated the cost-effectiveness of transfemoral TAVI using the SAPIEN XT system versus SAVR (in high surgical risk patients) or supportive pharmacotherapy (in inoperable patients) from the public health care perspective in Japan. Only findings from the analysis that compared TAVI to SAVR were considered relevant to the current report.

Summary of findings

Base-case results

- Total costs
    - SAVR: ¥6,169,068; TAVI: ¥7,725,818
- QALYs
    - SAVR: 4.3946; TAVI: 5.5586
- Incremental costs (versus SAVR)
    - TAVI: ¥1,556,749
- Incremental QALYs (versus SAVR)
    - TAVI: 1.1639
- ICER (incremental costs/incremental QALYs; versus SAVR)
    - TAVI: ¥1,337,525 per QALY

Probabilities of cost-effectiveness

- Using a willingness-to-pay threshold of ¥5,000,000/QALY, the probability of TAVI being cost-effective compared with SAVR was 99.9%

Scenario analysis (based on domestic studies)

- Total costs
    - SAVR: ¥6,116,945; TAVI: ¥7,098,560
- QALYs

- SAVR: 3.0564; TAVI: 5.1454
- Incremental costs (versus SAVR)
  - TAVI: ¥981,615
- Incremental QALYs (versus SAVR)
  - TAVI: 2.0890
- ICER (incremental costs/incremental QALYs; versus SAVR)
  - TAVI: ¥469,890 per QALY

Sensitivity analyses

- The ICER of TAVI versus SAVR remained below ¥5,000,000 across all sensitivity analyses

Authors' conclusion

"This is the first study evaluating the cost-effectiveness of TAVI in which a systematic literature review was conducted and Japanese claims data were used. The results demonstrated that transfemoral TAVI was cost-effective compared with SAVR for high-risk patients and with standard of care for inoperable patients. Assuming a cost-effectiveness threshold of ¥5 million/QALY, the probabilities of transfemoral TAVI being cost-effective compared with SAVR and standard of care were 99.9% and 93.9%, respectively, validating the robustness of these findings (p. 89)."[31]

Kuntjoro et al. (2020)[32]

Main study findings

A cost-utility analysis that examined the cost-effectiveness of transfemoral TAVI using balloon-expandable SAPIEN systems compared to SAVR in patients with severe aortic stenosis considered to be at intermediate or low surgical risk from the perspective of the National University Health System in Singapore.

Summary of findings

Base-case results

- Total costs
  - SAVR: S$69,140; TAVI: S$75,386
- QALYs
  - SAVR: 3.67; TAVI: 3.86
- Incremental costs (versus SAVR)
  - TAVI: S$5,852
- Incremental QALYs (versus SAVR)
  - TAVI: 0.21
- ICER (incremental costs/incremental QALYs; versus SAVR)
  - TAVI: S$33,833 per QALY

Probabilities of cost-effectiveness

- Using a willingness-to-pay threshold of S$73,167/QALY, the probability of TAVI being cost-effective compared with SAVR was 98.2%

Deterministic sensitivity analyses

- "The model was the most sensitive to changes of operational costs for transfemoral TAVI and SAVR. However, the models were robust as ICERs remain similar when applying significant changes on parameters (p. 428)."[32]

Scenario analyses

- "Shortening the time horizon while holding all other base-case assumptions constantly resulted in larger ICERs for transfemoral TAVI. Using the events rates based on the newer TAVI systems generated more favourable results for transfemoral TAVI. Assuming no new cases for long-term complications or the 2 treatments had same probabilities of stroke, myocardial infarction, and acute kidney injury beyond 2 years also led to higher ICERs (p. 428)."[32]

Authors' conclusion

"From the perspective of the Singapore healthcare system, transfemoral TAVI is highly likely to be a cost-effective treatment option for intermediate and low risk patients with severe symptomatic aortic stenosis, in comparison with SAVR. Our study would provide the first evidence for the potential of TAVI to be an alternative treatment to the conventional SAVR in Singapore. The positive result might contribute to the future formulation of local clinical practice guidelines or health policies (p. 432)."[32]

HIQA (2019)[24]

Main study findings

Cost-utility analysis (conducted as part of an HTA) that assessed the cost-effectiveness of TAVI versus SAVR in patients with severe symptomatic aortic stenosis at low (e.g., Society of Thoracic Surgeons predicted risk of mortality [STS-PROM] < 4%) or intermediate risk (e.g., STS-PROM ≥ 4 and < 8%) of surgical complications from the perspective of the publicly funded health and social care system in Ireland.

