Technoleg Iechyd Cymru
Health Technology Wales

Evidence Appraisal Report

Transcatheter Aortic Valve implantation to treat people with severe symptomatic aortic stenosis, who are at intermediate surgical risk

1. Purpose of the evidence appraisal report

This report aims to identify and summarise evidence that addresses the following question: Is transcatheter aortic valve implantation (TAVI) clinically and cost effective for severe symptomatic aortic stenosis in adults who are assessed by a heart team as being operable but at intermediate surgical risk?

Evidence Appraisal Reports are based on rapid systematic literature searches, with the aim of identifying the best published clinical and economic evidence on health technologies. This review is an adaptation of the Scottish Health Technologies Group (SHTG) Evidence note 91: Transcatheter aortic valve implantation (TAVI) for the treatment of patients with severe symptomatic aortic stenosis at intermediate surgical risk (SHTG 2019). HTW included an update to this review, and researchers critically evaluated this evidence. The draft Evidence Appraisal Report is reviewed by experts and by Health Technology Wales multidisciplinary advisory groups before publication.

2. Health problem

Aortic stenosis (AS) is an obstruction of normal blood flow across the aortic valve, caused by calcification, which may have degenerative, rheumatic or congenital aetiology (SHTG 2019). Aortic stenosis is the most common native heart valve disease in adults in Europe (Iung et al. 2003). It is most often seen in older people, increasing likelihood with age, due to degenerative calcification (Iung et al. 2003, Iung et al. 2005).

AS and the severity of disease is primarily diagnosed through echocardiography (Baumgartner et al. 2017). Most people with mild to moderate AS are asymptomatic, but people with severe AS are likely to develop symptoms that are associated with the narrowing of the valve and an overload of the left ventricle, such as syncope, exercise-induced angina, dyspnoea and congestive heart failure.

The prevalence of severe symptomatic AS is around 3% in those aged over 75 years old, but this rises steeply with age (Osnabrugge et al. 2013). Therefore, due to an ageing population, the prevalence will increase over the following decades.

Without intervention, patients with severe symptomatic AS have a poor prognosis with an average survival of two to three years (Sethi et al. 2009) and survival rates of only 15% to 50% at five years (Vahanian et al. 2012).

Surgical aortic valve replacement (SAVR) is the standard treatment for people with severe AS who are well enough for surgery (NICE 2017). An alternative procedure, transcatheter aortic valve implantation (TAVI) can be used for people of an increased operable risk (Baumgartner et al. 2017), and is a common treatment for those of inoperable or high surgical risk. However, more focus is turning to the use of TAVI in lower or intermediate risk populations. People at intermediate surgical risk is the population of interest for this evidence review.

3. Health technology

TAVI involves the insertion of a prosthetic valve, which functionally replaces the damaged aortic valve, using fluoroscopic and echographically guided minimally invasive procedures (SHTG 2019). The prosthetic valve is compressed within a dedicated delivery system and, once in place within the diseased aortic valve, its deployment allows its expansion and the compression of the native diseased valve against the wall of the aorta. Depending on the anatomy of the patient and device characteristics, the procedure can be performed by one of four different approaches. The transfemoral (TF) approach is the most common, but if the anatomy of the patient precludes access via the transfemoral route then other approaches are considered. These approaches are the subclavian/ transaxillary (S/T) approach, the transapical (TA) approach, and the transaortic (TAo) approach (SHTG 2019).

There are several TAVI systems commercially available. For intermediate operative risk, devices are available from two manufactures in the UK:

- Edwards SAPIEN TAVI balloon-expandable systems (Edwards Lifesciences).
- CoreValve Evolut R/PRO self-expandable systems (Medtronic).

Experts informed HTW that first generation TAVI devices (SAPIEN XT and CoreValve) are no longer used in current practice[1].

The reference treatment for TAVI is SAVR. SAVR with an artificial (biological or mechanical) prosthesis can be performed using different surgical approaches (full sternotomy and more minimally invasive procedures), different kinds of valves, and different kinds of valve anchoring techniques (sutured and sutureless).

4. Surgical risk assessment and epidemiology

The surgical risk of each individual patient is usually assessed by a specialised multidisciplinary heart team to estimate overall risk and to stratify patients to receive either palliative medical treatment (no valve replacement), medical treatment with reassessment on follow-up, SAVR, or TAVI. The team take into consideration surgical risk scores alongside the assessment of other characteristics, such as frailty or additional comorbidities (not covered by the scores).

The most commonly used surgical risk algorithms include STS Predicted Risk of Mortality (STS-PROM), logistic EuroSCORE and EuroSCORE II (SHTG 2019). These systems aim to identify and quantify several risk factors that help to predict mortality from cardiac surgery. STS-PROM calculates risk based on the demographic and clinical characteristics of each patient. It is available as an online statistical tool. EuroSCORE assigns scores to patient-related, cardiac-related, and surgery-related risk factors. In its first version, published in 1999, the predicted mortality (in percent) was simply a sum of weights assigned to the risk factors. The tool was later refined into a logistic regression equation (logistic EuroSCORE). The latest version of the model (EuroSCORE II) was launched in 2011 as an online tool and is frequently updated and enhanced.

[1] Expert consultation (August 2020).

The exact cut-off values for risk scores vary across the literature and can be arbitrary. For STS-Prom and EuroSCORE II, intermediate and low risk are defined by the ESC/EACTS guidelines as 4 to 8% and <4%, respectively (Baumgartner et al. 2017).

A model by De Sciscio et al. (2017), which assumed the overall prevalence of AS among people aged >60 years to be 4.5%, suggested that 7.5 million people in Europe are likely to have AS. Approximately 20% of these have severe AS and around 71% of those with severe AS are symptomatic. Based on this model, it is estimated that 873,700 people in Europe are eligible for open-heart surgery. The calculated proportion of this population with intermediate surgical risk is approximately 28.9%, resulting in an estimate of 252,500 people. The study went on to estimate that the number of people in the UK aged ≥75 years with severe symptomatic AS, who are at intermediate surgical risk and eligible for TAVI is 8,993 (95% Confidence interval (CI) 4,317–15,475) (De Sciscio et al. 2017). Based on these figures, HTW estimates that in Wales there would be approximately 423 people with severe AS at intermediate surgical risk, who would be eligible for TAVI.

The prevalence of AS is likely to increase with progressive ageing of the population in Europe. Currently, 20% of this population is ≥65 years old, with predictions that this proportion will rise to 24% by 2030 (SHTG 2019).

In NHS Wales, TAVI can be offered to people with severe symptomatic stenosis who are high risk or inoperable for SAVR (WHSSC 2019). Patients who are considered high risk or inoperable should be referred to a TAVI multidisciplinary team.

5. Evidence search methods

We searched for evidence that could be used to answer the review question: Is transcatheter aortic valve implantation (TAVI) clinically and cost effective for severe symptomatic aortic stenosis in adults who are assessed by a heart team as being operable but at intermediate surgical risk?

This report incorporated work from the Scottish Health Technologies Group (SHTG) (SHTG 2019), who adapted this initial report from the European Network for Health Technology Assessment (EUnetHTA) (EUnetHTA 2018). The original EUnetHTA searches were performed on 26 and 27 June 2017, and subsequent searches from SHTG were performed during 2018. As part of this review, HTW searched for new secondary evidence, randomised controlled trials and economic evidence, between up to 8 September 2020. Medline, Embase and the Cochrane Library were searched, as well as relevant websites, including those for ongoing clinical trials. The search strategy is available upon request.

The criteria used to select evidence for the appraisal are outlined in Appendix 1. These criteria were developed following comments from the Health Technology Wales (HTW) Assessment Group and UK experts.

Separate searches for evidence on organisational and patient issues were not undertaken, but any relevant evidence was identified from the clinical/economic searches.

Appendix 2 summarises the selection of articles for inclusion in the review.

6. Clinical effectiveness

The SHTG review reported on a EUnetHTA review and meta-analysis. EUnetHTA identified two randomised controlled trials (RCTs) that they included in the analysis: PARTNER 2 and SURTAVI (EUnetHTA 2018). Update searches from SHTG and HTW did not identify any additional RCTs that

were published after the EUnetHTA review. The RCTs and EUnetHTA analysis are discussed further in Section 6.2.

HTW's update searches identified six potentially relevant health technology assessments published from 2018. Two were the EUnetHTA and SHTG health technology assessments, included in this review. The third was a rapid response from Canadian Agency for Drugs and Technologies in Health (CADTH), published prior to the EUnetHTA work, and therefore excluded (CADTH 2018). A Norwegian HTA report was also identified, but was excluded from the clinical effectiveness review as only the economic evaluation was published (NIPH 2019). An HTA from Health Quality Ontario, was published after the EUnetHTA review but did not include new evidence (i.e. new RCTs), so was also excluded. Finally, the Health Information and Quality Authority (HIQA) for Ireland published a HTA on TAVI for low and intermediate risk populations (HIQA 2019); this was excluded due to population.

We identified eight potentially relevant systematic reviews, all of which were excluded. Three had meta-analyses comprising RCTs with other study types, such as observational data (Singh et al. 2018, Lazkani et al. 2019, Ueshima et al. 2019). Two had unclear risk subgrouping or unclear inclusion of other surgical risk patients (Ando et al. 2019, Fang et al. 2019). One study included non-comparative single arm studies (Borracci et al. 2019). The final two systematic reviews reported and analysed the same two RCTs from the EUnetHTA study; as these did not add any further evidence, these were also excluded from this review (Khan et al. 2019, Siontis et al. 2019).

Although our searches did not identify new RCTs, seven publications reported additional data from either the PARTNER 2 or SURTAVI trials. Of these, six did not fit our study selection criteria. One included a composite population of SURTAVI participants and registry data to evaluate a newer TAVI system (Baron et al. 2018). Two did not report relevant outcomes from our study selection criteria (Amrane et al. 2019, Cremer et al. 2018). One was excluded as it compared the impact of new onset left bundle branch block on outcomes (Nazif et al. 2019). One study compared consequences of neurological complications in the SURTAVI trial (Durko et al. 2018); this was excluded as the comparison did not fit the review question/selection criteria.

The remaining study from Makkar et al. (2020) reports outcomes at five-year follow-up in the PARTNER 2 trial.

The PARTNER 2 and SURTAVI trial use TAVI devices SAPIEN XT (Edwards Lifesciences) and CoreValve Evolut R (Medtronic). We did not identify any evidence (randomised controlled trials) that evaluated newer TAVI devices in patients with symptomatic AS, who are of intermediate risk.

6.1 Guidelines

The National Institute for Health and Care Excellence (NICE) interventional procedures guidance (IPG586) states that " current evidence on the safety and efficacy of transcatheter aortic valve implantation (TAVI) for aortic stenosis is adequate to support the use of this procedure provided that standard arrangements are in place for clinical governance, consent and audit." (NICE 2017).

The IPG also recommends that patient selection for TAVI should be carried out by an experienced multidisciplinary team, which must include interventional cardiologists experienced in the procedure, cardiac surgeons, an expert in cardiac imaging and, when appropriate, a cardiac anaesthetist and a specialist in elderly medicine. The multidisciplinary team should determine the risk level for each patient and the TAVI device most suitable for them (NICE 2017).

European guidelines from the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) recommend that the choice of the intervention should take into account the cardiac and extra-cardiac characteristics of the patient, the individual risk of surgery assessed by the judgement of the heart team, in addition to risk scores, the feasibility of TAVI, and local experience and outcome data (Baumgartner et al. 2017). British

Cardiovascular Intervention Society guidance recommends that MDTs should refer to the up-to-date guidelines from NICE and ESC/EACTS in order to inform decision making (BCIS 2019).

A joint statement on clinical selection for TAVI from the British Cardiovascular Society (BCS), Society for Cardiothoracic Surgery (SCTS), and the British Cardiovascular Intervention Society (BCIS) recommends that intermediate cases should be referred to the heart team for consideration, and TAVI considered if the patient is intermediate risk but has other risk factors that make TAVI preferable to SAVR. They also state that classification of patients as extreme, high, intermediate, or low-risk is dependent on multiple factors, including age, co-morbidity, and frailty. Surgical risk scores including STS-score, Logistic EuroSCORE, and EuroSCORE-II may be used. However, none of the existing surgical risk scores have been validated in TAVI, and all omit important clinical variables, including frailty. It is therefore recommended that risk status and optimal treatment modality is determined by the MDT after considering all relevant clinical information (BCS et al. 2017).

6.2 Randomised controlled trials and EUnetHTA meta-analysis

The EUnetHTA review identified two randomised controlled trials (RCTs): PARTNER 2 and SURTAVI (Leon et al. 2016, Reardon et al. 2017). Study characteristics for these studies are outlined in Table 1. The follow-up time was two years for both studies. The studies were funded by the manufacturers, with each study focusing on the respective devices. Update searches from SHTG and HTW did not identify any additional RCTs that were published after the EUnetHTA review for intermediate risk populations.

EUnetHTA conducted meta-analyses of outcomes from the two identified studies (EUnetHTA 2018). Primary outcomes in both trials were a composite of death from any cause or disabling stroke at 2-year follow-up; however, both studies reported most outcomes at follow-up after 30 days, 1 year, and 2 years.

In the PARTNER 2 trial, outcomes were reported using Kaplan Meier time-to-event analyses on available evidence at each time point (Leon et al. 2016). For various outcomes, the population at risk varied at each time point. As an example, at 2-year follow-up, 774 patients in the TAVI group (out of 1,011 participants randomized) and 695 patients in the SAVR group (out of 1,021 participants randomized) were available for the overall mortality outcome. This important attrition generated serious concerns regarding the available evidence at the 2-year follow-up.

For the SURTAVI trial, the reported data represented the results of an interim analysis after 1 year using a Bayesian approach (Reardon et al. 2017). Most patients reached this follow-up point; however, at the 2-year follow-up, there were considerably fewer patients. Thus, data for patients without a known outcome were imputed at the 2-year follow-up. As an example, for the mortality outcome at the 2-year follow-up, 280 patients were available for outcome measures in the TAVI group and 249 in the SAVR group. The SURTAVI trial reported both standard and modified intention-to-treat analysis with outcome imputation and sensitivity analysis. Hence, the study was considered at low risk of attrition bias at 30-day and 1-year follow-up but not at the 2-year follow-up.

Clinical effectiveness outcomes of the meta-analysis included:

- All-cause mortality
- Cardiac mortality
- Morbidity (symptoms)
- Aortic valve re-intervention
- Haemodynamic function on the valve
- Length of hospital stay

Table 2 summarises the outcomes from the meta-analysis, alongside the interpretation of evidence certainty using the GRADE evidence rating scale (Guyatt et al. 2008):

- High quality: we are very confident that the true effect lies close to that of the estimate of the effect.
- Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- Low quality: our confidence in the effect estimate is limited: the true effect might be substantially different from the estimate of the effect.
- Very low quality: we have little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

The primary outcome, composite of death from any cause or disabling stroke at two-year follow-up, was not included in the EUnetHTA meta-analysis and so is reported separately below.

6.2.1 Composite of death from any cause or disabling stroke (2-year follow-up)

In the PARTNER 2 trial, the Kaplan–Meier event rates were 19.3% in the TAVI group and 21.1% in the surgery group (hazard ratio [HR] in the TAVI group, 0.89, 95% confidence interval [CI] 0.73 to 1.09; p=0.25). Patients in a transfemoral subgroup had a lower rate of death or disabling stroke than those receiving surgery (HR 0.79, 95% CI 0.62 to 1.00; p = 0.05). In the transthoracic-access cohort, outcomes were similar in the two groups. However, the study was not powered for analysis of these subgroups.

In the SURTAVI Trial, the estimated incidence of the primary end point was 12.6% in the TAVR group and 14.0% in the surgery group (95% credible interval [Bayesian analysis] for difference, -5.2 to 2.3%; posterior probability of non-inferiority, > 0.999).

6.2.2 All-cause mortality

At 30-day follow-up, 3.1% of patients in the TAVI group had died, whereas 2.9% of patients had died in the SAVR group: TAVI was probably non-inferior to SAVR (RR 1.07, 95% CI 0.74 to 1.55, p=0.70; GRADE evidence: moderate).

At 2-year follow-up, 12.9% of patients had died in the TAVI group, whereas 12.7% had died in the SAVR group: it is uncertain whether TAVI is non-inferior to SAVR (RR 1.01, 95% CI 0.86 to 1.20, p=0.88; GRADE evidence: low).

6.2.3 Cardiac mortality

At 30-day follow-up, cardiac mortality was reported for 2.6% of patients in the TAVI group compared with 2.4% of patients in the SAVR group: TAVI is probably non-inferior to SAVR in terms of cardiac mortality (RR 1.11, 95% CI 0.75 to 1.66, p=0.60; GRADE evidence: moderate).

At 2-year follow-up, cardiac mortality was reported for 7.9% of patients in the TAVI group, compared with 8.2% in the SAVR group. In terms of cardiac mortality at patients -year follow-up, it is uncertain whether TAVI is non-inferior to SAVR (RR 0.96, 95% CI 0.78 to 1.19, p=0.73; GRADE evidence: low).

6.2.4 Morbidity - symptom reduction New York Heart Association (NYHA) classification

In the PARTNER 2 trial, 80% of patients were NYHA class III or higher at baseline. The investigators reported a significant reduction in symptoms to NYHA class II or I at 30-day follow-up in both the TAVI and control groups, and the NYHA class was maintained for 2 years (p <0.001). At 2-year follow-up, approximately 48% of patients in the TAVI group and approximately 52% in the surgery

group (read from graphic) remained in NYHA class I. No difference in effect was observed between the two groups at 1- or 2-year follow-up.

In the SURTAVI trial, 60% of the TAVI group and 58% of the SAVR group were NYHA class III or higher at baseline. After 2-year follow-up, there was a significant reduction to NYHA class II or I, with 62% NYHA class I in the TAVI and 58% in the SAVR group. No differences in effects were observed between the two groups at 1- or 2-year follow-up.

The authors of the EUnetHTA review downgraded the quality of evidence for this outcome due to concerns about bias (for example, imbalance in withdrawals between groups) and imprecision. They concluded that: it is uncertain whether TAVI has any effect on improving symptoms compared with SAVR at 1- or 2-year follow-up (GRADE evidence: very low).

6.2.5 Aortic valve re-intervention

At 30-day follow-up, aortic valve re-intervention was performed in 0.6% of patients in the TAVI group and 0.1% in the SAVR group: (RR 7.58, 95% CI 1.38 to 41.55, p=0.02; GRADE evidence: low).

At 2-year follow-up, aortic valve re-intervention was performed in 1.7% of the TAVI group and 0.4% of the SAVR group (RR 3.86, 95% CI 1.76 to 8.44, p=0.003; GRADE evidence: very low). Since there were serious concerns around attrition and imprecision it is uncertain whether TAVI increases the risk of aortic valve re-intervention

6.2.6 Haemodynamic function of the valve

Anticipated echocardiographic findings on aortic valve haemodynamics following successful SAVR and TAVI procedures include:

- Increased aortic valve area
- Increased left ventricular ejection fraction (LVEF)
- Decreased aortic valve gradients

In the PARTNER 2 trial, in both the TAVI and SAVR groups at 30 days, there was an improvement in the aortic valve area (1.7±0.5 cm^2 versus 1.5 cm^2±0.4, respectively; p <0.001 between groups), increased LVEF (56.9±10.2% versus 55.0±11.0%, respectively; p <0.004), as well as a decrease in the mean aortic valve gradients (9.7±3.5 mmHg versus 10.9±4.3 mmHg, respectively; p <0.001). These improvements persisted throughout the 2-year follow-up.

In the SURTAVI trial, from baseline to discharge, the mean aortic gradient improved in both the TAVI group (8.9±4.1 mmHg) and the SAVR group (12.4±5.7 mmHg); the difference between the two groups was statistically significant (p <0.001). This difference persisted throughout the 2-year follow-up. In addition, from baseline to discharge, the TAVI group had larger aortic valve areas than the SAVR group (2.1±0.6 cm^2 versus 1.8±0.6 cm^2, respectively) with a statistically significant difference. These improvements persisted throughout the 2-year follow-up.

6.2.7 Length of stay

In the PARTNER 2 trial, patients in the TAVI group had a significantly shorter duration of the index of hospitalisation (median, six days versus nine days; p <0.001) as well as a shorter duration of stay in the intensive care unit than those in the surgery group (median, two days versus four days; p <0.001).

In the SURTAVI trial, the duration of the index of hospitalisation was shorter in the TAVI than in the SAVR group (5.75±4.85 days versus 9.75±8.03 days, respectively; mean difference four days [95% CI -4.65 to -3.36]). No data regarding intensive care unit stays were provided.

The overall GRADE level of evidence for hospital stay was considered moderate.

Table 1. Study characteristics: RCTs in EUnetHTA meta-analysis

<table>
<tr><th>Reference</th><th>Study design</th><th>Population</th><th>Intervention / Comparator</th><th>Relevant outcomes</th><th>Additional notes/Comments on applicability</th></tr>
<tr>
<td>Leon et al. (2016)</td>
<td>Randomised controlled trial

Multicentre (n = 57, USA and Canada).

Enrolment from December 2011 to November 2013.

Follow up: 2 years</td>
<td>Patients with severe aortic stenosis and cardiac symptoms (n = 2,032).

Patients were considered to be intermediate risk by clinical assessment form a multidisciplinary heart team, using the STS risk score of > 4.0% and a (not prespecified) limit of 8.0%. People with a score < 4.0% but with a coexisting condition not represented in the risk model were also included.

<table>
<tr><th></th><th>TAVI (n = 1,011)</th><th>SAVR (n = 1,021)</th></tr>
<tr><td>Age (y, ±SD)</td><td>81.5±6.7</td><td>81.7±6.7</td></tr>
<tr><td>Sex (male, %)</td><td>548 (54.2)</td><td>560 (54.8)</td></tr>
<tr><td>STS score</td><td>5.8±2.1</td><td>5.8±1.9</td></tr>
</table>
</td>
<td>Intervention: TAVI (balloon-expandable SAPIAN XT heart-valve system, Edwards Lifesciences).

Patients assigned to TAVI underwent either transfemoral (n = 775) or transthoracic (n = 236) placement.

Comparator: SAVR</td>
<td>• Composite of mortality (any cause) or disabling stroke (primary outcome)
• All-cause mortality
• Cardiac mortality
• Morbidity (symptoms)
• Aortic valve reintervention
• Haemodynamic function
• Length of hospital stay
• Safety outcomes.</td>
<td>It is unclear whether the inclusion of low risk patients with coexisting conditions and STS scoring of < 4.0%, would affect the applicability of the population.

94 patients withdrew from the study, mainly due to a decision to not undergo surgery: 17 (1.7%) in the TAVI group and 77 (7.6%) in the SAVR group. It is unclear whether differences in withdrawal between the two groups might have created an imbalance in the prognostic characteristics of the two groups.</td>
</tr>
<tr>
<td>Reardon et al. (2017)</td>
<td>Randomised controlled trial (non-inferiority design)

Multicentre (n = 87; USA, Canada and Europe)

Enrolment June 19 2012 to June 30 2016

Follow up: 2 years</td>
<td>People with symptomatic, severe aortic stenosis who were determined as intermediate surgical risk by a multidisciplinary heart team (n = 1,746). The team used an STS risk score between 3% and 15% in addition to other coexisting illnesses (frailty and disability).

Modified ITT population:
<table>
<tr><th></th><th>TAVI (n = 864)</th><th>SAVR (n = 796)</th></tr>
<tr><td>Age (y, ±SD)</td><td>79.9±6.2</td><td>79.7±6.1</td></tr>
<tr><td>Sex (male, %)</td><td>498 (57.6)</td><td>438 (55.0)</td></tr>
<tr><td>STS score</td><td>4.4±1.5</td><td>4.5±1.6</td></tr>
</table>
</td>
<td>Intervention: TAVI (CoreValve or Evolut R)

724/863 (84%) patients had the CoreValve; 139/863 (16%) had the Evolut R.

Transfemoral access was preferred (93.6% of patients); subclavian or direct aortic approaches were used in patients with unsuitable iliofemoral anatomy.

Comparator: SAVR.</td>
<td>• Composite of mortality (any cause) or disabling stroke.
• All-cause mortality
• Cardiac mortality
• Morbidity (symptoms)
• Aortic valve re-intervention
• Haemodynamic function
• Length of hospital stay
• Safety outcomes.</td>
<td>This study incorporated a broader STS score (3-15%), versus the 4-8% range for intermediate risk. 20 patients (2.3%) and 33 (4.1%) patients had a score ≥ 8% in the TAVI and SAVR populations, respectively. 131 (15.2%) and 123 (15.5%) patients had a score < 8% in the TAVI and SAVR populations, respectively.</td>
</tr>
</table>

Reference	Study design	Population	Intervention / Comparator	Relevant outcomes	Additional notes/Comments on applicability
ITT: intention-to-treat; RCT: randomised controlled trial; SAVR: surgical aortic valve replacement; SD: standard deviation; STS score: Society of Thoracic Surgeons score; TAVI: transcatheter aortic valve implantation.					

Table 2. Clinical effectiveness outcomes from the EUnetHTA meta-analyses

Outcome	TAVI	SAVR	Relative effect	EUnetHTA GRADE interpretation of evidence certainty
All-cause mortality 30 days	58/1890 3.1%	54/1888 2.9%	RR 1.07 (95% CI 0.74 to 1.55) p=0.70	Moderate *
All-cause mortality 2 years	243/1890 12.9%	240/1888 12.7%	RR 1.01 (95% CI 0.86 to 1.20) p=0.88	Low * ^
Cardiac mortality 30 days	50/1890 2.6%	45/1888 2.4%	RR 1.11 (95% CI 0.75 to 1.66) p=0.60	Moderate *
Cardiac mortality 2 years	149/1890 7.9%	155/1888 8.2%	RR 0.96 (95% CI 0.78 to 1.19) p=0.73	Low * ^
Symptom reduction (NYHA class)	Both trials reported that symptoms were reduced at 30 days in both intervention groups. Neither trial identified a difference in degree of this effect at 1 or 2 year follow up.			Very low *^~#
Aortic valve re-intervention 30 days	11/1890 (0.6%)	1/1888 (0.1%)	RR 7.58 (95% CI 1.38 to 41.55) p=0.02	Low*$
Aortic valve re-intervention 2 years	33/1890 1.7%	8/1888 0.4%	RR 3.86 (95% CI 1.76 to 8.44) p=0.003	Very low$*^
Aortic valve gradient	In the PARTNER 2 trial mean aortic valve gradient decreased from baseline to 30 days in both study groups and was significantly lower in the TAVI arm at all time points of follow up. In the SURTAVI trial mean aortic valve gradient decreased from baseline to discharge in both study groups and was significantly lower in the TAVI arm at all time points of follow up.			Not assessed
Aortic valve area	In the PARTNER 2 trial aortic valve area improved from baseline and was significantly greater in the TAVI arm at all-time points of follow up. In the SURTAVI trial effective AV orifice areas were significantly greater in the TAVI arm at all-time points of follow up.			Not assessed
Length of hospital stay	Both trials reported significantly shorter durations of hospital stay in the TAVI group, but data could not be pooled. PARTNER 2 reported a median of 6 days for TAVI and 9 days for SAVR (p <0.001) In the SURTAVI trial, length of hospital stay was shorter by 4 days in the TAVI group than in the SAVR group (mean difference −4.00 days, 95% CI −4.65 to −3.36)			Moderate*

* In the PARTNER 2 trial 94 patients (17 TAVI and 77 SAVR withdrew after randomisation)
^ At two year follow up >30% and >50% of patients were lost to follow up
~ Risk of bias from subjective outcome
# No effect of treatment group (serious imprecision)
$ Large confidence interval (serious imprecision)

CI: confidence interval; RR: risk ratio; SAVR: surgical aortic valve replacement; TAVI: transcatheter aortic valve implantation.

6.2.8 Health-related quality of life

A meta-analysis of health-related quality of life outcomes was not undertaken by EUnetHTA.

In the SURTAVI trial, quality of life, as measured by the Kansas City Cardiomyopathy Questionnaire (KCCQ) summary score change at 30 days, demonstrated superiority in improved quality of life for patients after TAVI compared with SAVR. KCCQ summary score ranges from 0 to 100. An increase of 10 points or more from baseline corresponds to moderate or great clinical improvement (Reardon et al. 2017). The mean change from baseline to 30 days for TAVI was 18.39 ± 22.76 (N=819) compared with 5.88 ± 27.02 (N=700) for SAVR (mean difference 12.51, 95% CI 9.97 to 15.06). In both study groups the score improved significantly through 24 months of follow up (Reardon et al. 2017); mean change from baseline was similar for both TAVI and SAVR arms at 6 months (21.8±22.3 versus 21.3±22.3, mean difference 0.5, 95% CI -1.9 to 2.8) and 12 months (20.9±22.2 versus 20.6±22.2, mean difference -.3, 95% CI -2.2 to 2.9).

In the PARTNER 2 trial, KCCQ change from baseline (paired difference) in overall summary score at 30 days was 17.5 (95% CI 15.8 to 19.3, n=678) in patients receiving transfemoral TAVI, whilst for patients eligible for transfemoral TAVI receiving SAVR it was 3.2 (95% CI 1.3 to 5.5, n=551) (Baron et al. 2017). For patients receiving transthoracic TAVI, the change from baseline to 30 days was 6.4 (95% CI 2.5 to 10.3, n=196) compared with 5.6 (95% CI 1.5 to 9.6, n=180) for the patients not eligible for transfemoral TAVI receiving SAVR. At both 1 and 2 years follow up there were no significant differences between TAVI and SAVR disease-specific (KCCQ) or generic (SF-36) health status scores. EQ-5D utilities at 1 month were significantly improved in the transfemoral TAVI arm (paired difference 0.058, 95% CI 0.043 to 0.072, $p < 0.002$) but not with SAVR (paired difference -0.002, 95% CI -0.019 to 0.014, $p = 0.80$); significant improvements were observed in both arms as 1 and 2 years.

6.2.9 Safety

Safety outcomes examined in the meta-analysis of the PARTNER 2 and SURTAVI RCTs included:

- Stroke
- New atrial fibrillation
- Life-threatening or disabling bleeding
- Acute kidney injury
- Major vascular complications
- Permanent pacemaker implantation
- Paravalvular aortic regurgitation
- Endocarditis

Safety outcomes from the EUnetHTA meta-analysis are summarised in Table 3, alongside the interpretation of evidence certainty using the GRADE evidence rating scale.

6.2.9.1 Any stroke (stroke and disabling stroke)

At 30-day follow-up, stroke occurred in 4.1% of patients in the TAVI group and 5.5% in the SAVR group: compared with SAVR, it is uncertain whether TAVI has any effect on stroke at 30-day follow-up (RR 0.72 95% CI 0.44 to 1.20, p=0.21; GRADE evidence: very low).

At 2-year follow-up, the overall stroke occurrence was 7.7% in the TAVI group and 8.4% in the SAVR group: it is uncertain whether TAVI is non-inferior to SAVR in terms of stroke (RR 0.89, 95% CI 0.60 to 1.33, p=0.57; GRADE evidence: very low).

6.2.9.2 Disabling stroke

At 30-day follow-up, disabling stroke occurred in 2.3% of patients in the TAVI group and 3.3% in the SAVR group: it is uncertain whether TAVI has any effect on disabling stroke compared with SAVR (RR 0.70, 95% CI 0.48 to 1.02, p=0.07; GRADE evidence: low).

At 2-year follow-up, the overall disabling stroke occurrence was 4.2% in the TAVI group and 4.9% in the SAVR group: it is uncertain whether TAVI has any effect on disabling stroke compared with SAVR (RR 0.83, 95% CI 0.56 to 1.25, p=0.38; GRADE evidence: very low).

6.2.9.3 New atrial fibrillation

New atrial fibrillation occurred in 11% of patients in the TAVI group and 34% in the SAVR group. Moderate-quality evidence suggested that TAVI is probably superior to SAVR in terms of new atrial fibrillation occurrence (RR 0.32, 95% CI 0.27 to 0.37, p<0.00001).

6.2.9.4 Life-threatening or disabling bleeding

In the PARTNER 2 trial, life-threatening or disabling bleeding at 30-day follow-up occurred in 10% of the TAVI group compared with 43% of patients in the SAVR group. (RR 0.24, 95% CI, 0.20 to 0.29, p<0.001).

In the SURTAVI trial, there was no evidence of differences between the two treatments at 30-day, 1-year, and 2-year follow-up in terms of life-threatening or disabling bleeding. At 30-day follow up the risk of life-threatening or disabling bleeding was higher in the TAVI group (12.2%) than in the SAVR group (9.3%). The difference was not statistically significant. (95% credible interval -0.1 to 5.9). Data were not pooled because the heterogeneity was high (I^2 = 99%).

6.2.9.5 Acute kidney injury

Acute kidney injury was reported in both trials at 30-day, 1-year, and 2-year follow-up. At 30-day follow-up, acute kidney injury occurred in 1.0% of patients in the TAVI group and 2.2% in the SAVR group: compared with SAVR, TAVI reduces the occurrence of acute kidney injury (RR 0.47, 95% CI 0.27 to 0.80, p=0.006; GRADE evidence: very low)

At 2-year follow-up, the overall acute kidney injury occurrence was 2.2% in the TAVI group and 3.5% in the SAVR group: compared with SAVR, TAVI reduces the occurrence of acute kidney injury (RR 0.63, 95% CI 0.43 to 0.92, p=0.02; GRADE evidence: very low).

6.2.9.6 Major vascular complications

At 30-day follow-up, major vascular complications occurred in 6.9% of patients in the TAVI group and 3.1% in the SAVR group: compared with SAVR, TAVI may increase the incidence of major vascular complications (RR 3.03, 95% CI 0.79 to 11.67, p=0.11; GRADE evidence: low).

At 2-year follow-up, the overall occurrence of major vascular complications increased in both groups (7.7% in the TAVI group and 3.3% in the SAVR group) and the treatment effect remained substantially the same (RR 3.27, 95% CI 0.73 to 14.57, p=0.12).

6.2.9.7 New permanent pacemaker

Pacemaker implantation at 30-day follow-up was performed in 6.7% of patients in the SAVR groups in both studies.

In the PARTNER 2 trial, the incidence of permanent pacemaker implantation was higher in the TAVI group than in the SAVR group; however, there was no statistically significant difference between the groups at any follow-up point.

In the SURTAVI trial, the incidence of permanent pacemaker implantation at 30 days was significantly higher in the TAVI group (25.9%) than in the control group (6.6%) at all follow up points.

Data were not pooled because of considerable heterogeneity (I^2 >90%).

6.2.9.8 Paravalvular aortic regurgitation

At discharge (SURTAVI) or 30-day follow-up (PARTNER 2), incidence of severe or moderate paravalvular regurgitation occurred in 3.6% of patients in the TAVI group and 0.4% in the SAVR group. Compared with SAVR, TAVI probably increases the risk of paravalvular regurgitation (RR 9.18, 95% CI 3.97 to 21.22, p<0.00001; GRADE evidence: moderate)

At 1- and 2-year follow-up, additional paravalvular regurgitation occurred in similar proportions. At 2-year follow-up, compared with SAVR, TAVI might increase the risk of paravalvular regurgitation (RR 14.74, 95% CI 5.04 to 43.08, p<0.00001; GRADE evidence: low).

6.2.9.9 Endocarditis

In the PARTNER 2 trial, the incidence of endocarditis at 2-year follow-up was 1.2% in the TAVI group and 0.7% in the control group (RR 1.85, 95% CI 0.69 to 4.99, p=0.22).

Table 3. Safety outcomes from the EUnetHTA meta-analyses

Outcome	TAVI	SAVR	Relative effect	EUnetHTA GRADE interpretation of evidence certainty
Stroke 30 days	78/1890 4.1%	103/1888 5.5%	0.72 (95% CI 0.44 to 1.20) p=0.21	Very low*$∞
Stroke 2 years	145/1890 7.7%	159/1888 8.4%	0.89 (95% CI 0.60 to 1.33) p=0.57	Very low*$∞
Disabling stroke 30 days	43/1890 2.3%	62/1888 3.3%	0.70 (95% CI 0.48 to 1.02) p=0.07	Low*$
Disabling stroke 2 years	79/1890 4.2%	92/1888 4.9%	0.83 (95% CI 0.56 to 1.25) p=0.38	Very low*$^
New atrial fibrillation 30 day	204/1890 11%	641/1888 34%	0.32 (95% CI 0.27 to 0.37) p<0.00001	Moderate*
Life-threatening or disabling bleeding	In the PARTNER 2 trial, life-threatening or disabling bleeding at 30-day follow-up occurred in 10% of the TAVI group compared with 43% of patients in the SAVR group. (RR 0.24, 95% CI 0.20–0.29, p<0.001). In the SURTAVI trial, there was no evidence of differences between the two treatments at 30-day, 1-year, and 2-year follow-up in terms of life-threatening or disabling bleeding			Very low*∞$
Acute kidney injury 30 days	19/1890 1.0%	41/1888 2.2%	0.47 (95% CI 0.27 to 0.80) p=0.006	Very low*$
Acute kidney injury 2 years	42/1890 2.2%	67/1888 3.5%	0.63 (95% CI 0.43 to 0.92) p=0.02	Very low*$^
Major vascular complications 30 days ◊	131/1890 6.9%	59/1888 3.1%	3.03 (95% CI 0.79 to 11.67) p=0.11	Low*$

Outcome	TAVI	SAVR	Relative effect	EUnetHTA GRADE interpretation of evidence certainty
Major vascular complications 2 years	145/1890 7.7%	63/1888 3.3%	3.27 (95% CI 0.73 to 14.57) p=0.12	Not recorded
New permanent pacemaker 30 days	In the PARTNER 2 trial, the proportion of new permanent pacemakers at 30 days was 8.4% in the TAVI group and 6.7% in the control group with no evidence of significant difference between groups (RR 1.26, 95% CI 0.93 to 1.72). In the SURTAVI trial, the proportion of implanted pacemakers at 30 days was higher in the TAVI group (25.1%) than in the SAVR group (6.7%) with a statistically significant difference (RR 4.17, 95% CI 3.09 to 5.61).			Very low*∞
Paravalvular aortic regurgitation 30 days/at discharge	61/1692 3.6%	6/1624 0.4%	9.18 (95% CI 3.97 to 21.22) p<0.00001	Moderate*

* In the PARTNER 2 trial 94 patients (17 TAVI and 77 SAVR withdrew after randomisation)
^ At two year follow up >30% and >50% of patients were lost to follow up
~ Risk of bias from subjective outcome
# No effect of treatment group (serious imprecision)
$ Large confidence interval (serious imprecision)/and or very few events
∞ Substantial heterogeneity
◊The quality for this outcome was downgraded at 30-day follow-up because of a risk of bias (i.e., imbalance in withdrawals between the groups), and imprecision (i.e., wide CI). There was no downgrading for inconsistency even though heterogeneity was substantial (I2 = 90%) because the direction of the effect of treatment was the same for the two trials with statistically significant results: the inconsistency was between studies that showed moderate and large effects.

6.2.9.10 Additional safety outcomes from observational studies

The EUnetHTA review included two observational studies that provided data on safety (Bestehorn et al. 2015, Brennan et al. 2017).

A German registry study (n=763), examined risk of post-operative delirium (POD) and risk of in-hospital mortality (Bestehorn et al. 2015). The authors reported that, in the homogeneous groups with EuroSCORE 10% to 20% (EuroSCORE 13.5±2.7) the incidence of POD (requiring therapy) was around three times higher after SAVR compared with transfemoral TAVI: 12.8% for SAVR versus 3.9% for TAVI (p <0.01).

In-hospital mortality was higher in the SAVR group than in the transfemoral TAVI group: 5.1% versus 3.3%, respectively (p <0.01).

The second study, based on a US registry, reported risk of stroke at 1-year follow-up for three STS score subgroups, as in Table 4 (Brennan et al. 2017). Transfemoral TAVI access was used in 76% of the patients. Differences were not significant between the two procedures.

Table 4. Comparative risk of stroke at 1-year by STS predicted risk of mortality (Brennan et al. 2017)

Risk of stroke at 1-year			
STS PROM subgroup	TAVI	SAVR	Hazard Ratio
≥3% and <5%	3.8%	3.3%	1.06

Risk of stroke at 1-year			
STS PROM subgroup	TAVI	SAVR	Hazard Ratio
	n=1,953	n=1,850	(95% CI: 0.73 to 1.54)
≥5% and <8%	4.5% n=1,596	3.5% n=1,545	1.22 (95% CI: 0.83 to 1.79)
>8%	4.4% n=1,183	3.1% n=1,337	1.33 (95% CI: 0.87 to 2.03)

6.2.9.11 Device related harms

Across the analysis of available safety data for this patient group, it was not possible to directly compare devices and assess the contribution of device type to rates of reported adverse events.

6.2.9.12 Radiation exposure

TAVI is potentially associated with high radiation doses for both the patient and healthcare professionals.

The EUnetHTA assessment included expert opinion on radiation risks associated with the procedure. This noted that, in general, the additional risk of radiation induced cancer following a TAVI procedure will be small, in relation to the natural risk of morbidity and mortality in cancer. However, the age of patients will be important. Patients with intermediate risk are expected to be younger, with a slightly increased risk of stochastic effects as a result. Women in general have also a higher risk of radiation induced cancer, owing to breast glandules being relatively radio-sensitive. There may also be a dose contribution from the pre-surgery investigation and postsurgery follow-up. If, for example, a preoperative coronary angiography and three postoperative angiographs are being performed, the fatal risks are assumed to be doubled.

Tissue damage such as hair loss and skin reactions will be dependent on radiation dose. There will be large variations in tissue sensitivity between different persons and possibly also between different ethnicities.

Expert opinion from HTW consultation noted that in current practice, TAVI follow-up in uncomplicated cases would be with an echocardiogram (no radiation risk), and would be similar to the echocardiograph follow-up requirements for SAVR.

6.3 Five-year outcomes of PARTNER 2

HTW identified additional evidence published after the SHTG review reporting the five-year outcomes from the PARTNER 2 trial (Makkar et al. 2020). Patients were followed yearly for clinical endpoints and all clinical outcomes were analysed in the intent-to-treat population (all patients who were randomised for treatment, regardless of actual treatment received). Outcome data are summarised in Table 5.

At five years, data was available for 920 patients (91.0%) in the TAVI group and 831 (81.4%) patients in the SAVR group. Patients with the complete 5-year follow-up data had disparate baseline characteristics with patients missing follow-up data; patients with follow-up data were more likely to be male, to be NHYA class III or IV, and to have diabetes, and were less likely to have moderate or severe mitral regurgitation.

6.3.1 Clinical effectiveness outcomes

6.3.1.1 Composite of death from any cause or disabling stroke (5 year follow-up)

At five-year follow-up, incidence of composite death (any cause) or disabling stroke was 47.9% in the TAVI arm and 43.4% in the SAVR arm (HR 1.09, 95% CI 0.95 to 1.25).

In the transfemoral access cohort, incidence of death or disabling stroke was 44.5% with TAVI versus 42.0% with SAVE (HR 1.02, 95% CI 0.87 to 1.20). In the transthoracic-access cohort the incidence of death or disabling stroke was higher in the TAVI arm (59.3%) versus SAVR (48.3%; HR 1.32, 95% CI 1.02 to 1.71).

6.3.1.2 All-cause mortality (5 year follow-up)

Incidence of death from any cause was 46.0% in the TAVI group and 42.1% in the SAVR group (HR 1.09, 95% CI 0.95 to 1.25).

6.3.1.3 Cardiac mortality (5 year follow-up)

Cardiac mortality at 5-year follow-up was 29.4% in the TAVI group and 27.8% in the SAVR group (HR 1.02, 95% CI 0.85–1.23).

6.3.1.4 Symptom reduction, NYHA classification (5 year follow-up)

In the PARTNER 2 trial, 77.3% in the TAVI group and 76.1% in the SAVR group were classified as NHYA class III or IV. At five-year follow-up, Makkar et al. (2020) reported improvements in health status in both arms, with 89.0% in the TAVI arm and 92.7% in the SAVR arm classified as NYHA class I or II.