Summary of findings

Base-case results in intermediate-risk patients

- Total costs
  - SAVR: €42,879 (95% confidence interval (CI) = €36,493 to €49,946); TAVI: €42,681 (95% CI = €36,584 to €49,475)
- QALYs
  - SAVR: 4.942 (95% CI = 4.668 to 5.227); TAVI: 5.000 (95% CI = 4.746 to 5.262)
- Incremental costs (versus SAVR)
  - TAVI: € − 198 (95% CI = € − 8,193 to €7,643)
- Incremental QALYs (versus SAVR)
  - TAVI: 0.058 (95% CI = − 0.060 to 0.181)
- ICER (incremental costs/incremental QALYs)
  - TAVI: Dominant (i.e., treatment resulted in more QALYs and less costs)
- Incremental net monetary benefit
  - TAVI: €1,359 (95% CI = € − 6,755 to €9,685)

Base-case results in low-risk patients

- Total costs

- SAVR: €38,643 (95% CI = €31,071 to €48,328); TAVI: €38,256 (95% CI = €31,064 to €47,690)

- QALYs
  - SAVR: 6.181 (95% CI = 5.903 to 6.433); TAVI: 6.203 (95% CI = 5.929 to 6.448)
- Incremental costs (versus SAVR)
  - TAVI: € − 387 (95% CI = € − 8,355 to €7,702)
- Incremental QALYs (versus SAVR)
  - TAVI: 0.021 (95% CI = − 0.129 to 0.172)
- ICER (incremental costs/incremental QALYs)
  - TAVI: Dominant (i.e., treatment resulted in more QALYs and less costs)
- Incremental net monetary benefit
  - TAVI: €808 (95% CI = € − 7,837 to €9,417)

Probabilities of cost-effectiveness

- Using a cost willingness-to-pay threshold of €20,000 per QALY, the probability that TAVI was the cost-effective option was 61.8% in intermediate risk patients and 57.1% in high-risk patients

Sensitivity and scenario analyses

- "The cost-utility findings were robust to a wide range of sensitivity and scenario analyses (p. vi)."[24]

Authors' conclusion

"In both the intermediate and low surgical risk populations, TAVI was less costly and delivered more QALYs than SAVR (due to the short-term improvement in patients' health-related quality of life). The probability that TAVI was cost-effective at the €20,000 per QALY gained threshold was 61.8% in intermediate risk patients and 57.1% in low risk patients (p. vi)."[24]

Appendix 5: Overlap Between Included Systematic Reviews

Note that this appendix has been formatted for accessibility but has not been copy-edited.

Table 10: Overlap in Relevant Primary Studies Between Included Systematic Reviews

Primary study citation	Azraai et al. (2020)[25]	Health Technology Wales (2020)[22]	Ontario Health (2020)[23]	HIQA (2019)[24]	Gialama et al. (2018)[26]
Baron SJ, et al. Circulation. 2019; 139(7):877-888.	Yes	Yes	NI	Yes	NI
Doble B, et al. J Thorac Cardiovasc Surg. 2013;146(1):52-60.e3.	NI	NI	NI	NI	Yes
Fagerlund BC, et al. Oslo (NO): Norwegian Institute of Public Health; 2019.	NI	Yes	NI	NI	NI
Fairbairn TA, et al. Heart. 2013;99(13):914-920.	NI	NI	NI	NI	Yes
Gada H, et al. Am J Cardiol. 2012;109(9):1326-1333.	NI	NI	NI	NI	Yes
Gada H, et al. Ann Cardiothorac Surg. 2012;1(2):145-155.	NI	NI	NI	NI	Yes
Geisler BP, et al. EuroIntervention. 2019;15(11):e959-e967.	Yes	NI	NI	NI	NI
Goodall G, et al. J Med Econ. 2019;22(4):289-296.	Yes	Yes	NI	Yes	NI
Kaier K, et al. Eur J Health Econ. 2019;20(4):625-632.	NI	NI	NI	Yes	NI
Kodera S, et al. J Cardiol. 2017;71(3):223-229.	Yes	Yes	NI	NI	NI
Neyt M, et al. BMJ Open. 2012;2(3):e001032	NI	NI	NI	NI	Yes
Orlando R, et al. Health Technol Assess. 2013;17(33):1-86.	NI	NI	NI	NI	Yes
Osnabrugge RLJ, et al. Ann Thorac Surg. 2012;94(6):1954-1960.	Yes	NI	NI	NI	Yes
Reynolds MR, et al. J Am Coll Cardiol. 2016;67(1):29-38.	NI	NI	NI	NI	Yes
Reynolds MR, et al. J Am Coll Cardiol. 2012;60(25):2683-2692.	NI	NI	NI	NI	Yes
Ribera A, et al. Int J Cardiol. 2015;182:321-328	NI	NI	NI	NI	Yes