6.3.1.5 Aortic valve re-intervention (5 year follow-up)

Aortic valve re-intervention was performed in 3.2% of people in the TAVI group and 0.8% of people in the SAVR group (HR 3.28, 95% CI 1.32 to 8.13).

6.3.1.6 Haemodynamic function of the valve (5 year follow-up)

Makkar reported that the improvements from baseline observed in the TAVI and SAVR groups at initial follow-ups were maintained at five-year follow up for aortic valve area (1.50 cm^2 versus 1.37 cm^2, respectively) and mean aortic valve gradients (11.4 mmHg versus 10.8 mmHg, respectively).

Table 5. Clinical effectiveness outcomes at 5-year follow-up (PARTNER 2 trial)

Outcome	TAVI (n = 1,011)	SAVR (n = 1,021)	Relative effect
Death from any cause or disabling stroke	456 47.9%	388 43.4%	HR 1.09 (95% CI 0.95 to 1.25)
All-cause mortality	436 46.0%	370 42.1%	HR 1.09 (95% CI 0.95 to 1.25)
Cardiac mortality	245 29.4%	223 27.8%	HR 1.02 (95% CI 0.85 to 1.23)
Symptom reduction (NYHA class)	The authors reported improvement in health status at 5 years from baseline. At baseline, 77.3% and 76.1% of patients were NTHA Class II or IV, respectively; at five years, this reduced to 11.0% and 7.3%.		
Aortic valve re-intervention	21 3.2%	6 0.8%	HR 3.28 (95% CI 1.32 to 8.13)
Aortic valve gradient	The authors reported that the reduction in aortic valve gradient observed at initial follow-ups were maintained at 5 years: 11.4 mmHg for TAVI and 10.8 mmHg for SAVR.		
Aortic valve area	The authors reported that the improvement in aortic valve area observed at initial follow-ups were maintained at 5 years: 1.50 cm^2 in the TAVI arm versus 1.37 cm^2 in the SAVR arm.		

6.3.2 Health-related quality of life (5 year follow-up)

Health-related quality of life was assess using the Kansas City Cardiomyopathy Questionnaire-Overall Summary (KCCQ-OS) scores. At five years follow-up, change from baseline in overall summary score was 19.6 for the TAVI group and 20.5 for the SAVR group.

6.3.3 Safety

Safety outcomes from five-year follow-up are summarised in Table 6.

6.3.3.1 Any stroke (stroke or disabling stroke)

At five year follow-up, incidence of any stroke was 15.3% in the TAVI group and 12.5% in the SAVR arm (HR 1.15, 95% CI 0.89 to 1.49).

6.3.3.2 Disabling stroke

At five year follow-up, incidence of any stroke was 9.8% in the TAVI group and 8.6% in the SAVR group (HR 1.05, 95% CI 0.77 to 1.44).

6.3.3.3 New atrial fibrillation

Incidence of new atrial fibrillation was 15.8% in the TAVI arm and 30.4% in the SAVR arm (HR 0.43 95% CI 0.35 to 0.53).

6.3.3.4 New permanent pacemaker

By the five-year time point, pacemaker implantation was performed on 15.5% of patients in the TAVI arm and 13.0% of patients in the SAVR arm (HR 1.20, 95% CI 0.94–1.54).

6.3.3.5 Paravalvular aortic regurgitation

Incidence of moderate or severe paravalvular aortic regurgitation at five years was 4.1% in the TAVI group and 0.2% in the surgery group. Incidence of mild aortic regurgitation was 17.0% in the TAVI group and 3.5% in the surgery group.

6.3.3.6 Endocarditis

Incidence of endocarditis was 3.9% in the TAVI arm and 2.5% in the SAVR arm (HR 1.46, 95% CI 0.82 to 2.60).

Table 6. Safety outcomes at 5-year follow-up (PARTNER 2 trial)

Outcome	TAVI (n = 1,011)	SAVR (n = 1,021)	Relative effect
Stroke (any)	128 15.3%	107 12.5%	HR 1.15 (95% CI 0.89 to 1.49)
Disabling stroke	83 9.8%	75 8.6%	HR 1.05 (95% CI 0.77 to 1.44)
New atrial fibrillation	141 15.8%	291 30.4%	HR 0.43 (95% CI 0.35 to 0.53)
Life-threatening or disabling bleeding	NR		
Acute kidney injury	NR	NR	NR
Major vascular complications	NR	NR	NR

Outcome	TAVI (n = 1,011)	SAVR (n = 1,021)	Relative effect
New permanent pacemaker	138 15.5%	113 13.0%	HR 1.20 (95% CI 0.94 to 1.54)
Paravalvular aortic regurgitation	The authors report incidence of moderate or severe paravalvular aortic regurgitation was 4.1% in the TAVI group and 0.2% in the SAVR group. Whereas mild aortic regurgitation was 17.0% in the TAVI group and 3.5% in the SAVR group.		

6.4 Ongoing trials

EUnetHTA identified two ongoing trials focused on patients at intermediate surgical risk:

- SURTAVI trial (NCT01586910) International, multicentre, completion date Nov 2026
- DEDICATE trial (NCT03112980) German, multicentre, completion date Dec 2024

The UK TAVI trial (ISRCTN57819173) is focused on patients at intermediate or high surgical risk and is due to complete in 2022.

The ACURATE IDE trial (NCT03735667) is focused on patients at intermediate or higher surgical risk and is due to complete in 2030.

7. Economic evaluation

7.1 Cost effectiveness

7.1.1 Health economic evidence review

The titles and abstracts of records identified in the search for this research question were screened and 16 health economic studies were deemed potentially relevant. The full texts of these studies were reviewed against the inclusion/exclusion criteria. Following consideration of the full texts, six studies were excluded from the review. Three studies were excluded as they were systematic reviews of existing economic evidence (Azraai et al. 2020, Gialama et al. 2018, Huygens et al. 2018) and relevant studies within the systematic reviews have been included. Two studies were excluded because they were not cost-utility analyses (Kaier et al. 2019, Ontario Health 2020) and one study was excluded as it considered a high risk population (Inoue et al. 2020). The remaining ten studies were included in the review. One of the studies was deemed to be directly applicable to our decision context as it considered a UK perspective (SHTG 2019). The remaining nine studies were only partially applicable as they considered healthcare systems in other countries (Baron et al. 2019, Goodall et al. 2019, HIQA 2019, Kodera et al. 2018, NIPH 2019, Tam et al. 2018a, Tam et al. 2018b, Zhou et al. 2019, Tarride et al. 2019).

The cost-utility analysis conducted as part of the SHTG appraisal is summarised in Table 7 below. The analysis found TAVI to be more effective and more costly than SAVR with an ICER value of £98,965 per QALY indicating that it was not cost-effective at the commonly applied thresholds of £20,000 per QALY or £30,000 per QALY. Notably the result was found to be sensitive to changes in the cost of the procedure and in particular the cost of the TAVI valve. Sensitivity analysis suggested that the cost-effectiveness of TAVI became more favourable when the cost of the valve was less than £12,000 (although threshold was not specified).

The cost-utility analyses conducted in other settings present contrasting results (see Appendix 3 for further details on the studies). In four of the studies, TAVI was found to be more effective and less costly overall than SAVR and was therefore dominant (Baron et al. 2019, Goodall et al. 2019, HIQA 2019, Kodera et al. 2018, NIPH 2019, Tam et al. 2018a, Tam et al. 2018b, Zhou et al. 2019). In five of the studies, TAVI was found to be more effective and more costly overall (Baron et al. 2019, Goodall et al. 2019, HIQA 2019, Kodera et al. 2018, NIPH 2019, Tam et al. 2018a, Tam et al. 2018b, Zhou et al. 2019, Tarride et al. 2019). In three of the five studies, the resulting ICER was found to be below the cost-effectiveness threshold applied by the authors and it was therefore concluded that TAVI was cost-effective (Baron et al. 2019, Goodall et al. 2019, HIQA 2019, Kodera et al. 2018, NIPH 2019, Tam et al. 2018a, Tam et al. 2018b, Zhou et al. 2019, Tarride et al. 2019). In two of the five studies, the resulting ICER was found to be above the cost-effectiveness threshold applied by the authors and it was therefore concluded that TAVI was not cost-effective (Baron et al. 2019,

Goodall et al. 2019, HIQA 2019, Kodera et al. 2018, NIPH 2019, Tam et al. 2018a, Tam et al. 2018b, Zhou et al. 2019).

This marked difference in the results of the analyses was primarily driven by differences in the estimation of SAVR and TAVI procedure costs, variation in the length of stay reduction that could be expected with TAVI and different approaches taken to extrapolate outcomes beyond the period covered in key trials.

Table 7. Summary of included health economic study in the UK setting: SHTG cost-utility analysis (2019)

Study details	Study population and design	Data sources	Results	Quality assessment
Author and year: SHTG (2019) **Country:** Scotland **Type of economic analysis:** Cost-utility analysis **Perspective:** Scottish healthcare perspective **Currency:** UK pound sterling (£) **Price year:** Not stated (but likely to be 2018 prices) **Time horizon:** Lifetime **Discounting:** Costs and life years were discounted at 3.5% per year **Potential conflict of interest:** None	**Population** People with severe symptomatic aortic stenosis at intermediate surgical risk **Interventions** Transcatheter aortic valve implantation (TAVI) **Comparator** Surgical aortic valve replacement (SAVR) **Study design** Cost-utility analysis using Markov model	**Source of baseline and effectiveness data:** All clinical data (mortality and complication rates) were based on the full intention-to-treat population in PARTNER 2 which compared TAVI using the Sapien XT valve with SAVR in intermediate risk patients. Trial outcomes were used for the two years where data was available. Beyond two years, it was assumed that the risk of complications in both procedure arms was zero. Mortality beyond two years was informed by general population mortality multiplied by a hazard ratio of 1.15 to reflect the heightened risk of mortality in this patient group. **Source of resource use and cost data:** Procedure costs were derived from local Scottish data including the cost of theatre time, radiology, laboratory, other treatments and an inpatient day. Additional costs associated with subsequent length of stay were also added. The reference cost for the TAVI procedure excludes the cost of the valve. Data on valve costs was sourced from Scottish National Procurement. The valve cost utilised in the base-case was the balloon-expandable Sapiens valve without a rebate. Complication costs were derived from a mix of NHS Reference Costs and expert opinion. Follow-up costs were applied at 12 month intervals in both procedure arms. Follow-up	**Costs** TAVI: £34,995 SAVR: £22,051 Incremental: £12,945 **QALYs** TAVI: 3.93 SAVR: 3.80 Incremental: 0.13 **ICER (cost per QALY)** £98,965 per QALY **Sensitivity analysis** Deterministic sensitivity analysis was conducted where model inputs were varied across their 95% CI or across a pre-defined range. The results were found to be sensitive to changes in procedure costs as well as trial reported mortality and between-group-differences in health utility scores. The effect of the TAVI valve cost on the base case ICER was further investigated in an additional sensitivity analysis. It was found that the cost-effectiveness of TAVI became more favourable when the cost of the valve was less than £12,000. Probabilistic sensitivity analysis	**Applicability** Analysis was deemed to be directly applicable as it considered a UK healthcare perspective. **Limitations** The analysis was considered to be of high quality with only minor limitations, which relate to uncertainty in the evidence base as well as uncertainty around the cost of procedures.

Study details	Study population and design	Data sources	Results	Quality assessment
		cost was higher following TAVI to account for the use of echocardiogram and electrocardiogram. **Source of quality of life data:** The quality of life utilities used in the model were derived from EQ-5D values reported in the PARTNER 2 study according to time and intervention. Beyond the two year trial period, it was assumed that there was no difference in QoL between strategies. The last QoL value in the SAVR arm was applied to all subsequent cycles (in both arms).	showed that TAVI had a 26.9% probability of being cost-effective at a threshold of £20,000/QALY.	
EQ-5D: EuroQol 5 dimensions (quality of life measure); ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; SHTG: Scottish Health Technologies Group.				

7.1.2 De novo economic analysis

HTW developed an economic analysis to estimate the cost-effectiveness of TAVI in comparison to SAVR for people with severe symptomatic aortic stenosis at intermediate surgical risk (see Appendix 4 for full details of analysis).

The economic analysis was based largely on the economic analysis conducted by SHTG. The model was re-built using information provided in the SHTG report and adapted to match the context of NHS Wales. The model considered a lifetime horizon with all costs and benefits relevant to the UK NHS and personal social services (PSS) considered. Future costs and benefits were discounted at a rate of 3.5% per year as recommended by NICE.

Following the approach taken in the SHTG analysis, the model was based primarily on mortality and complication rates from the full intention-to-treat population in PARTNER 2 which compared TAVI using the Sapien XT valve with SAVR in intermediate risk patients. Beyond the two-year trial period, it was assumed that the risk of complications in both procedure arms was zero. Mortality beyond two years was informed by general population mortality multiplied by a hazard ratio of 1.15 to reflect the heightened risk of mortality in this patient group.

The quality of life values applied in the model were derived from EQ-5D values reported over time in the PARTNER 2 study for each intervention. Beyond the two-year trial period, it was assumed that there was no difference in QoL between strategies. The last QoL value in the SAVR arm was applied to all subsequent cycles (in both arms). Again, this matches the approach taken in the SHTG analysis.

Procedure costs and other relevant costs were sourced from NHS Reference costs 2018/19 where possible. The cost of the TAVI valve is not included in the reference cost of the procedure and this has therefore been considered separately based on data provided by WHSCC.

The results of the analysis are presented in table 8. The results were consistent with the SHTG analysis with TAVI found to be more effective and more costly than SAVR with a resulting ICER of £94,512 indicating that it was not cost-effective as the ICER exceeds the threshold of £20,000 per QALY. Sensitivity analysis demonstrated that the analysis was sensitive to changes in the cost of the TAVI and SAVR procedure. Notably, this included a scenario where the total costs reported by HIQA for the TAVI and SAVR procedure (converted to UK prices) were applied. In this scenario TAVI was found to be more effective and less costly than SAVR (i.e. dominant). Threshold analysis showed that TAVI becomes cost-effective at a threshold of £20,000 per QALY, when the cost of the TAVI valve is ≤£7,752.

In probabilistic sensitivity analysis, at a threshold of £20,000 per QALY, TAVI was found to have a 27% probability of being cost-effective while SAVR was found to have a 73% probability of being cost-effective.

Table 8. Base case results (presented on a per patient basis)

Treatment	Cost		QALYs		ICER (cost per QALY)
	Total	Incremental	Total	Incremental	
SAVR	£19,880	-	4.27	-	-
TAVI	£29,025	£9,145	4.36	0.10	£94,512

8. Organisational Issues

HTW's searches identified three studies pertaining to organisational considerations: one study on the beliefs and practices regarding TAVI (Asteggiano et al. 2018), and an additional study and systematic review on the learning curve for TAVI (Thivilliers et al. 2020, Wassef et al. 2018). None of these were specific to the intermediate risk population.

In addition, SHTG performed an additional search to identify evidence on the relationship between procedural volume and outcomes.

8.1 TAVI learning curve

Expert opinion sourced by HTW reported that additional training to implement TAVI valves in current centres would only be required if the centres were required to implement new valves; each valve has different training requirements and centres should have expertise in more than one valve type. Experts also noted that additional training would be needed if new centres were required when expanding the indicated patient population for TAVI (beyond high / inoperable risk).

The systematic review by Thivilliers et al. (2020) aimed to identify prospective TAVI studies between 2007 and 2017 and analyse the quality of information reported about the learning curve. They identified 68 relevant studies on TAVI, of which 37 reported details on a learning curve. A " roll-in" period was only included in eight studies and reporting was limited. The majority of the studies (n = 65) did not disclose proctorship/supervision details. The authors concluded that although many studies mention learning curves as a core component of TAVI, the amount and quality of data on the learning curve is relatively poor.

Wassef et al (2018) analysed the learning curve of 16 centres (n = 3,403), classifying operators experience as initial (1 to 75), early (76 to 150), intermediate (151 to 225), high (226 to 300) and very high (>300). Unadjusted clinical and procedural outcomes are detailed in Table 9.

Table 9. Summary of outcome with learning curve

Outcome	Initial experience (n=1,141)	Early experience (n = 780)	Moderate experience (n = 549)	High experience (n = 354)	Very high experience (n = 579)
Procedural outcomes					
Device success	873 (76.5) p = 0.22	633 (81.2) p = 0.985	473 (86.2) p= 0.032	296 (83.6) p= 0.523	465 (80.3)
Procedure time, min	135.0 ± 80.0 p=0.001	78.0 ± 77.0 p=0.805	47.0 ± 45.0 P=<0.001	79.0 ± 53.0 P= 0.940	83.0 ± 38.2
Contrast volume, ml	143 ± 95 p=0.001	139 ± 124 p<0.001	77 ± 44 P =1.000	56 ± 32 P=0.101	78 ± 51
Surgical conversion	21 (1.8) P= 0.860	9 (1.2) P=0.255	5 (0.9) P=0.192	7 (2) P=0.982	14 (2.4)
Clinical outcomes					
Death	109 (9.6) p=<0.001	62 (7.9) P=0.002	32 (5.8) P=0.115	17 (4.8) P=0.525	19 (3.3)
Early safety endpoint	314 (27.5) p<0.001	222 (28.5) p<0.001	143 (26.0) P=0.032	80 (22.6) P=0.098	86 (14.9)
Bleeding	129 (11.3) p<0.001	63 (8.1) P=0.111	35 (6.4) P=0.767	26 (7.3) P=0.429	30 (5.2)
Vascular complication	121 (10.6) P=0.001	87 (11.2) P=0.001	70 (12.8) p<0.001	34 (9.6) P=0.043	31 (5.4)
Stroke	35 (3.1) P=0.532	27 (3.5) P=0.336	19 (3.5) P=0.387	9 (2.5) P=0.963	12 (2.1)
Myocardial infarction	21 (1.8) p=1.00	5 (0.6) p=0.145	8 (1.5) P=0.953	2 (0.6) P=0.342	11 (1.9)

Outcome	Initial experience (n=1,141)	Early experience (n = 780)	Moderate experience (n = 549)	High experience (n = 354)	Very high experience (n = 579)
New dialysis	20 (1.8) P=0.429	11 (1.4) P=0.780	1 (0.2) P=0.430	1 (0.3) P=0.708	5 (0.9)
New permenant pacemaker	172 (15.1) p=0.007	106 (13.6) p=0.085	64 (11.7) P=0.612	72 (20.3) p<0.001	56 (9.7)
Moderate-severe aortic deficiency	59 (5.8) P=0.914	20 (3.1) P=0.974	5 (1.1) P=0.891	15 (4.2) P=1.000	42 (8.1)
Length of stay post-TAVI, days	15.4 ± 37.4 P=0.001	12.2 ± 13.8 P=0.117	11.1 ± 22.2 P=0.452	9.0 ± 8.0 P=0.988	9.0 ± 18.0
Values are n (%) or mean ± SD. Very high experience (>300 procedures) group used as a reference group for pairwise comparison.					

8.2 TAVI beliefs and practices

Asteggiano et al. (2018) performed a survey to ascertain the current opinion of health care professionals on the access to TAVI, patient selection criteria, and the perceived benefits, complication and future applications of TAVI. The survey included 18 multiple choice questions (including five questions on demographics), and was developed by the European Society for Cardiology (ESC) Council for Cardiology Practice (CCP) using a free web-based survey tool. The survey was shared to the subscribers of the ESC CCP journal for completion between 1 November 2015 and 31 December 2015.

Of the 50,840 invited to complete the survey, 1,245 (2.4%) completed the survey in full; 57.4% were in-hospital cardiologists, 28.8% were out-of-hospital cardiologists and 13.8% were GPs or other health care professionals. The majority of participants (77.5%) were based in Europe.

The majority (70.1%) of participants said that they diagnosed between 1 to 5 cases of severe aortic stenosis each month. 41.2% reported free access to TAVI and 62.7% reported referring between 1 to 10 patients for TAVI in the current year. 16.8% of respondents had referred no patients for TAVI, and of these respondents the barriers to access were TAVI availability (50.5%), lack of eligible candidates (37.4%), long waiting lists (9.5%) or lack of belief in TAVI (2.6%).

The most common reasons for not referring a patient for either TAVI or SAVR was that the patient was high-risk or inoperable (55.5%) or the patient having a short life expectancy (30.5%), and the most commonly reported reasons for choosing TAVI over SAVR was surgical risk score (56.9%), comorbidities (31.8%). Patient choice was the main reason for TAVI over SAVR in 1.9% of cases.

When asked about preferred management of a patient with severe aortic stenosis aged 75 years and over, 49.2% of participants said they would refer the patient for SAVR, whereas 45.7% said they would refer the patient for TAVI. The most commonly perceived complications for TAVI were stroke (28.9%), vascular complications (25.1%), conduction deficits (23.5%) and aortic regurgitation (22.4%). The most commonly perceived benefits were improvement in quality of life (37.2%), faster recovery time (33.7%), and minimally invasive surgery (27.6%). Finally, 82% of respondents thought that TAVI is or may become a viable option for lower-risk patients.

8.3 Association between procedure volumes and outcomes

SHTG undertook an additional specific search to identify evidence on the relationship between the volume of TAVI procedures and outcomes. The results of this search are summarised below.

8.3.1 Guidelines

A 2008 position statement from the British Cardiovascular Intervention Society (BCIS) and the Society of Cardiothoracic Surgeons (SCTS) noted that (BCIS & SCTS 2008):

"… it is difficult to stipulate a minimum number of cases per year for a TAVI programme. Competence is obviously more important than numbers. However a minimum annual number of 24 cases per TAVI unit may be reasonable, but given the learning curve and infrastructure needed we believe somewhere in the order of >50 cases per year to be optimal."

The European Association for Cardio-Thoracic Surgery (EACTS) issued a position statement on adult cardiac surgery in 2016. It noted that TAVI should be performed in cardiac surgical units of larger size and/or those providing continuous 24 hours a day, 7 days a week surgical and cardiological care (Pagano et al. 2016).

Consensus guidelines from US joint societies; American Association for Thoracic Surgery (AATS) American College of Cardiology (ACC) Society for Cardiovascular Angiography and Interventions (SCAI) Society of Thoracic Surgeons (STS), in 2018 set out institutional recommendations and requirements for transcatheter aortic valve replacement. For optimal outcomes, the recommended procedure volume was ≥50 cases per year or 100 cases over 2 years (Bavaria et al. 2019).