Primary study citation	Azraai et al. (2020)[25]	Health Technology Wales (2020)[22]	Ontario Health (2020)[23]	HIQA (2019)[24]	Gialama et al. (2018)[26]
Evidence Note 91. Edinburgh (UK): Scottish Health Technologies Group; 2019.	NI	Yes	NI	NI	NI
Evidence Development Pilot Project. Edinburgh (UK): Scottish Health Technologies Group; 2010.	NI	NI	NI	NI	Yes
Tam DY, et al. Ann Thorac Surg. 2018;106(3):676-684	NI	NI	Yes	NI	NI
Tam DY, et al. Eur Heart J Qual Care Clin Outcomes. 2020;0:1-8.	Yes	Yes	NI	Yes	NI
Tam DY, et al. J Thorac Cardiovasc Surg. 2018;155(5):1978-1988.e1.	Yes	Yes	NI	Yes	NI
Tarride JE, et al. Clinicoecon Outcomes Res. 2019;11:477-486.	NI	Yes	NI	NI	NI
Zhou J, et al. Circulation. 2019;140:A14484-A.	Yes	NI	NI	NI	NI
Zhou J, et al. Int J Cardiol. 2019;294:17-22.	Yes	Yes	NI	Yes	NI

NI = the primary study was not included in the systematic review; HIQA = Health Information and Quality Authority; SHTG = Scottish Health Technologies Group; Yes = the primary study was included in the systematic review.

Appendix 6: References of Potential Interest

Note that this appendix has been formatted for accessibility but has not been copy-edited.

Health Technology Assessments — Published Prior to 2018

1. Health Quality Ontario. Transcatheter aortic valve Implantation for Treatment of Aortic Valve Stenosis: A Health Technology Assessment. *Ont Health Technol Assess Ser*. 2016;16(19):1-94. PubMed

Overviews of Systematic Reviews — Published Prior to 2018

2. Kularatna S, Byrnes J, Mervin MC, Scuffham PA. Health Technology Assessments Reporting Cost-Effectiveness of Transcatheter aortic valve Implantation. *Int J Technol Assess Health Care*. 2016 Jan;32(3):89-96. PubMed

Review Articles

3. Adams HSL, Ashokkumar S, Newcomb A, MacIsaac AI, Whitbourn RJ, Palmer S. Contemporary review of severe aortic stenosis. *Intern Med J.* 2019 Mar;49(3):297-305. PubMed

4. Baron S, Reynolds MR, Cohen DJ. Economic Considerations for TAVR Vs. SAVR: Historical Perspective and Future Predictions. *Latest in Cardiology*. 2019. https://www.acc.org/latest-in-cardiology/articles/2019/06/18/07/43/economic-considerations-for-tavr-vs-savr Accessed 2021 Jun 28.

5. Witberg G, Patterson T, Redwood S, Prendergast B. Future Directions. Transcatheter aortic valve Implantation for Low-risk Patients: Inevitable Evolution or a Step Too Far? *Rev Esp Cardiol (Engl)*. 2019 Aug;72(8):664-671. PubMed

6. Manolis AS. Transcatheter aortic valve implantation economics: a grisly reality. *Ann Cardiothorac Surg*. 2017 Sep;6(5):516-523. PubMed

Poster Presentations

7. Reardon MJ, Geisler BP, Popma JJ, et al. Cost-effectiveness of Transcatheter Aortic Valve Implantation in Patients at Intermediate Surgical Risk: A Model-based Analysis based on the SURTAVI Trial Using Contemporary Cost Data. Poster session presented at EuroPCR 2019, the annual Course of the European Association of Percutaneous Cardiovascular Interventions (EAPCI) of the European Society of Cardiology (ESC), Paris, France. https://europe.medtronic.com/content/dam/medtronic-com/xd-en/c/od08315-tavi-ir-cea/190522-europcr-e-poster-surtavi-cea.pdf Accessed 2021 Jun 28.