8.3.2 Primary studies

Six potentially relevant studies were excluded on the basis that they analysed information from administrative databases (Ando et al. 2018, Badheka et al. 2015, de Biasi et al. 2016, Kaier et al. 2018, Khera et al. 2017, Panaich et al. 2016). These databases collate routine data, often for purposes of reimbursement, and have limitations in terms of information on patient characteristics of specific relevance to TAVI case-mix adjustment such as echocardiographic parameters, surgical risk and frailty scores. Additionally, although such databases provide large numbers of procedures for analysis, the risk of coding errors is likely to be high.

Four studies were identified where datasets used were specifically focused on TAVI research (Bestehorn et al. 2017, Carroll et al. 2017, Verma et al. 2017, Wassef et al. 2018). A variety of methodologies were described and a range of short term outcome measures explored. Parameters of each study are outlined in Table 10.

In the most recently published study, data submitted to an international registry by 16 large academic centres (2006-2015) were used to investigate the association between annual volume group allocation and all-cause mortality and a composite safety endpoint (both 30-day measures) (Wassef et al. 2018). Although it is a strength of the study that it incorporated a range of international contexts, it was unclear how centres were selected for the analysis and complete data were only available for 65% (2,205/3,403) of procedures. Centres contributed to different volume groups depending only on their annual volume per calendar year (2006-2015) so the analysis does not compare centres. In a logistic regression model, adjustment was made for factors including; gender, body mass index, left ventricular ejection fraction, STS risk score, transfemoral approach and prosthesis generation (for example; SAPIEN, SAPIEN XT, SAPIEN 3).

When compared with procedures allocated to the high annual institutional volume (>100) category, procedures allocated to the low annual institutional volume category (<50) were associated with greater risk of mortality at 30 days, RR 2.70 (95% CI 1.44 to 5.07) p=0.002 and worse early safety outcome, RR 1.60 (95% CI 1.17 to 2.17) p=0.003. There were no statistically significant differences between the intermediate and high volume categories for these two outcomes. Comparison between low and intermediate categories was not provided.

Carroll et al. (2017) reported an analysis of 42,988 cases from the US Transcatheter Valve Registry between 2011 and 2015. The study used a case sequence approach to study the association between cumulative hospital volume (increasing experience) and risk-adjusted in-hospital outcomes. Thus, this analysis investigated the association between case volume (combining both learning curve period and post-stabilisation period) and outcome. The rationale for this method was to take into account that some centres were still within the learning curve period. Median cumulative hospital volume was 80 cases and a quarter of the centres had completed fewer than 30 cases. Case sequence procedure volume (cases one to 400) was included in the statistical model as a continuous variable although patient characteristics, described within quartiles, were provided in the study report. Risk adjustment included patient and procedural factors including device iteration which were combined into a procedural risk score.

In risk-adjusted analyses, there was a statistically significant linear association between increasing TAVI volume and reducing in-hospital mortality (p=0.023) and vascular complications (p=0.003). There was a statistically significant non-linear association between increasing TAVI volume and reducing in-hospital bleeding (p<0.001). There was no statistically significant association observed between TAVI volume and rate of in-hospital stroke (p=0.14). In the subgroup of transfemoral procedures, comprising 71% of total procedures the relationship between increasing case number and reduced in-hospital mortality became statistically insignificant when adjusted for patient and procedural characteristics (p=0.15). However, there was a statistically significant association with benefits in rates of vascular complications and bleeding (p<0.0001). Non-transfemoral TAVI was not investigated as a subgroup due to the small number of sites performing more than 100 procedures.

A study from Germany examined 2014 data from 87 centres contributing to a National registry (Bestehorn et al. 2017). The maturity of the TAVI programme at each centre was not identified. The association between annual number of transfemoral TAVI procedures performed per hospital and in-hospital mortality was explored. Emergency procedures, transapical procedures and procedures undertaken in hospitals with 10 or fewer procedures were excluded. Number of procedures was examined both as a continuous variable and as a categorical variable. The categories comprised the following groupings: 11-50, 50-99, 100-149, 150 to 199 and ≥200 procedures. Data were adjusted using the German Aortic Valve Score (GAV 2.0) allowing an observed versus expected (O/E) ratio to be calculated for each patient. When the lowest volume group (22 centres, 701 patients, mortality 5.6%+/-5.0%) were compared with the highest volume group (14 centres, 3,618 patients, mortality 2.4%+/-1.0%) the O/E ratio was 1.1+/-1 (range 0 to 3.9) for the low volume group compared with 0.5+/-0.2 (range 0.1 to 0.7) for the high volume group. There was a statistically significant trend (p=0.001) towards decreasing O/E ratios with increasing hospital volumes. The study report states that rates of major complications were not different between the low and high-volume hospitals but these data are not presented.

In a small study, Verma et al. (2017) compared outcomes from January 2014 to June 2015 between low (n=21 procedures), medium (n=62 procedures) and high volume (n=98 procedures) US centres. Data were compiled from an electronic medical records system and multivariate regression and propensity score adjustment methods were used to adjust for confounding factors. These included; atrial fibrillation, left bundle branch block, left ventricle ejection fraction<50% and STS surgical risk score ≥12%. The primary endpoint was a 30-day composite measure comprising all-cause mortality, dialysis dependent renal failure, post procedure cerebrovascular accident, need for new permanent pacemaker and hospital readmission. This endpoint was experienced by 76% of participants in the low volume site, 50% of participants in the medium volume site and 39% of those having procedures in the high volume centre. Multivariate analysis found an odds ratio of experiencing the primary endpoint at the large volume site was 0.33 (95% CI 0.16 to 0.65) p=0.001 when compared with the intermediate and low volume centres. This finding was driven by the 30-day readmission rate.

In subgroup analysis, TAVI outcomes at a large volume centre were not significantly different than at a low and intermediate volume centre for patients having TAVI by alternate access (non-transfemoral) odds ratio (OR) 0.51 (95% CI 0.20 to 1.27, p=0.15).

There is consistency across the retrospective observational studies (datasets up to 2015) that short-term mortality outcomes for TAVI are better in high volume settings compared with low volume settings. Data on the relationship between hospital procedure volume and in-hospital or 30-day complications were inconsistent. None of the studies were able to robustly support any specific minimum institutional procedure volume cut-off. It may be that the relationship between volume and outcomes for TAVI will diminish as technologies evolve, experience increases and outcomes improve (Kaier et al. 2018). Balancing the clinical significance of differences in outcome with geographic access to TAVI was highlighted in a US discussion paper (Rogers et al. 2018) and the statistical challenges of assessing the quality of procedures at low annual volume (<50) centres also requires consideration (Bavaria et al. 2019).

Table 10. SHTG summary of volume outcome studies

Study details	Centres/ procedures	Volume definitions (annual)	Outcomes
Wassef et al. (2018) International Registry North and South America and Europe	16/2,205 2006-2015	Low (1-49) Intermediate (50-100) High (>100)	30 day mortality 30 day composite safety endpoint (death, stroke, major bleeding, vascular complications, conversion, renal failure)
Carroll et al. (2017) US Transcatheter Valve Registry	395/42,988 2011-2015	Cumulative volume as a continuous variable	In-hospital outcomes Mortality Vascular complications Bleeding Stroke
Bestehorn et al. (2017) German QA registry on aortic valve replacement (AQUA)	87/9,924 2014	11-50/50-99/100-149/150-199/≥200 Categorical and continuous analysis	In-hospital mortality
Verma et al. (2017) US Health System Electronic medical records	3/181 2014-2015	Low (<40) Intermediate (40-75) High (>75)	30 day composite (all-cause mortality, haemodyalysis, permanent pacemaker, cardiac re-admission)

8.4 Coronavirus (COVID-19) considerations

Experts informed HTW that current practice is impacted by the COVID-19 pandemic; this includes new pathways to facilitate patient treatment. It is unclear what impact this may have on the cost-effectiveness of TAVI.

European Society of Cardiology (ESC) have published guidelines on the diagnosis and management of cardiovascular disease during the COVID-19 pandemic (ESC 2020). It states that in the context of the COVID-19 pandemic, all cases should be discussed by the heart team and indications for TAVI extended to include intermediate and selected low-risk patients. Increased use of transfemoral TAVI (when feasible) may allow optimal utilization of resources by avoiding general anaesthesia and intubation, shortening (or preventing) ICU stay and accelerating hospital discharge and recovery.

9. Patient issues

Studies relevant to the patient and social aspects section of the EUnetHTA review did not report the surgical risk of patients in their sample, except for two studies which reported that patients were at high surgical risk.

9.1 Patient's experiences of undergoing TAVI

The SHTG review identified three primary studies were identified that looked at patients' experiences of undergoing TAVI (Astin et al. 2017, Baumbusch et al. 2017, Olsson et al. 2018). Study characteristics are presented in Table 11.

Study quality was assessed using the Quality of Reporting Tool (QuaRT) (Carroll et al. 2012). All studies were of good or satisfactory reporting quality, providing clarity and detail on the sampling of participants, and the collection and analysis of data. None of the studies failed to provide a clear description on one or more of these points. One of the studies (Olsson et al. 2018) was said to have been able to apply a more appropriate method than the one used, although the study design was still transparent and otherwise robust. Overall, study quality does not limit the findings.

One study (Baumbusch et al. 2017) of good quality looked at the experiences of patients and their caregivers of undergoing TAVI, and of the recovery process in the first year following the procedure. TAVI was the only treatment option available to patients included in the study due to other cardiac issues, comorbidities or frailty, which made them ineligible for a surgical procedure. The study reported that some patients experienced an immediate positive change in their quality of life (QoL) and relief from AS symptoms after undergoing TAVI. It must be noted that the study was conducted in a single centre in Canada that had a substantial experience of TAVI treatment. The study indicated, however, that a small number of patients continued to experience health issues related to comorbidities or frailty which impacted the way they felt about their QoL following TAVI. For some patients, there was dissonance between expectations of TAVI and the reality of ongoing physical, functional and social limitations one year post-TAVI. Patients reported that their expectations were shaped partly by what they heard from clinicians prior to undergoing the procedure. Caregivers also reported having to manage their expectations of the recovery process. The study identified the importance of providing patient counselling in relation to managing expectations around functional ability and QoL post TAVI. Furthermore, the study indicated that some patients were happy with short hospital stays, while others were not. It must be noted that the study was conducted in Canada where TAVI is provided in centrally coordinated sites and, therefore, some patients had to travel long distances to the procedure site. Patients in the study also highlighted the importance of receiving information about the recovery period to facilitate early transition home, as well as about the post-procedure recovery at home to support caregivers.

A second study (Olsson et al. 2018) of satisfactory quality looked at patients' experiences before undergoing TAVI and at 6 months follow-up. Before having the procedure, some patients expressed concerns about undergoing TAVI, referencing potential health complications or even death. Some patients in the study felt that they were being exposed to an intervention which was quite novel, which added to concerns. However, others were optimistic about undergoing TAVI because they had confidence in the doctors and felt informed and able to participate in treatment decisions.

The study also described patients' experiences of the recovery process, which was viewed as problematic for some but was described as 'surprisingly simple' by others. It must be noted that in this study patients were given full anaesthesia which entailed intensive care afterwards. Some patients reported long stays in the hospital after TAVI due to complications, side effects, or comorbidities. Patients also spoke about other diseases which impaired their potential for a

good social life, and that undergoing TAVI did not improve that. The slow recovery process for some resulted in depression, nightmares and thoughts of suicide. Some patients reported feeling weak and tired after TAVI and were unhappy about becoming dependent on the care of others. Disappointment was also expressed when patients' expectations of undergoing TAVI did not match the outcome or when complications occurred. In contrast, for some patients TAVI was easy to undergo and they were grateful for the experience due to less pain and time for recovery than other surgeries.

Several patients were surprised by the fast recovery in comparison to their own experience from heart surgery. These patients shared improvement in wellbeing and QoL, relating to fewer problems with breathing, increased weight, ability to stay independent and take part in social activities, and experience of joy. The feeling of improvements and fewer symptoms provided energy and hope for the future; having projects for the future was described by patients as giving meaning to life and helping them forget to problems.

A third study (Astin et al. 2017) of good quality explored patients' views on how TAVI influenced their QoL between one and three months postoperatively. The study highlighted how patients' decisions to have TAVI was influenced by participants perceived QoL before the procedure. The study found that those with significant symptom burden, which restricted functional and social activities leading to a negative impact upon QoL, felt that they had little choice but to undergo TAVI. A key concern for patients as their AS progressed, was facing mortality and the impact it would have on their family and friends. Patients reported feeling scared, lonely and short-tempered as they waited for TAVI. Pre-TAVI consultations with the doctor about risks, benefits and potential outcomes for TAVI, as well as likely prognosis in case no treatment was given, were perceived as a catalyst for reflection about the reality of mortality. However, for many of the participants in the study, TAVI offered a source of hope as they had access to a treatment option that could improve their life where they thought there had been none. TAVI was seen by study participants as an intervention that could treat a life threatening heart condition and was preferable to SAVR. Despite being aware of their limiting health conditions, and the potential risks surrounding TAVI, patients described their gratitude about having access to the intervention and reported their perception of TAVI leading to a longer life span.

The reduced symptom burden and the prospect of a longer life was described by patients as 'life changing' and was seen as the mechanism through which TAVI made an impact on QoL. Many patients, for example, reported experiencing less fatigue after TAVI, as well as an improvement in breathing. The study reported patients' feelings of confidence and security, which was related to the tangible improvement in heart function. The increase in the level of confidence regarding their physical health helped patients return to some of the activities that they had previously stopped doing. However, the scale of improvement was affected by the existence of other health conditions. For patients living with several comorbidities, it was sometimes challenging to evaluate the impact of TAVI on their own symptom burden and QoL because it was difficult to understand which physical symptoms could be attributed to which health condition.

Following recovery from the TAVI procedure, many participants noted a marked improvement in the nature of relationships with 'significant others' in their lives, whereby patients felt they could be 'of use' to others. For some patients TAVI provided an opportunity to undergo other health interventions that had previously been unavailable due to poor health. Only one patient in the study shared regret about undergoing TAVI due to their symptom burden not changing to the extent they had hoped.

Table 11. SHTG summary of qualitative studies exploring patients' experiences of undergoing TAVI

Study details	Aim	Patient characteristics (N, Mean age)	Follow-up	Country	Data collection & analysis methods	Quality
Baumbusch et al. (2017)	Explore patients' and family caregivers' perspectives on the recovery experience after TAVI	N patients=31 (13 men; 18 women); Mean age=81 N caregivers=15 (10 women; 11 men); Mean age=78.5	One year	Canada	Joint semi-structured interviews with caregivers and patients.	Good
Olsson et al. (2018)	Explore how patients experienced the recovery process from TAVI	N=19 (11 men; 8 women) Mean age men=80 Mean age women=82	Six months	Sweden	Interviews. Grounded theory	Satisfactory
Astin et al. (2017)	Provide an in-depth understanding of patients' views about the impact of TAVI on self-reported quality of life	N=46 at 1-month follow-up N=43 at 3-month follow-up Mean age=81.7	One and three months	UK	Mixed-methods Interviews. Framework analysis	Good

9.2 Patient's decision-making about undergoing TAVI

The SHTG review identified three primary studies were identified that looked at patients' decision-making around undergoing TAVI. Study characteristics are presented in Table 12. Study quality was assessed using the Quality of Reporting Tool (QuaRT) (Carroll et al. 2012). All studies were of good reporting quality, providing clarity and detail on the sampling of participants, and the collection and analysis of data. No studies failed to provide a clear description on one or more of these points. Study quality does not limit the findings.

One study (Lauck et al. 2016) of good quality explored the factors influencing the decision-making process of patients before undergoing the TAVI procedure. One of the most common factors was the alleviation of their symptom burden, such as the experience of severe fatigue, chest pain or shortness of breath. Patients who have had a previous experience of cardiac treatment perceived TAVI as a new minimally invasive treatment option. Patients also spoke about the anticipated outcome from undergoing TAVI; many patients included in the study believed that TAVI would extend their life. All study participants expressed hope that TAVI would improve their QoL and mental wellbeing. Both healthcare professionals and informal social support resources - provided by family, friends and community members - were perceived as essential sources of information, decision-making guidance and facilitators of referral for TAVI. Patients also considered their broader obligations, responsibilities in their life, and relationship with others when making the decision to seek treatment. The shorter recovery time and potential benefits of TAVI were seen as very advantageous for participants who had obligations which they wanted to resume following the procedure.

A second study (Olsson et al. 2016) of good quality examined the patterns in patients' influence on decision-making around TAVI. The study identified three patterns in decision-making process - ambivalent, obedient, and reconciled. The pattern of ambivalence was characterised by patients being unsure about the diagnosis and the benefits or effects of undergoing TAVI. The study identified that the decision became easier when patients shared the responsibility with others in their lives. The pattern of obedience was characterised by being doubtful about the value of the operation. Some of the patients were influenced by the recommendations from their doctors, while others relied mostly on their family member's opinion. The pattern of reconciliation was characterised by participants' realisation that their lives were threatened by the bad health prognosis and as a result they were confident and sure that the decision to undergo TAVI treatment was right. Some of the patients in this group expressed gratitude for getting another chance and impatience to get it done. The study concluded that it is important for healthcare professionals to observe patients' patterns of decision making in order to provide the most appropriate support.

A third study (Skaar et al. 2017) of good quality explored the conditions for autonomous choice for adults who recently underwent TAVI. The majority of patients experienced receiving good and well-adjusted amount of risk information, although some of them disclosed ambivalence about how much they wanted to know about complications. Trust in the doctors and their medical expertise was an important element in the decision-making process. Despite having trust in the doctors, some patients seeked a second opinion if they were not reassured by their doctor's advice. Self-determination based on personal identity was another condition for making an autonomous choice to undergo TAVI. Several patients, however, highlighted that they felt an obligation to their relatives to accept a treatment that was recommended.

Table 12. SHTG summary of qualitative studies exploring patients' decision-making about undergoing TAVI

Study details	Aim	Patient characteristics (n, Mean age)	Country	Data collection & analysis methods	Quality
Lauck et al. (2016)	Explore factors influencing the decision-making process of older individuals to undergo TAVI	n=15 (9 men; 6 women) Mean age=86	Canada	Semi-structured qualitative interviews	Good
Olsson et al. (2016)	Describe the decision-making process about undergoing TAVI treatment	n=24 (15 men; 9 women) Mean age=80.7	Sweden	Interviews	Good
Skaar et al. (2017)	Explore the conditions for an autonomous choice experienced by older adults who recently underwent TAVI	n=10 (4 men; 6 women) Median age=83.5	Norway	Interviews	Good

HTW searches identified one subsequent study (Marsh et al. 2019) that aimed to explore which TAVI and SAVR outcomes patients considered important, patient-weighed benefits and risks, and patient's intervention preference. Eligibility criteria included: at least 19 years of age, a self-reported diagnosis of aortic valve disease, be a resident of the US and to have received SAVR or TAVI in the past 10 years. Participants were recruited via email, and from the membership of patient organisations Heart Valve Voice, Mended Hearts and the American Heart Association. The sample included 219 participants and there were substantial heterogeneity in patient's preferences. On average, patients put greater value on attributes that were associated with TAVI, such as lower mortality rate, minimal invasiveness of the procedure, quicker time to recovery,

over the valuation of the time over which SAVR has been shown to be effective. Authors reported that 79.5% of patients prefer TAVI based on a Monte Carlo simulation.

9.3 Patient surveys

HTW sought additional patient evidence from patient organisations. Two forms of involvement were obtained: a written patient consultation from Heart Valve Voice and patient questionnaires from the patient network at the British Heart Foundation. Heart Valve Voice

Heart Valve Voice is a UK heart valve disease charity (https://heartvalvevoice.com/). Heart Valve Voice works with patients and clinicians to help increase the awareness of heart valve disease in the UK and improve diagnosis and treatment. In 2019 it published 'State of the Nation: Heart Valve Disease in Wales' report looking at the cardiovascular landscape in Wales. A written consultation based on this report was provided to HTW. The principle points for consideration from this consultation are summarised below.

- The decision to treat, and which is the most appropriate treatment, should be a joint decision between the patient and clinician, and based on their wants and needs, and quality of life factors.
- Access to innovative treatment is poor in Wales compared to the rest of the UK and across Europe.
- Many North Wales patients are referred across the border
- Limited access and restrictions to minimally invasive procedures, such as TAVI, are a restriction on patient choice and shared decision making
- If we do not increase access to innovative treatments, such as TAVI, and instil a culture in cardiovascular care that is centred on shared decision-making and patient choice, then we move ever further away from the European guidelines, set out by the European Society of Cardiology (ESC).
- The impact of the COVID-19 pandemic needs to be considered as it has affected the current position of the landscape and increased risks of attending hospitals.

9.3.1 British Heart Foundation

The British Heart Foundation (BHF) agreed to disseminate questionnaires to their Welsh and UK patient networks for individual patients to complete (https://www.bhf.org.uk/). A questionnaire was designed with input from health researchers, the BHF and PPI experts with HTW. Three questionnaires were returned. Pooled results of responses highlighted the following principle findings:

- Patients responded positively to having the option of TAVI and would recommend the TAVI procedure to others.
- Patients report that living with severe aortic stenosis and other related heart conditions can have an impact on daily life, including breathlessness and difficulty walking.
- Patients were satisfied with the care they received while undertaking TAVI and were positive about the process.
- Patients reported recovery times of 2-3 weeks, during which they could perform light exercise.

Patients consider having options for their treatment to be of high importance as well as having procedures explained fully.

10. Conclusions

Based on evidence from two RCTs, for patients with severe AS at intermediate surgical risk, TAVI is non-inferior to SAVR in terms of all-cause mortality and cardiac mortality at 30-day follow-up.

TAVI is associated with reduced length of hospital stay compared with SAVR. It remains unclear whether TAVI is better or worse than SAVR in terms of symptom improvement.

Moderate-quality evidence suggests that, compared with SAVR, TAVI reduces new-onset atrial fibrillation and increases the risk of paravalvular regurgitation. However, the relative effects of TAVI on the following outcomes is uncertain: stroke, acute kidney injury, new permanent pacemaker, major vascular complications, aortic valve reintervention, and life threatening and/or disabling bleeding.

Five-year outcomes for the PARTNER 2 trial have been subsequently published. Rates for all-cause mortality, cardiac mortality and disabling stroke were similar between the TAVI and SAVR arms at five years, and haemodynamic function and reduction in NYHA status was maintained from initial follow-ups. Incidence of new atrial fibrillation was higher in the SAVR arm, whereas incidence of paravalvular aortic regurgitation (mild or moderate) and valve re-intervention was higher in the TAVI arm.

The EUnetHTA meta-analysis was based on follow-up data up to 2 years, and subsequent 5 year outcome data was identified for PARTNER 2 only. This leaves uncertainty surrounding the long-term durability of the valve in an intermediate risk population, who are likely to have a longer life expectancy than the higher/inoperable risk population. HTW did not identify any long term comparative data of device durability for TAVI versus SAVR.

The two RCTs evaluated older, first-generation devices that experts noted are no longer used, which may limit their applicability to current practice. Furthermore, expert input sought by HTW noted that non-transfemoral access is reduced in current practice compared to the trials, as is use of general anaesthetic.

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. This is further reflected in sensitivity analysis conducted in the HTW analysis, in which the result was found to be sensitive to changes in the cost of the TAVI and SAVR procedure. Therefore, local prices for the TAVI and SAVR procedure play a crucial role in determining cost-effectiveness.

Increased TAVI annual hospital volume is associated with improved clinical outcomes. Although no studies were able to support any specific cut-off values, the evidence base indicates that low procedure volume centres (<50 per year) should be avoided.

Pre-TAVI consultations with patients and their caregivers should emphasise the potential effects and risks of the procedure in the context of the individual's comorbidities and frailty in order to support treatment decision and informed consent. Furthermore, in order to provide the most appropriate support, it is important that healthcare professionals are aware of how individual patients make decisions about undergoing TAVI. Healthcare professionals should also provide adequate information about the post-procedure recovery process to patients and their caregivers.

11. Contributors

This topic was proposed by Dr Andrew Champion, Assistant Director of Evidence Evaluation, Welsh Health Specialised Services Committee.

The HTW staff and contract researchers involved in writing this report were:

- J Washington, Information Specialist – literature searches
- L Elston, Health Services Researcher - clinical author
- M Prettyjohns, Principal Researcher – health economics author
- A Evans, PPI Officer – PPI lead and author
- G Hopkins, Health Services Researcher – quality assurance check
- S McAllister, Project Manager – project management

The HTW Assessment Group advised on methodology throughout the scoping and development of the report.

A range of clinical experts from the UK provided material and commented on a draft of this report. Their views were documented and have been actioned accordingly. All contributions from reviewers were considered by HTW's Assessment Group. However, reviewers had no role in authorship or editorial control, and the views expressed are those of Health Technology Wales.

Experts who contributed to this appraisal:

- Ameer Ally, Head of Market Access & Government Affairs UKI, Edwards Lifesciences
- Professor Richard Anderson, Consultant Cardiologist
- Dr Clare Appleby, Consultant Cardiologist, Clinical Lead for Intervention and TAVI. Liverpool Heart and Chest Hospital
- James Barry, Cardiologist, Swansea Bay University Health Board
- Miss Indu Deglurkar, Consultant Cardiothoracic Surgeon & President of the Welsh Cardiothoracic Society
- Christopher Fawsitt, Senior Health Economist, Health Information and Quality Authority of Ireland
- Natalie Hallas, Health Economics and Commissioning Manager, Medtronics
- Patricia Harrington, Head of Assessment, Health Information and Quality Authority of Ireland
- David Hildick-Smith, Professor of Cardiology, British Cardiovascular Interventions Society
- Jan Kovac, Consultant cardiologist, honorary professor of interventional cardiology
- Dheeraj Mehta, Consultant Cardiac Surgeon, Lead Cardiothoracic Surgeon, UHW
- Dr Michael Mullen, Consultant Cardiologist, Lead for structural heart intervention, Barts Health NHS Trust, London
- Dr Andrew Sharp, Consultant Cardiologist, University Hospital of Wales
- Dr Dave Smith, Consultant cardiologist and lead for structural intervention, Swansea Bay University Health Board
- Michelle Sullivan, Health Economics and market access, Boston Scientific
- Lorna Thompson, Health Services Researcher, Healthcare Improvement Scotland (Scottish Health Technologies Group)
- Prof Ulrich Von Oppell, Consultant Cardiac surgeon University Hospital of Wales
- Richard Wheeler, Consultant Cardiologist, Clinical Director Cardiothoracic Department University Hospital of Wales, Cardiff
- Claire Williams, Consultant Cardiologist Royal Glamorgan Hospital
- Mr Afzal Zaidi, Consultant Cardiothoracic Surgeon and Clinical Director Cardiothoracic Surgery, Morriston Hospital, Swansea UHB

12. References

Amrane H, Deeb GM, Popma JJ, et al. (2019). Causes of death in intermediate-risk patients: the randomized surgical replacement and transcatheter aortic valve implantation trial. Journal of Thoracic and Cardiovascular Surgery. 158(3): 718-28.e3. doi: https://dx.doi.org/10.1016/j.jtcvs.2018.11.129

Ando T, Adegbala O, Villablanca PA, et al. (2018). Failure to rescue, hospital volume, and in-hospital mortality after transcatheter aortic valve implantation. American Journal of Cardiology. 122(5): 828-32. doi: https://doi.org/10.1016/j.amjcard.2018.05.020

Ando T, Ashraf S, Villablanca PA, et al. (2019). Meta-analysis comparing the incidence of infective endocarditis following transcatheter aortic valve implantation versus surgical aortic valve replacement. American Journal of Cardiology. 123(5): 827-32. doi: https://dx.doi.org/10.1016/j.amjcard.2018.11.031

Asteggiano R, Bramlage P, Richter DJ. (2018). European Society of Cardiology Council for Cardiology Practice worldwide survey of transcatheter aortic valve implantation beliefs and practices. European Journal of Preventive Cardiology. 25(6): 608-17. doi: https://dx.doi.org/10.1177/2047487318760029

Astin F, Horrocks J, McLenachan J, et al. (2017). The impact of transcatheter aortic valve implantation on quality of life: a mixed methods study. Heart and Lung. 46(6): 432-8. doi: https://doi.org/10.1016/j.hrtlng.2017.08.005

Azraai M, Gao L, Ajani AE. (2020). Cost-effectiveness of transcatheter aortic valve intervention (TAVI) compared to surgical aortic valve replacement (SAVR) in low-intermediate surgical risk patients. Cardiovascular Revascularization Medicine. [Article in Press]. doi: https://dx.doi.org/10.1016/j.carrev.2020.01.009

Badheka AO, Patel NJ, Panaich SS, et al. (2015). Effect of hospital volume on outcomes of transcatheter aortic valve implantation. American Journal of Cardiology. 116(4): 587-94. doi: https://doi.org/10.1016/j.amjcard.2015.05.019

Baron SJ, Arnold SV, Wang K, et al. (2017). Health status benefits of transcatheter vs surgical aortic valve replacement in patients with severe aortic stenosis at intermediate surgical risk: results from the PARTNER 2 randomized clinical trial. JAMA Cardiology. 2(8): 837-45. doi: https://doi.org/10.1001/jamacardio.2017.2039

Baron SJ, Thourani VH, Kodali S, et al. (2018). Effect of SAPIEN 3 transcatheter valve implantation on health status in patients with severe aortic stenosis at intermediate surgical risk: results from the PARTNER S3i trial. JACC: Cardiovascular Interventions. 11(12): 1188-98. doi: https://dx.doi.org/10.1016/j.jcin.2018.02.032

Baron SJ, Wang K, House JA, et al. (2019). Cost-Effectiveness of Transcatheter Versus Surgical Aortic Valve Replacement in Patients With Severe Aortic Stenosis at Intermediate Risk. Circulation. 139(7): 877-88. doi: https://dx.doi.org/10.1161/CIRCULATIONAHA.118.035236

Baumbusch J, Lauck SB, Achtem L, et al. (2017). Understanding experiences of undergoing transcatheter aortic valve implantation: one-year follow-up. European Journal of Cardiovascular Nursing. 17(3): 280-8. doi: https://doi.org/10.1177/1474515117738991

Baumgartner H, Falk V, Bax JJ, et al. (2017). 2017 ESC/EACTS Guidelines for the management of valvular heart disease. European Heart Journal. 38(36): 2739-91. doi: https://doi.org/10.1093/eurheartj/ehx391

Bavaria JE, Tommaso CL, Brindis RG, et al. (2019). 2018 AATS/ACC/SCAI/STS Expert Consensus Systems of Care Document: operator and institutional recommendations and requirements for transcatheter aortic valve replacement: a joint report of the American Association for Thoracic Surgery, American College of Cardiology, Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons. Annals of Thoracic Surgery. 107(2): 650-84. doi: https://doi.org/10.1016/j.athoracsur.2018.07.001

BCIS. (2019). Service Specification for Transcatheter Aortic Valve Implantation (TAVI): recommendations of the British Cardiovascular Intervention Society (BCIS). British Cardiovascular Intervention Society. Available at: https://www.bcis.org.uk/resources/bcis-guidance-documents/service-specification-for-transcatheter-aortic-valve-implantation-tavi/ [Accessed 17 Sept 2020].

BCIS, SCTS. (2008). Transcatheter Aortic Valve Implantation (TAVI): a position statement. British Cardiovascular Intervention Society (BCIS) and the Society of Cardiothoracic Surgeons (SCTS). Available at: http://www.bcis.org.uk/wp-content/uploads/2016/12/BCIS-SCTS-position-statement.pdf [Accessed 27 July 2020].

BCS, SCTS, BCIS. (2017). Joint Statement on clinical selection for Trans-catheter Aortic Valve Implantation (TAVI). British Cardiovascular Society ,Society for Cardiothoracic Surgery and the British Cardiovascular Intervention Society. Available at: https://www.bcis.org.uk/wp-content/uploads/2017/08/TAVI-commissioning-statement-final.pdf [Accessed 17 Sept 2020].

Bestehorn K, Bestehorn M, Fleck E. (2015). Influence of different approaches of aortic valve replacement on the incidence of post-operative delirium in intermediate risk patients – a matched pair analysis. Current Medical Research and Opinion. 31(12): 2157-63. doi: https://doi.org/10.1185/03007995.2015.1092125

Bestehorn K, Eggebrecht H, Fleck E, et al. (2017). Volume-outcome relationship with transfemoral transcatheter aortic valve implantation (TAVI): insights from the compulsory German Quality Assurance Registry on Aortic Valve Replacement (AQUA). EuroIntervention. 13(8): 914-20. doi: https://doi.org/10.4244/eij-d-17-00062

Borracci RA, Navia DO, Kotowicz V, et al. (2019). Single-arm meta-analysis of Argentine studies reporting in-hospital mortality after aortic valve replacement in low and intermediate risk patients. Revista Argentina de Cardiología. 87(4): 271-80. doi: http://dx.doi.org/10.7775/rac.v87.i4.15693

Brennan JM, Thomas L, Cohen DJ, et al. (2017). Transcatheter versus surgical aortic valve replacement: propensity-matched comparison. Journal of the American College of Cardiology. 70(4): 439-50. doi: https://doi.org/10.1016/j.jacc.2017.05.060

CADTH. (2018). Transcatheter aortic valve implantation for patients with severe aortic stenosis at various levels of surgical risk: a review of clinical effectiveness. Rapid Response RD0043-000. Canadian Agency for Drugs and Technologies in Health. Available at: https://www.cadth.ca/transcatheter-aortic-valve-implantation-patients-severe-aortic-stenosis-various-levels-surgical-risk [Accessed 17 Sept 2020].

Carroll C, Booth A, Lloyd-Jones M. (2012). Should we exclude inadequately reported studies from qualitative systematic reviews? An evaluation of sensitivity analyses in two case study reviews. Qualitative Health Research. 22(10): 1425-34. doi: https://doi.org/10.1177/1049732312452937

Carroll JD, Vemulapalli S, Dai D, et al. (2017). Procedural experience for transcatheter aortic valve replacement and relation to outcomes: the STS/ACC TVT Registry. Journal of the American College of Cardiology. 70(1): 29-41. doi: https://doi.org/10.1016/j.jacc.2017.04.056

Cremer PC, Zhang Y, Alu M, et al. (2018). The incidence and prognostic implications of worsening right ventricular function after surgical or transcatheter aortic valve replacement: insights from PARTNER IIA. European Heart Journal. 39(28): 2659-67. doi: https://dx.doi.org/10.1093/eurheartj/ehy251

de Biasi AR, Paul S, Nasar A, et al. (2016). National analysis of short-term outcomes and volume-outcome relationships for transcatheter aortic valve replacement in the era of commercialization. Cardiology. 133(1): 58-68. doi: https://doi.org/10.1159/000440694

De Sciscio P, Brubert J, De Sciscio M, et al. (2017). Quantifying the shift toward transcatheter aortic valve replacement in low-risk patients: a meta-analysis. Circulation: Cardiovascular Quality and Outcomes. 10(6). doi: https://doi.org/10.1161/circoutcomes.116.003287

Durko AP, Reardon MJ, Kleiman NS, et al. (2018). Neurological complications after transcatheter versus surgical aortic valve replacement in intermediate-risk patients. Journal of the American College of Cardiology. 72(18): 2109-19. doi: https://dx.doi.org/10.1016/j.jacc.2018.07.093

ESC. (2020). ESC Guidance for diagnosis and management of cvd during the COVID-19 pandemic. European Society of Cardiology. Available at: https://www.escardio.org/Education/COVID-19-and-Cardiology/ESC-COVID-19-Guidance [Accessed 17 Sept 2020].

EUnetHTA. (2018). Transcatheter aortic valve implantation (TAVI) in patients at intermediate surgical risk. Joint Action 3 WP4 OTCA06. European Network for Health Technology Assessment. Available at: https://www.eunethta.eu/wp-content/uploads/2018/12/OTCA06-TAVI-FOR-THE-TREATMENT-OFPATIENTS-AT-INTERMEDIATE-SURGICAL-RISK-FINAL-1.pdf [Accessed 17 Sept 2020].

Fang F, Tang J, Zhao Y, et al. (2019). Transcatheter aortic valve implantation versus surgical aortic valve replacement in patients at low and intermediate risk: a risk specific meta-analysis of randomized controlled trials. PloS One. 14(9): e0221922. doi: https://dx.doi.org/10.1371/journal.pone.0221922

Gialama F, Prezerakos P, Apostolopoulos V, et al. (2018). Systematic review of the cost-effectiveness of transcatheter interventions for valvular heart disease. European Heart Journal Quality of Care & Clinical Outcomes. 4(2): 81-90. doi: https://dx.doi.org/10.1093/ehjqcco/qcx049

Goodall G, Lamotte M, Ramos M, et al. (2019). Cost-effectiveness analysis of the SAPIEN 3 TAVI valve compared with surgery in intermediate-risk patients. Journal of Medical Economics. 22(4): 289-96. doi: https://dx.doi.org/10.1080/13696998.2018.1559600

Guyatt GH, Oxman AD, Vist GE, et al. (2008). GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 336(7650): 924-6. doi: https://doi.org/10.1136/bmj.39489.470347.AD

HIQA. (2019). HTA of transcatheter aortic valve implantation (TAVI). Health Information and Quality Authority. Available at: https://www.hiqa.ie/reports-and-publications/health-technology-assessment/hta-transcatheter-aortic-valve-implantation [Accessed 04 Jun 2020].

Huygens SA, Takkenberg JJM, Rutten-van Molken M. (2018). Systematic review of model-based economic evaluations of heart valve implantations. European Journal of Health Economics. 19(2): 241-55. doi: https://dx.doi.org/10.1007/s10198-017-0880-z

Inoue S, Nakao K, Hanyu M, et al. (2020). Cost-effectiveness of transcatheter aortic valve implantation using a balloon-expandable valve in Japan: experience from the Japanese Pilot Health Technology Assessment. Value in Health Regional Issues. 21: 82-90. doi: https://dx.doi.org/10.1016/j.vhri.2019.07.013

Iung B, Baron G, Butchart EG, et al. (2003). A prospective survey of patients with valvular heart disease in Europe: the Euro Heart Survey on valvular heart disease. European Heart Journal. 24(13): 1231-43. doi: https://doi.org/10.1016/s0195-668x(03)00201-x

Iung B, Cachier As, Baron G, et al. (2005). Decision-making in elderly patients with severe aortic stenosis: why are so many denied surgery? European Heart Journal. 26(24): 2714-20. doi: https://doi.org/10.1093/eurheartj/ehi471

Kaier K, Oettinger V, Reinecke H, et al. (2018). Volume–outcome relationship in transcatheter aortic valve implantations in Germany 2008–2014: a secondary data analysis of electronic health records. BMJ Open. 8(7): e020204. doi: https://doi.org/10.1136/bmjopen-2017-020204

Kaier K, von Zur Muhlen C, Zirlik A, et al. (2019). Estimating the additional costs per life saved due to transcatheter aortic valve replacement: a secondary data analysis of electronic health records in Germany. European Journal of Health Economics. 20(4): 625-32. doi: https://dx.doi.org/10.1007/s10198-018-1023-x

Khan SU, Riaz H, Khan MU, et al. (2019). Meta-analysis of temporal and surgical risk dependent associations with outcomes after transcatheter versus surgical aortic valve implantation. American Journal of Cardiology. 124(10): 1608-14. doi: https://dx.doi.org/10.1016/j.amjcard.2019.07.066

Khera S, Kolte D, Gupta T, et al. (2017). Association between hospital volume and 30-day readmissions following transcatheter aortic valve replacement. JAMA Cardiol. 2(7): 732-41. doi: https://doi.org/10.1001/jamacardio.2017.1630

Kodera S, Kiyosue A, Ando J, et al. (2018). Cost effectiveness of transcatheter aortic valve implantation in patients with aortic stenosis in Japan. Journal of Cardiology. 71(3): 223-9. doi: https://dx.doi.org/10.1016/j.jjcc.2017.10.008

Lauck SB, Baumbusch J, Achtem L, et al. (2016). Factors influencing the decision of older adults to be assessed for transcatheter aortic valve implantation: an exploratory study. European Journal of Cardiovascular Nursing. 15(7): 486-94. doi: https://doi.org/10.1177/1474515115612927

Lazkani M, Singh N, Howe C, et al. (2019). An updated meta-analysis of TAVR in patients at intermediate risk for SAVR. Cardiovascular Revascularization Medicine. 20(1): 57-69. doi: https://dx.doi.org/10.1016/j.carrev.2018.04.001

Leon MB, Smith CR, Mack MJ, et al. (2016). Transcatheter or surgical aortic-valve replacement in intermediate-risk patients. New England Journal of Medicine. 374(17): 1609-20. doi: https://doi.org/10.1056/NEJMoa1514616

Makkar RR, Thourani VH, Mack MJ, et al. (2020). Five-year outcomes of transcatheter or surgical aortic-valve replacement. New England Journal of Medicine. 382(9): 799-809. doi: https://dx.doi.org/10.1056/NEJMoa1910555

Marsh K, Hawken N, Brookes E, et al. (2019). Patient-centered benefit-risk analysis of transcatheter aortic valve replacement. F1000Research. 8: 394. doi: https://dx.doi.org/10.12688/f1000research.18796.4

Nazif TM, Chen S, George I, et al. (2019). New-onset left bundle branch block after transcatheter aortic valve replacement is associated with adverse long-term clinical outcomes in intermediate-risk patients: an analysis from the PARTNER II trial. European Heart Journal. 40(27): 2218-27. doi: https://dx.doi.org/10.1093/eurheartj/ehz227

NHS. (2020). 2018/19 National Cost Collection data. National Health Service. Available at: https://www.england.nhs.uk/national-cost-collection/ [Accessed 16 Sept 2020].

NICE. (2017). Transcatheter aortic valve implantation for aortic stenosis. Interventional procedures guidance IPG586. National Institute for Health and Care Excellence. Available at: https://www.nice.org.uk/guidance/ipg586 [Accessed 17 Sept 2020].

NIPH. (2019). Health technology assessment of Transcatether aortic valve implantation (TAVI) as treatment of patients with severe aortic stenosis and intermediate surgical risk – Part 2. Health economic evaluation. Norwegian Institute of Public Health. Available at: https://www.fhi.no/en/publ/2019/Transcatether-aortic-valve-implantation-as-treatment-of-patients-with-severe-aortic-stenosis-and-intermediate-surgical-risk/ [Accessed 17 Sept 2020].

Olsson K, Näslund U, Nilsson J, et al. (2016). Patients' decision making about undergoing transcatheter aortic valve implantation for severe aortic stenosis. Journal of Cardiovascular Nursing. 31(6): 523-8. doi: https://doi.org/10.1097/jcn.0000000000000282

Olsson K, Näslund U, Nilsson J, et al. (2018). Patients' experiences of the transcatheter aortic valve implantation trajectory: a grounded theory study. Nursing open. 5(2): 149-57. doi: https://doi.org/10.1002/nop2.124

ONS. (2019). National life tables, UK: 2016 to 2018. Office for National Statistics. Available at: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/bulletins/nationallifetablesunitedkingdom/2016to2018 [Accessed 16 Sept 2020].

Ontario Health. (2020). Transcatheter aortic valve implantation in patients with severe, symptomatic aortic valve stenosis at intermediate surgical risk: a health technology assessment. Ontario Health Technology Assessment Series 20(2). Health Quality Ontario. Available at: https://www.hqontario.ca/evidence-to-improve-care/health-technology-assessment/reviews-and-recommendations/transcatheter-aortic-valve-implantation-in-patients-with-severe-symptomatic-aortic-valve-stenosis-at-intermediate-surgical-risk [Accessed 21 Sept 2020].

Osnabrugge RLJ, Mylotte D, Head SJ, et al. (2013). Aortic stenosis in the elderly: disease prevalence and number of candidates for transcatheter aortic valve replacement: a meta-analysis and modeling study. Journal of the American College of Cardiology. 62(11): 1002-12. doi: https://doi.org/10.1016/j.jacc.2013.05.015

Pagano D, Kappetein AP, Sousa-Uva M, et al. (2016). EACTS clinical statement: guidance for the provision of adult cardiac surgery. European Journal of Cardio-Thoracic Surgery. 50(6): 1006-9. doi: https://doi.org/10.1093/ejcts/ezw300

Panaich SS, Patel NJ, Patel N, et al. (2016). Hospital volume and in-hospital outcomes after transcatheter aortic valve implantation. American Journal of Cardiology. 117(6): 1028-9. doi: https://doi.org/10.1016/j.amjcard.2015.12.020

Reardon MJ, Van Mieghem NM, Popma JJ, et al. (2017). Surgical or transcatheter aortic-valve replacement in intermediate-risk patients. New England Journal of Medicine. 376(14): 1321-31. doi: https://doi.org/10.1056/NEJMoa1700456

Rogers T, Khan JM, Edelman JJ, et al. (2018). Summary of the 2018 Medicare Evidence Development & Coverage Advisory Committee (MEDCAC) for transcatheter aortic valve replacement. Cardiovascular Revascularization Medicine. 19(8): 964-70. doi: https://doi.org/10.1016/j.carrev.2018.10.009

Sethi S, Daniel T, Howell J, et al. (2009). A commissioning framework for transcatheter aortic valve implantation (TAVI) for severe symptomatic aortic stenosis. Available at: http://bcis.org.uk/wp-content/uploads/2016/12/TAVI-National-Commissioning-Framework-FINAL-160309.pdf [Accessed 17 Sept 2020].

SHTG. (2019). Transcatheter aortic valve implantation (TAVI) for the treatment of patients with severe symptomatic aortic stenosis who are at intermediate surgical risk. Evidence Note 91. Scottish Health Technologies Group. Available at: http://www.healthcareimprovementscotland.org/our_work/technologies_and_medicines/topics_assessed/shtg_04-19.aspx [Accessed 17 Sept 2020].

Singh K, Carson K, Rashid MK, et al. (2018). Transcatheter aortic valve implantation in intermediate surgical risk patients with severe aortic stenosis: a systematic review and meta-analysis. Heart, Lung & Circulation. 27(2): 227-34. doi: https://dx.doi.org/10.1016/j.hlc.2017.02.032

Siontis GCM, Overtchouk P, Cahill TJ, et al. (2019). Transcatheter aortic valve implantation vs. surgical aortic valve replacement for treatment of symptomatic severe aortic stenosis: an updated meta-analysis. European Heart Journal. 40(38): 3143-53. doi: https://dx.doi.org/10.1093/eurheartj/ehz275

Skaar E, Ranhoff AH, Nordrehaug JE, et al. (2017). Conditions for autonomous choice: a qualitative study of older adults' experience of decision-making in TAVR. Journal of Geriatric Cardiology. 14(1): 42-8. doi: https://doi.org/10.11909/j.issn.1671-5411.2017.01.007

Tam DY, Hughes A, Fremes SE, et al. (2018a). A cost-utility analysis of transcatheter versus surgical aortic valve replacement for the treatment of aortic stenosis in the population with intermediate surgical risk. Journal of Thoracic and Cardiovascular Surgery. 155(5): 1978-88.e1. doi: https://dx.doi.org/10.1016/j.jtcvs.2017.11.112

Tam DY, Hughes A, Wijeysundera HC, et al. (2018b). Cost-Effectiveness of Self-Expandable Transcatheter Aortic Valves in Intermediate-Risk Patients. Annals of Thoracic Surgery. 106(3): 676-83. doi: https://dx.doi.org/10.1016/j.athoracsur.2018.03.069

Tarride JE, Luong T, Goodall G, et al. (2019). A Canadian cost-effectiveness analysis of SAPIEN 3 transcatheter aortic valve implantation compared with surgery, in intermediate and high-risk severe aortic stenosis patients. Clinicoeconomics & Outcomes Research. 11: 477-86. doi: https://dx.doi.org/10.2147/CEOR.S208107

Thivilliers AP, Ladarre R, Merabti O, et al. (2020). The learning curve in transcatheter aortic valve implantation clinical studies: a systematic review. International Journal of Technology Assessment in Health Care. 36(2): 152-61. doi: https://dx.doi.org/10.1017/S0266462320000100

Ueshima D, Fovino LN, D'Amico G, et al. (2019). Transcatheter versus surgical aortic valve replacement in low- and intermediate-risk patients: an updated systematic review and meta-analysis. Cardiovascular Intervention and Therapeutics. 34(3): 216-25. doi: https://dx.doi.org/10.1007/s12928-018-0546-5

Vahanian A, Alfieri O, Andreotti F, et al. (2012). Guidelines on the management of valvular heart disease (version 2012): The Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). European Journal of Cardio-Thoracic Surgery. 42(4): S1-S44. doi: https://doi.org/10.1093/ejcts/ezs455

Verma DR, Pershad Y, Lazkani M, et al. (2017). Volume-outcome relationships for transcatheter aortic valve replacement-risk-adjusted and volume stratified analysis of TAVR outcomes. Indian Heart Journal. 69(6): 700-6. doi: https://doi.org/10.1016/j.ihj.2017.04.017

Wassef AWA, Rodes-Cabau J, Liu Y, et al. (2018). The learning curve and annual procedure volume standards for optimum outcomes of transcatheter aortic valve replacement: findings from an international registry. JACC: Cardiovascular Interventions. 11(17): 1669-79. doi: https://doi.org/10.1016/j.jcin.2018.06.044

WHSSC. (2019). Trans-catheter Aortic Valve Implantation (TAVI) for Severe Symptomatic Aortic Stenosis (SSAS). Specialised Services Commissioning Policy CP58. Welsh Health Specialised Services Committee. Available at: http://www.whssc.wales.nhs.uk/sitesplus/documents/1119/CP58%20TAVI%20final%20V1%200%2029.03.18.pdf [Accessed 17 Sept 2020].

Zhou J, Liew D, Duffy SJ, et al. (2019). Cost-effectiveness of transcatheter aortic valve implantation compared to surgical aortic valve replacement in the intermediate surgical risk population. International Journal of Cardiology. 294: 17-22. doi: https://dx.doi.org/10.1016/j.ijcard.2019.06.057

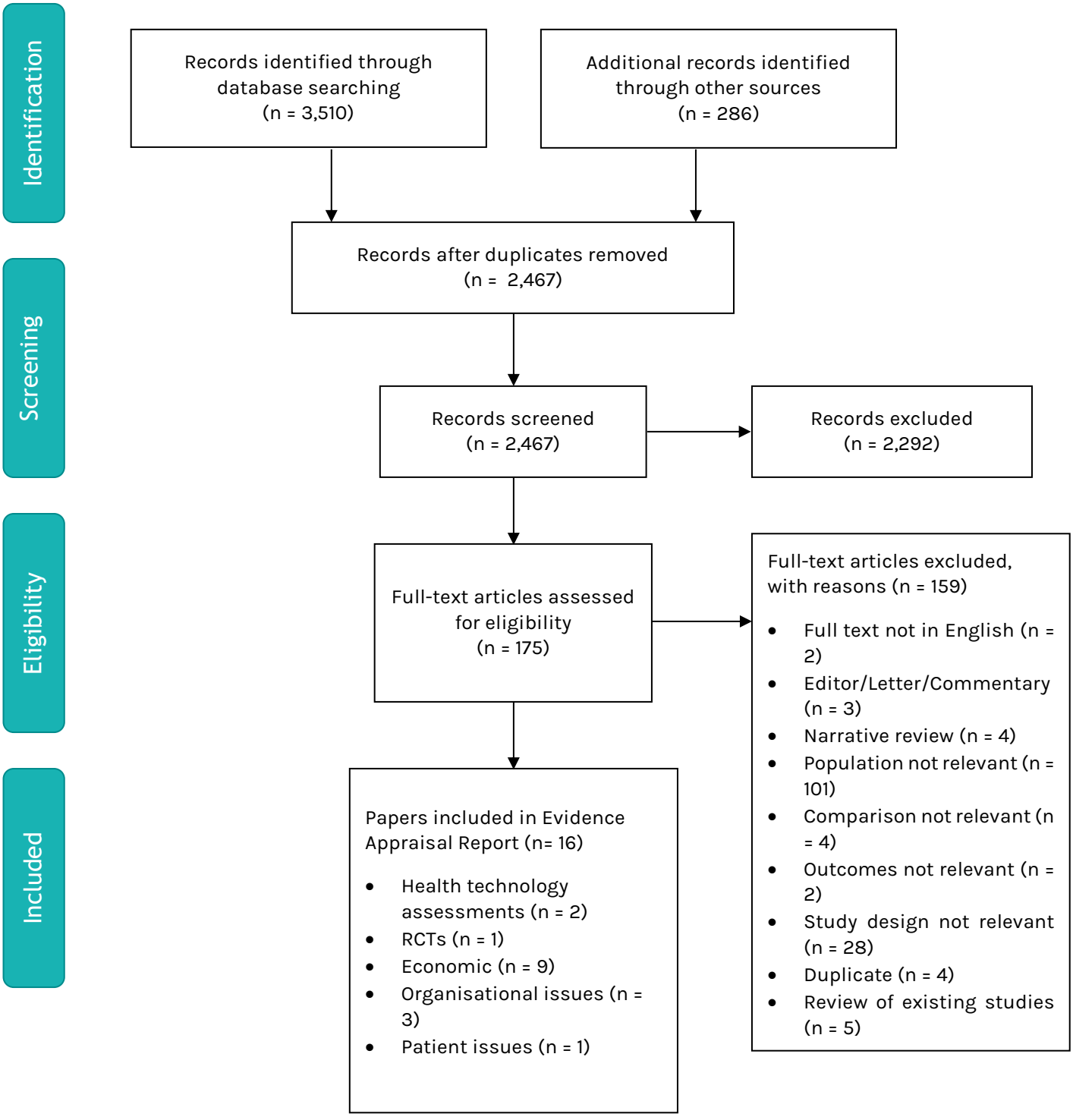
Appendix 1. PICO framework

Research Question	Is transcatheter aortic valve implantation (TAVI) clinically and cost effective for severe symptomatic aortic stenosis in adults who are assessed by a heart team as being operable but at intermediate surgical risk?

	Inclusion criteria	**Exclusion criteria**
Population	Adults with severe symptomatic aortic stenosis who are assessed by a heart team as being operable but at intermediate surgical risk	Patients of other surgical risk (low, high, inoperable)
Intervention	Transcatheter aortic valve implantation (TAVI) devices	
Comparison/ Comparators	Surgical aortic valve replacement (SAVR)	
Outcome measures	**Clinical effectiveness** • Overall mortality • Cardiac mortality • Health related quality of life • Morbidity (SHTG reported symptom reduction using New York Heart Association (NYHA) classification) • Aortic valve re-intervention • Haemodynamic function of the valve • Length of stay **Safety** • Stroke • New atrial fibrillation • Life-threatening or disabling bleeding • Acute kidney injury • Major vascular complications • Permanent pacemaker implantation • Parvalvular aortic regurgitation • Endocarditis	

Study design	We will include the following clinical evidence in order of priority: • Systematic reviews. • Randomised or non-randomised trials. For this search, we will only focus on 'high priority' evidence as part of an update to the SHTG report. We will also search for economic evaluations or original research that can form the basis of an assessment of costs/cost comparison.
Search limits	Searches will be restricted to those published from 2018 onwards.
Other factors	SHTG report (2019) (http://www.healthcareimprovementscotland.org/our_work/technologies_and_medicines/topics_assessed/shtg_04-19.aspx)

Appendix 2. PRISMA flow diagram outlining selection of papers for clinical and cost effectiveness



Appendix 3: Summary of studies included in economic evidence review

Table 1. Summary of included health economic studies from non-UK settings

Study details	Study population and design	Data sources	Results	Quality assessment
Author and year: Baron 2019 **Country:** United States (US) **Type of economic analysis:** Cost-utility analysis **Perspective:** US healthcare system **Currency:** US dollars ($) **Price year:** 2016 **Time horizon:** Lifetime **Discounting:** Costs and benefits discounted at 3% per year **Potential conflict of interest:** Funded by a research grant from Edwards Lifesciences Inc.	**Population** Patients with severe, symptomatic aortic stenosis at intermediate surgical risk **Interventions** TAVI using the SAPIEN XT valve (XT-TAVI) TAVI using the SAPIEN 3 valve (S3-TAVI) **Comparator** Surgical aortic valve replacement (SAVR) **Study design** Cost-utility analysis using Markov model	**Source of baseline and effectiveness data:** Data for XT-TAVI in comparison to SAVR was sourced from the PARTNER 2 trial. Effectiveness data on S3-TAVI was sourced from the S3i registry and this was compared against SAVR using effectiveness data on SAVR from the PARTNER 2 trial. In all cases where trial data was used, it was based upon the as-treated population (rather than the full intention to treat cohort). Trial outcomes were used for the two years where data was available. Beyond two years, survival was projected using general mortality estimates from US life tables with a calibration factor based upon observed between 6 and 24 months in the PARTNER 2 trial. In the base case, it was assumed that mortality rates beyond two years were equivalent in TAVI and SAVR arms. **Source of resource use and cost data:** Costs associated with the TAVI and SAVR procedures were estimated using resource utilisation data from the PARTNER 2 trial in combination with Medicare claims data.	**XT-TAVI in comparison to SAVR** **Costs** XT-TAVI: $227,363 SAVR: $235,312 Incremental: -$7,949 **QALYs** XT-TAVI: 5.16 SAVR: 5.01 Incremental: 0.15 **ICER (cost per QALY)** XT-TAVI found to be dominant **S3-TAVI in comparison to SAVR** **Costs** S3-TAVI: $231,179 SAVR: $240,871 Incremental: -$9,692 **QALYs** SE-TAVI: 5.29 SAVR: 5.01 Incremental: 0.27 **ICER (cost per QALY)** SE-TAVI found to be dominant **Subgroup analysis** Subgroup analyses were	**Applicability** The analysis was deemed to be only partially applicable to the UK NHS because it considered the US healthcare system. **Limitations** Some potentially serious limitations were identified with the analysis. In particular: • Use of data from a non-randomised study for the comparison of S3-TAVI and SAVR • Extrapolation of cost and QALY outcomes beyond the trial period was based on assumed differences between treatment arms, based on differences in the preceding two years. A more conservative approach would have been to assume equivalence following the trial period. • Cost of TAVI procedure is likely to vary as it is influenced by the cost of the TAVI valve, which varies by manufacturer and is

Study details	Study population and design	Data sources	Results	Quality assessment
Lead author received consulting income from Edwards Lifesciences and research support from Boston Scientific Inc. Seven other authors reported potential conflicts with either consulting income or research support from Edwards Lifesciences, St. Jude Medical, Medtronic, Boston Scientific, Abbott Vascular, Sanofi, Cordis, Bayer, Corvia Medical, Meril Life Sciences, Claret Medical, Sorin Medical and Direct Flow Medical. Two other authors reported holding equity, one in Entourage Medical and another in Thubrikar Aortic Valve, Dura Biotech, and BioTrace Medical		Probabilistic matching was used to link trial patients with Medicare claims data. Linkage was successful for 78% of patients treated with XT-TAVI and SAVR and 77% of patients treated with S3-TAVI. For patients with linked Medicare claims, costs were estimated based on hospital charges, which were converted to costs based on cost-to-charge ratios. For patients without linked Medicare claims, costs were estimated using regression models based on those patients with linked data. A valve cost of $5,000 was assumed for the SAVR procedure while a valve cost of $32,500 was assumed for TAVI procedures. Future costs beyond the two year trial period were projected using a regression model based on the last follow-up period for each comparison (12–24 months for XT-TAVI versus SAVR and 6–12 months for S3-TAVI versus SAVR). **Source of quality of life data:** Quality of life estimates were based on responses to the EQ-5D questionnaire which was administered as part of the PARTNER 2 trial, with values at baseline, one month, 12 months and 24 months. Responses were converted to health state utilities with an algorithm derived from a US population reference group. QALYs were calculated for each patient as	considered for different populations based on variations in age, gender, Society of Thoracic Surgery (STS) risk score, and previous coronary artery bypass graft (CABG) surgery status. In all cases, the results were found to be consistent with the base case analysis with TAVI found to remain dominant. In the comparison between XT-TAVI and SAVR, subgroup analyses were also considered based on access route (transfemoral or transthoracic). The results were found to be very different for each access route. With a transfemoral access route, XT-TAVI was found to be dominant but with a transthoracic access route XT-TAVI was found to be dominated (i.e. less effective and more costly). **Sensitivity analysis** In deterministic sensitivity analysis, the cost-effectiveness of both XT-TAVI and S3-TAVI was found to be insensitive to changes in most parameters. Notable exceptions were changes to annual follow-up cost after TAVI and changes to long-term mortality.	often available at lower prices through privately negotiated contracts. 1. • Uncertainty around the long-term durability of TAVI valves with the potential for higher lifetime costs if frequent repeat valve procedures are required.

Study details	Study population and design	Data sources	Results	Quality assessment
		the time-weighted average of the patient's utility values, with the midpoint between assessments used as the transition between health states. It was assumed that utilities at 6 months were the same as those at 12 months to avoid overestimating the recovery time for SAVR. Beyond the two year trial period, utilities were estimated by use of linear regression models based on available data at 24 months.	In probabilistic sensitivity analysis, at a threshold of $50,000 per QALY, XT-TAVI and S3-TAVI were both found to have a 100% probability of being cost-effective in comparison to SAVR.	
Author and year: Goodall 2019 **Country:** France **Type of economic analysis:** Cost-utility analysis **Perspective:** French collective (all payer) perspective **Currency:** Euros (€) **Price year:** 2016 **Time horizon:** 15 years (lifetime horizon) **Discounting:**	**Population** Patients with severe, symptomatic aortic stenosis at intermediate surgical risk **Interventions** TAVI with SAPIEN 3 device **Comparator** SAVR **Study design** Cost-utility analysis using Markov model	**Source of baseline and effectiveness data:** Survival, clinical event rates (complications and re-interventions) and quality of life values were sourced from the PARTNER II study. Mortality data from the trial was used for the first two years. Beyond the two year trial period, mortality was extrapolated using a linear function which was adjudged to provide the best fit against general population estimates for a matched population. Mortality for patients treated with TAVI was derived from a propensity-adjusted comparison of the outcomes applied as a relative risk to SAVR mortality, Beyond one year, TAVI mortality was projected relative to SAVR outcomes using the same linear projection. Complication and re-intervention rates in the model were based on PARTNER II data	**Costs** TAVI: €34,157 SAVR: €34,596 Incremental: -€439 **QALYs** TAVI: 4.06 SAVR: 3.65 Incremental: 0.41 **ICER (cost per QALY)** TAVI found to be dominant **Sensitivity analysis** One-way sensitivity analysis showed the analysis to be insensitive to changes in most parameters that were varied. The input values with the most notable effect on the outcomes were the TAVI and SAVR admission costs. Some of the changes to these values led to TAVI being more costly overall.	**Applicability** The analysis was deemed to be only partially applicable to the UK NHS because it considered the healthcare system in France. **Limitations** Some potentially serious limitations were identified with the analysis. In particular: • Use of assumptions to extrapolate beyond the PARTNER II trial period. In some cases, the assumptions did not reflect the most conservative approach as it was assumed that there would be differences between TAVI and SAVR beyond the trial period. • Cost of TAVI procedure is likely to vary as it is

Study details	Study population and design	Data sources	Results	Quality assessment
Costs and benefits discounted at 4% per year **Potential conflict of interest:** This analysis was funded by Edwards Lifesciences Lead author and another author were reported to be employees of Edwards Lifesciences. Two authors were reported to be employees of IQVIA, who received consulting fees for the development of the cost-effectiveness model. Another author was reported to be a full time employee of Statesia, who received consulting fees for the development of the analysis from the cost-effectiveness model. Another author has received consulting fees as a member of the		for the trial period. Beyond the trial period, values were extrapolated by retaining the last observed values for the duration of the time horizon. **Source of resource use and cost data:** The index admission costs for TAVI and SAVR procedures were sourced from 'Programme de Medicalisation des Systemes d'Information' (PMSI) data. A weighted average of costs by severity level was applied. The cost of the TAVI device is not included in the tariff prices and was therefore added separately based on the 2016 price (price not reported). Differential costs of cardiac rehabilitation for both interventions were included based on PMSI data. The cost of managing adverse events were also included and primarily based on data from PMSI. One exception was the cost of managing stroke which was based upon a publication by Chevreul et al. 2013, which was selected because of the exhaustiveness of the costs identified. The cost of re-hospitalisation were derived from observational data in the French TAVI and SAVR populations. **Source of quality of life data:** Quality of life values applied in the model were derived from the EQ-5D values reported in the PARTNER II study according to time and intervention. Values	In probabilistic sensitivity analysis, TAVI was found to have a 100% probability of being cost-effective at a threshold of €15,000 per QALY.	influenced by the cost of the TAVI valve, which varies by manufacturer and is often available at lower prices through privately negotiated contracts. • Uncertainty around the long-term durability of TAVI valves with the potential for higher lifetime costs if frequent repeat valve procedures are required.

Study details	Study population and design	Data sources	Results	Quality assessment
scientific committee on the cost-effectiveness model and as a participant to the manuscript. Editorial assistance in the development of the manuscript was funded by Edwards Lifesciences.		reported in the PARTNER II trial were converted to French quality of life estimates using published EQ-5D valuations for France. Beyond two years, the final value in each arm was assumed to apply.		
Author and year: HIQA 2019 **Country:** Ireland **Type of economic analysis:** Cost-utility analysis **Perspective:** Publicly funded health and social care system in Ireland **Currency:** Euros (€) **Price year:** 2019 **Time horizon:** 15 years **Discounting:**	**Population** Patients with severe symptomatic aortic stenosis at low or intermediate risk of complications **Interventions** TAVI **Comparator** SAVR **Study design** Cost-utility analysis using Markov model	**Source of baseline and effectiveness data:** The PARTNER 2 trial was selected as the primary source of evidence because it used a TAVI valve (SAPIEN XT) which is still marketed and used in clinical practice in Ireland. The PARTNER 2 trial was used as the source of postoperative clinical events at 30 days as well as major complications and mortality at 30 days, one year and two years. The effectiveness of TAVI was parameterised in the model using relative risks which were applied to the events rates in the SAVR arm. This treatment effect was only applied to events for which there was an observable difference between TAVI and SAVR (acute kidney injury, atrial fibrillation, major bleeding, paravalvular regurgitation, and vascular complications at 30 days, and rehospitalisation at two years). Note there was also an observable difference in the rate of aortic re-intervention at 30 but this	**Costs** TAVI: €42,681 SAVR: €42,879 Incremental: -€198 **QALYs** TAVI: 5.00 SAVR: 4.94 Incremental: 0.06 **ICER (cost per QALY)** TAVI found to be dominant **Sensitivity analysis** A range of deterministic sensitivity analysis were conducted. The results were found to be most sensitive to changes in the cost of the TAVI and SAVR procedures. Indeed, TAVI was no longer found to be cost-effective when the lower estimate was assumed for the cost of the	**Applicability** The analysis was deemed to be only partially applicable to the UK NHS because it considered the healthcare system in Ireland. **Limitations** The analysis was considered to be of very high quality with only minor limitations identified. • Disutilities applied to postoperative complications may have led to double counting as these are likely to have already been were captured in the quality of life estimates from trial data. However, authors recognised this possibility and ran a scenario analysis without postoperative disutilites and found that the

Study details	Study population and design	Data sources	Results	Quality assessment
Costs and benefits were discounted at 4% per year **Potential conflict of interest:** None		was modelled as a probability in the TAVI arm (rather than a RR) because there were no events observed in the SAVR arm. The probability of all other events was assumed to be equivalent in TAVI and SAVR arms due to the lack of evidence of a difference in treatment outcomes. Beyond the two year period covered in the trial, it was assumed that the rate of clinical events would be equivalent in TAVI and SAVR arms. **Source of resource use and cost data:** Estimated costs relating to each procedure as well as health state costs were primarily derived from relevant Diagnostic Related Group (DRG) codes in Ireland. DRG codes associated with TAVI and SAVR between 2015 and 2018 were collated using the HIPE Reporting Database and a weighted cost was estimated for each procedure. The costs capture the cost of the procedure and follow-up outpatient costs as well as the cost of adverse events or complications. Therefore, separate costs for postoperative costs were not considered in the model as they would already be captured in the weighted cost of each procedure. The estimated cost of TAVI was €27,777 while the estimated cost of SAVR was €29,342.	SAVR procedure or the higher estimate was assumed for the TAVI procedure. The analysis was found to be somewhat sensitive to changes in other parameters, such as quality of life at one year following TAVI or SAVR, but not to the extent that the conclusion of the analysis changed. Numerous scenario analyses were conducted. Most notably, a scenario analysis was conducted based on the PARTNER S3i registry to reflect second-generation devices (such as SAPIEN 3). There were fewer postoperative and major complications with the newer TAVI device and therefore there were lower costs and greater QALY gains relative to SAVR than the first-generation device. A meta-analysis of the first- and second-generation devices was also undertaken to investigate the impact of using a mix of evidence from PARTNER 2 and PARTNER S3i. TAVI was still found to be less costly and more effective than SAVR. In probabilistic sensitivity analysis, at a threshold of €20,000 per QALY, the	conclusion remained unchanged. • Evidence based on a first-generation device and may not reflect the likely improved clinical outcomes with newer devices. However, authors attempted to capture this in a scenario analysis in which observational evidence from the PARTNER S3i registry was used. • Cost of TAVI procedure is likely to vary as it is influenced by the cost of the TAVI valve, which varies by manufacturer and is often available at lower prices through privately negotiated contracts.

Study details	Study population and design	Data sources	Results	Quality assessment
		Health state costs associated with each major complication and rehospitalisation were derived from related DRGs. A monthly follow-up cost for patients that experienced a disabling stroke was based on a value from a previous HIQA HTA on mechanical thrombectomy. The analysis also considered the cost of buying and developing a new catheterisation laboratory to meet the increased demand for TAVI procedures. Based on publically cited costs, it was estimated that it would cost €4.9 million to purchase and develop developing a new catheterisation laboratory. Based on an expected throughput of 17.5 TAVI patients per week, an annual depreciation rate of 10% and running costs of €2,700 per week, it was estimated that the capital cost per TAVI patient was €1,193. **Source of quality of life data:** Quality of life estimates for the 'alive/well' health state after TAVI and SAVR were sourced from Baron et al. (2017) who reported EQ-5D data for patients from PARTNER 2 at baseline, 30 days, six months and one year. Quality of life estimates were only reported up to one year. Therefore, beyond this point, the last observed quality of life estimates (i.e. at one year) was used for TAVI and SAVR. To reflect the impact of advancing age on quality of life, a utility decrement was applied annually using	probability that TAVI was cost-effective was 61.8%.	

Study details	Study population and design	Data sources	Results	Quality assessment
		information from Ara and Brazier (2011). Utility decrements were applied to patients that experienced postoperative complications. However, recognising the possibility of double-counting, this aspect was removed in a scenario analysis. Quality of life values for health states following acute kidney injury, myocardial infarction, stroke and rehospitalisation were also applied using values from relevant published studies.		
Author and year: Kodera 2018 **Country:** Japan **Type of economic analysis:** Cost-utility analysis **Perspective:** Japanese public healthcare payer **Currency:** Japanese yen (¥) **Price year:** Not reported **Time horizon:**	**Population** Two populations were considered in the analysis: • Operable patients with severe symptomatic aortic stenosis at intermediate surgical risk. • Inoperable patients with severe symptomatic aortic stenosis Note that only the details of the analysis for the intermediate group are presented here because it is the population of interest for this review.	**Source of baseline and effectiveness data:** The mortality for all treatments was based on that data from the PARTNER trial cohorts and the Optimized Catheter Valvular Intervention (OCEAN) TAVI registry, which is a Japanese TAVI registry. Authors report that survival with TAVI was 10% superior to SAVR. Based on data from the OCEAN TAVI registry, TAVI was estimated to have a procedural 30-day mortality rate of 2.1% compared to 4.1% in patients that received SAVR. Hospitalisation rates with TAVI and SAVR were based on the PARTNER trial, which showed a higher hospitalization rate with TAVI compared to SAVR (9.0% with TAVI and 8.4% with SAVR).	**Costs** TAVI: ¥8,039,694 SAVR: ¥6,316,178 Incremental: ¥1,723,516 **QALYs** TAVI: 4.81 SAVR: 4.59 Incremental: 0.22 **ICER (cost per QALY)** ¥ 7,523,821 per QALY **Sensitivity analysis** A series of one-way sensitivity analyses were conducted. The model was found to be most sensitive to variation in the long-term mortality rate of TAVI and the TAVI cost.	**Applicability** The analysis was deemed to be only partially applicable to the UK NHS because it considered the healthcare system in Japan. **Limitations** Some potentially serious limitations were identified. Most notably: • Lack of sufficient detail provided on how many key inputs were derived • Key clinical data was based on trial data and registry data. The methods of combining data from the sources was not always clear

Study details	Study population and design	Data sources	Results	Quality assessment
10 years **Discounting:** Costs and benefits were discounted at 2% per year **Potential conflict of interest:** None	**Interventions** TAVI (using transfemoral approach) **Comparator** SAVR **Study design** Cost-utility analysis using Markov model	**Source of resource use and cost data:** The analysis included costs associated with the procedure, complications, hospitalisation and drug costs. The cost of the TAVI valve was based upon the list price of the Edwards Sapien valve and the Sapien XT valve in Japan (¥4,530,000). Based on data from the OCEAN TAVI registry, it was estimated that TAVI costs ¥6,000,000. The authors estimated the TAVI procedural cost as ¥5,000,000 and the hospital cost as ¥1,000,000. Based on various reports, SAVR was estimated to cost ¥4,500,000. The cost of follow-up and complications were estimated from a published economic evaluation of aspirin in the primary prevention of cardiovascular disease in Japan. **Source of quality of life data:** Quality of life estimates were sourced from EQ-5D data from the PARTNER trial. A quality of life value was applied for the patient health state prior to the TAVI and SAVR procedure and another was applied for the health state following the procedure. Quality of life in each of these estimates was assumed to be equivalent with TAVI and SAVR procedures. Quality of life in hospitalised patients was	Variations in time horizon were also considered and it was found that a longer time horizons resulted in a better ICER for TAVI. In a scenario analysis, the mortality rate for transapical TAVI was considered in addition to transfemoral TAVI, resulting in a higher overall mortality rate. In this scenario the ICER was found to increase to ¥56,528,188 per QALY. A threshold analysis was conducted on the TAVI mortality rate and TAVI cost. It was found that TAVI became cost-effective at a threshold of ¥5,000,000 per QALY if the TAVI mortality rate was less than 6.3% per year or if the TAVI cost was less than ¥5,427,439 Probabilistic sensitivity analysis was also conducted. It was found that, at a threshold of ¥5,000,000 per QALY, TAVI had a 46% probability of being cost-effective.	• Used quality of life estimates from a study in patients at high risk rather than intermediate risk • Cost of TAVI procedure is likely to vary as it is influenced by the cost of the TAVI valve, which varies by manufacturer and is often available at lower prices through privately negotiated contracts. • Uncertainty around the long-term durability of TAVI valves with the potential for higher lifetime costs if frequent repeat valve procedures are required.

Study details	Study population and design	Data sources	Results	Quality assessment
		assumed to be 0.48.		
Author and year: NIPH 2019, **Country:** Norway **Type of economic analysis:** Cost-utility analysis **Perspective:** Norwegian healthcare perspective **Currency:** Norwegian kroner (NOK) **Price year:** 2018 **Time horizon:** 2 year in base case but expected lifetime considered in scenario analysis **Discounting:** Costs and benefits were discounted at 2% per year **Potential conflict of interest:** None	**Population** Patients with severe aortic stenosis at intermediate surgical risk **Interventions** TAVI **Comparator** SAVR **Study design** Cost-utility analysis using Markov model	**Source of baseline and effectiveness data:** All transition probabilities were based on clinical outcome data for TAVI and SAVR at 30 days, one year and two years from the PARTNER 2A trial. This includes data on mortality as well as complications and clinical events. In the sensitivity analysis in which the modelled time horizon was extended beyond the trial period, general mortality data for the Norwegian population (age-adjusted) was applied for year two onwards. A hazard ratio of 1.5 was applied to reflect increased mortality in patient with a non-functioning valve. **Source of resource use and cost data:** The average cost for TAVI and SAVR procedures were sourced from data from Oslo University Hospital. Cost estimates included the costs of surgery, medicines, materials and length of stay in the ward and intensive care unit. Rehabilitation costs after TAVI and SAVR were estimated as the average of estimates based on DRG codes (from the Norwegian Directorate of Health) and per-diem costs from Unicare Hokksund. Based on the judgement of a panel of clinical experts, it was assumed that patients need seven days of institutionalised	**Costs** TAVI: NOK 414,526 SAVR: NOK 343,607 Incremental: NOK 70,920 **QALYs** TAVI: 1.17 SAVR: 1.11 Incremental: 0.07 **ICER (cost per QALY)** NOK 1,037,083 per QALY **Sensitivity analysis** A series of sensitivity analyses were conducted. The results were found to be most sensitive to changes in procedure related cost data. Threshold analysis showed that the cost of the TAVI system would have to reduce by 30-40 % to be cost-effective at a threshold of NOK 275,000 per QALY. A scenario analysis was conducted in which the time horizon of the model was extended to a lifetime horizon. The extended time horizon improved incremental QALYs and thereby reduced the ICER to	**Applicability** The analysis was deemed to be only partially applicable to the UK NHS because it considered the healthcare system in Norway. **Limitations** Some potentially serious limitations were identified. Most notably: • Primary analysis considers a relatively short time horizon of two years, which may not capture all relevant differences between interventions. • The inclusion of a quality of life decrement for TAVI and SAVR procedures is likely to have led to double counting as this is likely to have already been captured in the data from the PARTNER trial. • Likewise, the inclusion of quality of life decrements for complications is likely to have led to double counting as this is likely to have already been captured in the data from the PARTNER trial.

Study details	Study population and design	Data sources	Results	Quality assessment
		rehabilitation after TAVI and 20 days after SAVR. Long-term medical management following was not considered in the analysis as this is standardised in Norway regardless of the type of procedure undertaken. Costs for managing complications were mostly derived from costs associated with the relevant DRG code from the Norwegian Directorate of Health. Since some complications occur immediately or very shortly after the TAVI or SAVR procedure, it was assumed that they can be treated within the same hospitalisation episode as the procedure. The cost of treating paravalvular leak was estimated based on assumptions in combination with information from PARTNER 2A. In PARTNER 2A, 22 of the 33 (66%) patents that had a paravalvular leak got a second TAVI placed within the first valve. The authors estimated that the implantation of a new valve during the same procedure raised costs by 30%. **Source of quality of life data:** Quality of life values for "functioning valve" and "valve failure" health states were based on EQ-5D data from the PARTNER trial. Quality of life decrements were applied for undergoing the procedures. A disutility of 0.005 was assumed for patients receiving	NOK 800,275. A further analysis was conducted in which a lifetime horizon was considered as well as a reduction in baseline age from 80 to 70. In this scenario, the ICER was further reduced to NOK 643,758. While the ICERs were lower in these scenarios than the base case, the conclusion remains the same. The results of the probabilistic sensitivity analysis showed that SAVR had a higher probability of being cost-effective than TAVI at all thresholds considered (NOK 0 to NOK 825,000 per QALY).	• Cost of TAVI procedure is likely to vary as it is influenced by the cost of the TAVI valve, which varies by manufacturer and is often available at lower prices through privately negotiated contracts. 2.

Study details	Study population and design	Data sources	Results	Quality assessment
		TAVI while a disutility of 0.027 was assumed for patients receiving SAVR. These values were based on a report on TAVI to the SHTG, which was developed by the Health Economics Appraisal Team at Glasgow University. Quality of life decrements for complications were based on studies in the literature that reported quality of life using EQ-5D values.		
Author and year: Tam 2018a **Country:** Canada **Type of economic analysis:** Cost-utility analysis **Perspective:** Canadian healthcare system payer **Currency:** Canadian dollars ($) **Price year:** 2016 **Time horizon:** Lifetime horizon **Discounting:** Costs and outcomes	**Population** Patients with severe symptomatic aortic stenosis at intermediate surgical risk **Interventions** TAVI **Comparator** SAVR **Study design** Cost-utility analysis using Markov model	**Source of baseline and effectiveness data:** Mortality estimates and complication rates at 30 days were obtained from the intention-to-treat cohort of the SURTAVI trial. After 30 days, transition probabilities were based on clinical endpoints at one and two years from SURTAVI. The probability of death in patients with permanent stroke was obtained from a study into long-term survival and causes of death after stroke. After the two year trial period, it was assumed that complication rates would be equivalent in both treatment arms. Mortality after two years was based on general mortality estimates from Canadian life tables. **Source of resource use and cost data:** Procedural costs for TAVI and SAVR were primarily sourced from the Ontario Schedule of Benefits, with expert from two TAVI implanters used to determine billing	**Costs** TAVI: $44,299 SAVR: $32,994 Incremental: $11,305 **QALYs** TAVI: 6.42 SAVR: 6.28 Incremental: 0.15 **ICER (cost per QALY)** $76,736 per QALY **Sensitivity analysis** A series of one-way sensitivity analyses were conducted. The analysis was found to be most sensitive to changes in the cost of the TAVI valve, 30-day mortality rates, proportion of patients with strokes and length of stay in the ICU and ward. The ICER was found to surpass $50,000 per QALY when the cost	**Applicability** The analysis was deemed to be only partially applicable to the UK NHS because it considered the Canadian healthcare system. **Limitations** Some potentially serious limitations were identified. Most notably: • Quality of life data based on values from a high-risk population which may have led to overestimating the QoL difference between the two arms • The inclusion of quality of life decrements for complications is likely to have led to double counting as this is likely to have already been captured in the data from the CoreValve trial.

Study details	Study population and design	Data sources	Results	Quality assessment
were discounted at 1.5% per year **Potential conflict of interest:** One of the authors declared a financial relationship with Edwards LifeSciences and Medtronic, Inc		codes. Ward and ICU costs were obtained from a Hospital in Toronto, Canada and combined with length of stay data from the SURTAVI trial. The cost for the TAVI valve system was obtained from the device manufacturer (Medtronics Inc). Periprocedural complication costs were obtained from the Canadian Institute for Health Information Patient Cost Estimator Case Mix Group for persons older than 80 years in Ontario. Costs for the long-term state of permanent and disabling stroke was estimated from a study of trends in mortality, length of stay and cost in patients with ischemic stroke in Alberta, Canada. **Source of quality of life data:** Quality of life estimates for the 'alive/well' health states were based on EQ-5D data from the CoreValve US High Risk Pivotal Trial, using data for baseline, one month, 6 months and 12 months. Quality of life decrements for major bleeding, vascular complications, acute kidney injury, atrial fibrillation, and non-disabling stroke were obtained from a prospective observational cohort study of TAVI and SAVR patients. Quality of life decrements for pacemaker and cardiogenic shock were estimated from a prospective QoL study after TAVI, using	of TAVI was greater than $17,397. In probabilistic sensitivity analysis, at a threshold of $50,000 per QALY, TAVI was found to have 52.9% probability of being cost-effective.	• Initial procedural costs for SAVR and TAVI were derived using expert opinion • Cost of TAVI procedure is likely to vary as it is influenced by the cost of the TAVI valve, which varies by manufacturer and is often available at lower prices through privately negotiated contracts. • Uncertainty around the long-term durability of TAVI valves with the potential for higher lifetime costs if frequent repeat valve procedures are required.

Study details	Study population and design	Data sources	Results	Quality assessment
		data from the German Aortic Valve Registry. Quality of life decrements for re-hospitalisation were obtained from a French cost-effectiveness model of patients with atrial fibrillation. Quality of estimates for people with disabling stroke were obtained from a meta-analysis of quality of life estimates for stroke. Quality of life estimates for people with short-term episodes of hospitalisation were obtained from a study of outcomes in patients hospitalised for heart failure.		
Author and year: Tam 2018b **Country:** Canada **Type of economic analysis:** Cost-utility analysis **Perspective:** Canadian third-party payer **Currency:** Canadian dollars ($) **Price year:** 2016 **Time horizon:** Lifetime horizon	**Population** Patients with severe aortic stenosis at intermediate surgical risk. **Interventions** TAVI **Comparator** SAVR **Study design** Cost-utility analysis using Markov model	**Source of baseline and effectiveness data:** Data on clinical end points at 30 days, one year and two years were obtained from the intention-to-treat cohort from the PARTNER 2 Trial. This included data on mortality, stroke, re-hospitalisation, major vascular complication, life-threatening or disabling bleeding, acute kidney injury, and new-onset atrial fibrillation. After the two year trial period, it was assumed that complication rates would be equivalent in both treatment arms. Mortality after two years was based on general mortality estimates from Canadian life tables. The proportion of patients with acute kidney injury progressing to dialysis was estimated from the PARTNER 1A trial (as data was not provided in PARTNER 2). The same proportion was assumed in both	**Costs** TAVI: $46,904 SAVR: $36,356 Incremental: $10,547 **QALYs** TAVI: 5.63 SAVR: 5.40 Incremental: 0.23 **ICER (cost per QALY)** $46,083 per QALY **Sensitivity analysis** A series of one way sensitivity analyses were performed to examine the impact of key parameters. The analysis was found to be most sensitive to changes in the cost of the TAVI valve ICU length of stay, 30-day mortality	**Applicability** The analysis was deemed to be only partially applicable to the UK NHS because it considered the Canadian healthcare system. **Limitations** • Quality of life data based on values from a high-risk population which may have led to overestimating the QoL difference between the two arms • The inclusion of quality of life decrements for complications is likely to have led to double counting as this is likely to have already been captured in the data from the PARTNER trial.

Study details	Study population and design	Data sources	Results	Quality assessment
Discounting: Costs and outcomes were discounted at 1.5% per year **Potential conflict of interest:** One of the authors received research funding from Edwards Lifesciences and Medtronic Inc. Another author serves as a proctor for Medtronic Inc		treatment arms. The probability of death during long-term dialysis was estimated from a published study of mortality among patients receiving dialysis. The probability of death in patients with long-term strokes was obtained from a study of long-term survival and causes of death after stroke. **Source of resource use and cost data:** Procedural costs for TAVI and SAVR were primarily sourced from the Ontario Schedule of Benefits, with input from two TAVI implanters used to determine billing codes. Ward and ICU costs were obtained from a Hospital in Toronto, Canada and combined with length of stay data from the PARTNER 2 trial. Costs for both the TAVI valve system ($24,000) and the surgical valve ($6,000) were obtained from the device manufacturer, Edwards Lifesciences. Periprocedural complication costs were obtained from the Canadian Institute for Health Information Patient Cost Estimator Case Mix Group for persons older than 80 years in Ontario. Costs for the long-term state of permanent and disabling stroke was estimated from a study of trends in mortality, length of stay and cost in patients with ischemic stroke in Alberta, Canada. **Source of quality of life data:**	rate and the proportion of patients with strokes. The ICER was found to exceed $50,000 per QALY when the cost of the TAVI valve system was greater than $25,100. In probabilistic sensitivity analysis, at a threshold of $50,000 per QALY, TAVI was found to have 52.7% probability of being cost-effective. A further scenario was considered in which the analysis was restricted to TAVI with a transfemoral access route. In this scenario, the ICER was found to decrease to $24,790 per QALY.	• Proportion of patients with acute kidney injury that progress to dialysis was based on evidence from high risk patients • Initial procedural costs for SAVR and TAVI were derived using expert opinion • Cost of TAVI procedure is likely to vary as it is influenced by the cost of the TAVI valve, which varies by manufacturer and is often available at lower prices through privately negotiated contracts. • Uncertainty around the long-term durability of TAVI valves with the potential for higher lifetime costs if frequent repeat valve procedures are required.

Study details	Study population and design	Data sources	Results	Quality assessment
		Quality of life values for the 'alive/well' health state was based on EQ-5D data at baseline, six months and 12 months from the PARTNER 1A trial (authors state that PARTNER 2 trial wasn't used because of absence of specific quality of life data). Quality of life decrements for major bleeding, vascular complications, acute kidney injury, atrial fibrillation, and non-disabling stroke were obtained from a prospective observational cohort study of TAVI and SAVR patients. Quality of life decrements for pacemaker and cardiogenic shock were estimated from a prospective QoL study after TAVI, using data from the German Aortic Valve Registry. Quality of life decrements for re-hospitalisation were obtained from a French cost-effectiveness model of patients with atrial fibrillation. Quality of estimates for people with disabling stroke were obtained from a meta-analysis of quality of life estimates for stroke. Quality of life estimates for hospitalisation were obtained from a study of outcomes in patients hospitalised for heart failure. Quality of estimates for people undergoing dialysis were estimated from a study of quality of life in patients with renal failure.		
Author and year: Tarride 2019 **Country:**	**Population** Two populations were considered in the analysis:	**Source of baseline and effectiveness data:** Key clinical inputs (mortality and complication rates) for patients treated	**Costs** TAVI: $70,556 SAVR: $57,083 Incremental: $13,473	**Applicability** The analysis was deemed to be only partially applicable to the UK NHS because it considered

Study details	Study population and design	Data sources	Results	Quality assessment
Canada **Type of economic analysis:** Cost-utility analysis **Perspective:** Canadian third-party payer perspective **Currency:** Canadian dollars ($) **Price year:** 2018 **Time horizon:** 15 years **Discounting:** Costs and benefits were discounted at 1.5% per year **Potential conflict of interest:** Study was funded by an unrestricted grant from Edwards Lifesciences. Lead author reports grants from Edwards Lifesciences, during the conduct of the study and personal fees from Edwards	1. patients with severe aortic stenosis at intermediate surgical risk 2. patients with severe aortic stenosis at high surgical risk. Note that only the details of the analysis for the intermediate group are presented here because it is the population of interest for this review. **Interventions** TAVI **Comparator** SAVR **Study design** Cost-utility analysis using Markov model	with TAVI and SAVR were based on 30-day and one-year outcomes from the PARTNER II study. It was reported that further data on all clinical outcomes was available up to two years for the SAVR arm. Beyond the trial period, mortality rates were extrapolated. A linear function was selected based on goodness of fit tests and clinical plausibility comparing predictions to general population mortality data. Trial data and extrapolations based on the last observed data were used for other clinical events. **Source of resource use and cost data:** The cost of TAVI using the SAPIEN 3 device was estimated based on the manufacturer list price ($25,000). The cost of the SAVR device ($6,000) was derived from a recent Canadian cost-effectiveness study. Post-procedure inpatient costs were calculated using unpublished data from the Canadian Institute of Health Information (CIHI) for individuals undergoing TAVI or SAVR. Physician fees for SAVR and TAVI were based on expert opinion and the Ontario Schedule of Benefits for Physician Services. Costs for complications and events were derived from the published literature, the CIHI patient cost calculator and Alberta Health costing.	**QALYs** TAVI: 5.10 SAVR: 4.62 Incremental: 0.48 **ICER (cost per QALY)** $28,154 per QALY **Sensitivity analysis** A series of one-way sensitivity analyses were conducted. Most of the modelled variations in inputs were found to have a minimal impact on the cost-effectiveness result. A notable exception was the scenario in which the time horizon was reduced to five years. In this scenario the ICER was found to exceed $50,000 per QALY. In probabilistic sensitivity analysis, the probability of TAVI being cost-effective was 91% at a threshold of $50,000 and per QALY.	the Canadian healthcare system. **Limitations** Some potentially serious limitations were identified. Most notably: • Mortality and clinical events were based on evidence from a non-randomised study • Use of assumptions to extrapolate beyond the PARTNER trial period did not reflect the most conservative approach as it was assumed that there would be differences between TAVI and SAVR beyond the trial period. • Beyond the one year trial period, it was assumed that quality of life is improved in patients with TAVI. A more conservative approach would have been to assume equivalence beyond the trial period. • Initial procedural costs for SAVR and TAVI were derived using expert opinion • Cost of TAVI procedure is likely to vary as it is influenced by the cost of the TAVI valve, which varies by manufacturer and is

Study details	Study population and design	Data sources	Results	Quality assessment
Lifesciences, outside the submitted Work. Two of the authors were reported to be employees of Edwards Lifesciences. Another author reported grants from Edwards Lifesciences Inc, during the conduct of the study.		Medication costs were also incorporated in the analysis. It was assumed that SAVR patients with non-mechanical heart valves and all TAVI patients would be given clopidogrel 75mg for the first six months after the procedure. SAVR patients with mechanical valves were assumed to receive warfarin 5.8mg per day for the rest of their lives. **Source of quality of life data:** Quality of life values for each health state were based on EQ-5D data at one year from the PARTNER trial, valued using a Canadian EQ-5D algorithm. Beyond one year, quality of life values of 0.79 and 0.78, were applied for patients treated with TAVI and SAVR, respectively. For patients with stroke, a weight of 0.6826 was applied to the procedure and time-specific utility values. No additional quality of life decrements were applied for other clinical events and complications as it was assumed that the impact of these would already be captured in the quality of life data from the trial. However, the impact of using quality of life decrements for complications was explored in sensitivity analysis.		often available at lower prices through privately negotiated contracts. • Uncertainty around the long-term durability of TAVI valves with the potential for higher lifetime costs if frequent repeat valve procedures are required.
Author and year: Zhou 2019 **Country:**	**Population** Patients with severe symptomatic aortic stenosis at	**Source of baseline and effectiveness data:** The majority of the transition probabilities in the model (including those for	**Costs** TAVI: $50,515 SAVR: $60,144 Incremental: -$9,629	**Applicability** The analysis was deemed to be only partially applicable to the UK NHS because it considered

Study details	Study population and design	Data sources	Results	Quality assessment
Australia **Type of economic analysis:** Cost-utility analysis **Perspective:** Australian healthcare system perspective **Currency:** Australian dollars ($) **Price year:** 2018 **Time horizon:** 10 years **Discounting:** Costs and benefits were discounted at 5% per year **Potential conflict of interest:** One of the authors serves as a proctor and advisory board member for Medtronic and as a proctor for Abbott. Another authors serves as a proctor for Medtronic	intermediate surgical risk **Interventions** TAVI (using SAPIEN 3) **Comparator** SAVR **Study design** Cost-utility analysis using Markov model	mortality, stroke and complications) were estimated from event rates at 30 days and one year from the PARTNER S3i study. Beyond the one year period covered in the PARTNER S3i study, general mortality estimates from Australian Life Tables were used to estimate mortality in the SAVR arm. A hazard ratio (HR) comparing TAVI and SAVR mortality was applied to estimate mortality in the TAVI arm. HR was set to 1 in the base but was varied in sensitivity analysis using the 95% CIs reported in the PARTNER 2A trial. It was assumed that there were no short-term complications in either treatment arm beyond one year. Long-term risk of stroke was estimated from a systematic review of stroke incidence in the elderly and assumed to be equal in both treatment arms. Relative risks from studies in the literature were used to reflect higher rates of stroke and mortality in patients with a history of previous stroke. **Source of resource use and cost data:** TAVI prosthesis cost ($23,932) was estimated from the Australian Medicare Benefits Schedule (MBS). The cost of the SAVR valve ($6,858) was estimated from the Australian National Hospital Costs Data Collection (NHCDC) database.	**QALYs** TAVI: 4.13 SAVR: 3.82 Incremental: 0.31 **ICER (cost per QALY)** TAVI found to be dominant **Sensitivity analysis** A series of one-way sensitivity analyses were conducted. The analysis was found to be most sensitive to changes in length of stay following TAVI and SAVR, the cost per day of hospitalisation, the cost of the valve prostheses, and the hazard ratio of mortality between groups. However, notably, TAVI remained cost-effective (ICER less than $50,000 per QALY gained) when each of these parameters were varied. Threshold analysis was also conducted and it was found that substantial variations were required to change the conclusion of the analysis. In order for TAVI to be cost-effective at a threshold of $50,000 per QALY, TAVI length of stay had to exceed SAVR length of stay or the TAVI valve cost had to exceed $47,962.	the Australian healthcare system. **Limitations** Some potentially serious limitations were identified in the analysis: • Key clinical input data was based on evidence from a non-randomised study (PARTNER S3i) • The inclusion of quality of life decrements for complications is likely to have led to double counting as this is likely to have already been captured in the data from the PARTNER trial. • Cost of TAVI procedure is likely to vary as it is influenced by the cost of the TAVI valve, which varies by manufacturer and is often available at lower prices through privately negotiated contracts. • Uncertainty around the long-term durability of TAVI valves with the potential for higher lifetime costs if frequent repeat valve procedures are required.

		Costs of the TAVI and SAVR procedures were estimated from MBS item numbers, assuming that the amount reimbursed by Australian Medicare reflects the cost to the healthcare system. Hospitalisation cost was estimated by obtaining the average daily cost for cardiac valve procedures reported in the NHCDC and multiplying by the length of stay reported in the PARTNER S3i trial for TAVI and SAVR. Complication costs were estimated from relevant codes in the NHCDC database. Monthly costs for the long-term state of stroke were estimated from an Australian study of long-term stroke costs. **Source of quality of life data:** Quality of life values for being 'alive and well' following TAVI and SAVR were estimated from EQ-5D data at baseline, one month and 12 months from the PARTNER S3i trial. Quality of life values were assumed to be equal in both study arms after 18 months. Transient quality of life decrements were applied for complications based on values sourced from various studies in the literature. The lower quality of life in patients with stroke was estimated from an Australian study reporting quality of life among stroke survivors.	In probabilistic sensitivity analysis, at a threshold of $50,000 per QALY, TAVI was found to have a 92% probability of being cost-effective.	

Study details	Study population and design	Data sources	Results	Quality assessment
Abbreviations QALY: quality-adjusted life year; ICER: incremental cost-effectiveness ratio; EQ-5D: EuroQol five-dimensions questionnaire; TAVI: transcatheter aortic valve implantation; SAVR: surgical aortic valve replacement				

Appendix 4: Cost-effectiveness analysis

1. Background and objective

An economic analysis was developed to estimate the cost-effectiveness of TAVI in comparison to SAVR for people with severe symptomatic aortic stenosis at intermediate surgical risk. The economic analysis was based largely on the economic analysis conducted as part of SHTG's appraisal of TAVI for the treatment of patients with severe symptomatic aortic stenosis at intermediate surgical risk.

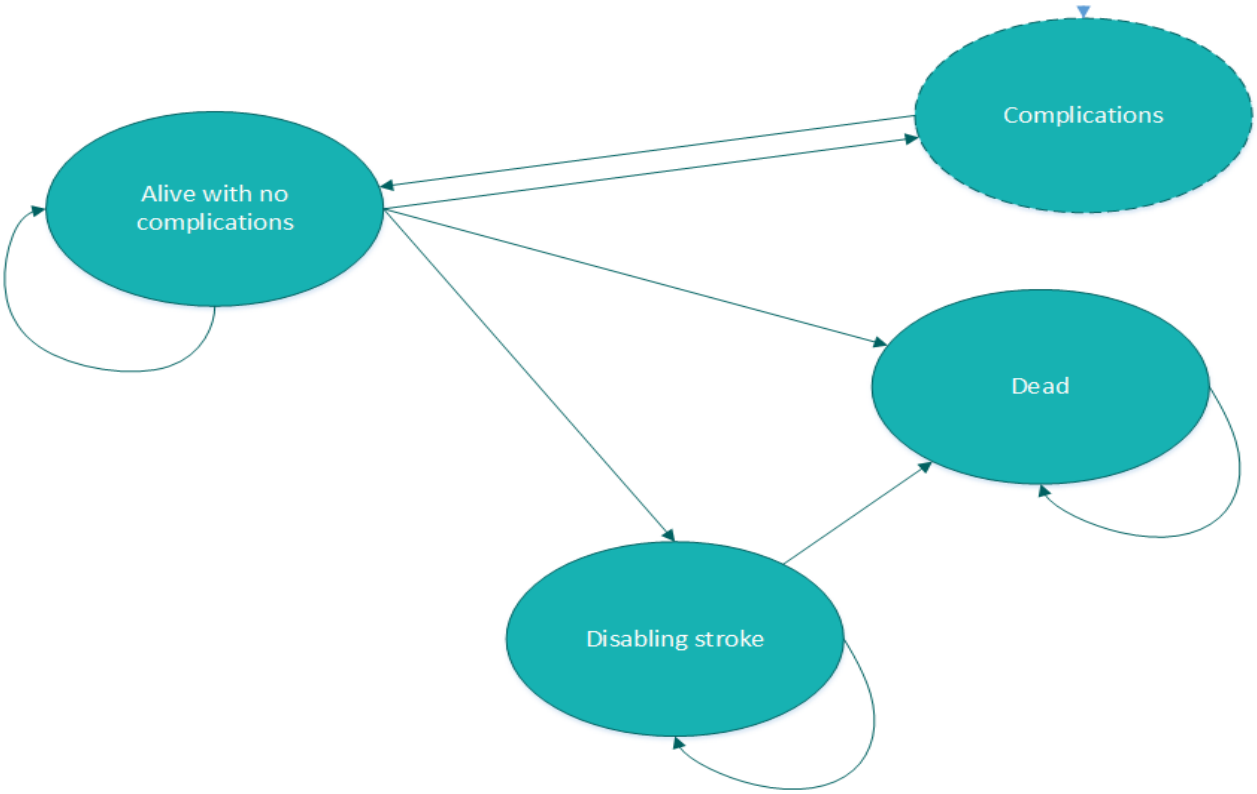
2. Methods

2.1 Model structure

A Markov disease progression model was developed using Microsoft Excel to compare the cost-effectiveness of TAVI in comparison to SAVR for the treatment of patients with severe symptomatic aortic stenosis at intermediate surgical risk. The analysis took the perspective of the UK NHS and personal social services (PSS). A lifetime horizon was considered to fully capture the period over which outcomes are likely to differ between the strategies. The model used one month cycles to capture the level of detail required (based on time points in the key clinical data). Future costs and benefits were discounted at a rate of 3.5% per year as recommended in the NICE reference case.

The model structure is depicted in Figure 1, which shows that health states and how patients can transition between them at each model cycle. There are three main health states; 'alive with no complications', 'disabling stroke' and 'dead'. There is also a complication health state to which patients may transition for one cycle before returning to the alive with no complications health state (i.e. the impact of complications is captured as a 'one-off' event). The 'dead' health state was modelled as an absorbing state, meaning that patients cannot transition from this state to any other health state.

Figure 1: Markov model diagram



2.2 Clinical data

Following the approach adopted in the economic analysis developed by the SHTG, the key clinical data applied in the model were sourced from the full intention to treat (ITT) population in PARTNER 2, which compared TAVI using the Sapien XT valve with SAVR in intermediate risk patients. The trial reported complication and mortality outcomes for patients treated with TAVI and SAVR at various time points over the two year trial period. The complication and mortality rates applied in the analysis are presented in Table 1.

It should be noted that many of the differences in complications rates were not statistically significant. The impact of only considering statistically significant differences in complications was considered in sensitivity analysis.

Table 1: Complication and mortality rates

Outcomes	SAVR			TAVI		
	30 days	1 year	2 years	30 days	1 year	2 years
Transient ischemic attack (TIA)	0.4%	0.1%	0.0%	0.9%	0.1%	0.1%
Non-disabling stroke	1.8%	0.1%	0.0%	2.3%	0.1%	0.0%
Myocardial infarction (MI)	1.9%	0.1%	0.1%	1.2%	0.1%	0.1%
Major vascular complication	5.0%	0.0%	0.0%	7.9%	0.0%	0.0%
Life-threatening or disabling bleeding	43.4%	0.3%	0.2%	10.5%	0.5%	0.2%
Acute kidney injury (stage III)	3.1%	0.2%	0.1%	1.3%	0.2%	0.0%
New atrial fibrillation	26.4%	0.1%	0.0%	9.1%	0.1%	0.1%
New permanent pacemaker	6.8%	0.2%	0.1%	8.5%	0.1%	0.2%
Endocarditis	0.0%	0.1%	0.0%	0.0%	0.1%	0.0%

Outcomes	SAVR			TAVI		
	30 days	1 year	2 years	30 days	1 year	2 years
Aortic-valve re-intervention	0.0%	0.0%	0.0%	0.4%	0.1%	0.0%
Coronary obstruction	0.6%	0.0%	0.0%	0.4%	0.0%	0.0%
Disabling stroke	4.3%	0.1%	0.1%	3.2%	0.2%	0.1%
Death from any cause	3.6%	0.8%	0.4%	3.0%	0.7%	0.4%

Beyond the two year trial follow-up period, it was assumed that the risk of complications was zero (in both the TAVI and SAVR arms). Mortality rates after two years were assumed to be equivalent in both arms. Mortality rates were estimated using Office for National Statistics (ONS) Life Tables which give the general mortality rate for the UK population based on age and gender (ONS 2019). The baseline age and gender profile used in the model was based upon the mean age and gender from PARTNER 2 (81.6 years old and 55% male). Following the approach adopted in the SHTG analysis, the general mortality rate was adjusted by a hazard ratio of 1.15 to account for the higher risk of mortality in patients with severe aortic stenosis.

2.3 Costs

The costs considered in the model reflect the perspective of the analysis, thus only costs that are relevant to the UK NHS & PSS were included. Where possible, all costs were estimated in 2019 prices.

2.3.1 Procedure costs

The cost of the TAVI procedure was sourced from NHS reference costs 2018/19 (NHS 2020). The cost of the procedure differs depending on the approach used as well as any comorbidities and complications (captured using 'CC scores' in reference costs). For each procedure type, a weighted average cost was estimated based upon the proportion of cases within each CC score category. The cost of TAVI using a transfemoral approach was estimated to be £6,913 while the cost of TAVI using an alternative approach (such as a transthoracic approach) was estimated to be £10,318.

The reference cost for the TAVI procedure does not include the cost of the valve. TAVI valve prices are not publically available as they are commercial in confidence. In the base case analysis, the cost of the TAVI valve was sourced from a Canadian cost-effectiveness study (Tarride et al. 2019) which reported a manufacturer list price of $25,000 for the SAPIEN 3 device (equivalent to £14,996). This cost was used as it appears to be one of the few publically available prices for the valve. Alternative valve costs were applied in sensitivity analysis based on data from the Welsh Health Specialised Services Committee (WHSCC).

The cost of the SAVR procedure was sourced from NHS reference costs 2018/19 (NHS 2020). A weighted average cost of £11,649 was estimated based on the proportion of cases within each CC category in NHS reference costs. Note that the cost of the SAVR valve is included within the reference cost and it was therefore not necessary to estimate this cost separately.

Alternative cost estimates were sourced from the economic analysis developed as part of the technology appraisal by the Health Information and Quality Authority (HIQA 2019). The HIQA analysis estimated costs for the TAVI and SAVR procedures using Hospital Inpatient Enquiry (HIPE) data between 2015 and 2018 and the relevant Diagnostic Related Group (DRG) codes in Ireland. The estimated costs included the cost of the procedure, complications and follow-up outpatient costs associated with the index hospital admission. The estimated weighted cost of TAVI was €27,777 (equivalent to £24,213) and the estimated cost of SAVR was €29,342 (£25,577). The impact of using these alternative cost estimates was explored in sensitivity analysis.

2.3.2 Critical care costs

The procedure costs for TAVI and SAVR from NHS reference costs include some of the length of stay costs associated with the procedures. However, length of stay in critical care, such as the intensive care unit (ICU) would incur an additional cost.

Length of stay in ICU was based on data from PARTNER 2, which showed that patients spent a median of 2 days in ICU following TAVI and 4 days in ICU following SAVR. The cost per day in ICU was estimated from NHS Reference cost 2018/19, which reports different costs depending upon the number of organs supported. A weighted average cost of £1,417 per day in ICU was estimated using the proportion of cases within each organ category.

The length of stay in ICU reported in the PARTNER 2 trial may not be an accurate reflection of current practice. Previous economic analyses have assumed a lower number of ICU days than that reported in PARTNER 2. For example, in the analysis by SHTG, it was assumed that there was no ICU stay following TAVI and one day in ICU following SAVR. It was also assumed that there would be three days in a cardiology unit following TAVI using the transfemoral approach, four days for TAVI using an alternative approach and four days in a cardiology unit following SAVR. The impact of applying alternative estimates for the number of ICU days is explored in sensitivity analysis.

2.3.3 Complication costs

The cost of managing complications following TAVI or SAVR were estimated following the approach adopted in the SHTG analysis. The SHTG derived complication costs from a mix of NHS Reference Costs and clinical expert opinion. Where NHS Reference Costs were used, they have been updated to reflect the most recent version (NHS Reference Costs 2018/19). Complication costs which were based upon expert opinion have been inflated to 2019 prices.

Table 2: Complication costs

Health state	Cost	Source
Disabling stroke	£6,044.51	NHS Reference Costs 2018/19
Transient ischemic attack (TIA)	£2,108.32	NHS Reference Costs 2018/19
Non-disabling stroke	£3,224.30	NHS Reference Costs 2018/19
Myocardial infarction (MI)	£2,366.95	NHS Reference Costs 2018/19
Major vascular complication	£2,545.85	Expert opinion in SHTG analysis. Original value inflated to 2019 prices
Life threatening or disabling bleeding	£1,018.34	Expert opinion in SHTG analysis. Original value inflated to 2019 prices
Acute kidney injury	£2,833.75	NHS Reference Costs 2018/19
New atrial fibrillation	£509.17	Expert opinion in SHTG analysis. Original value inflated to 2019 prices
New permanent pacemaker	£3,199.60	NHS Reference Costs 2018/19
Endocarditis	£5,399.23	NHS Reference Costs 2018/19
Aortic-valve re-intervention	£3,055.02	Expert opinion in SHTG analysis. Original value inflated to 2019 prices
Coronary obstruction	£1,018.34	Expert opinion in SHTG analysis. Original value inflated to 2019 prices
Sources: NHS (2020) and SHTG (2019)		

2.3.4 Follow-up costs

The cost of annual follow-up appointments were included in both arms of the model. The cost per follow-up appointment was estimated to be £135, based upon a face-to-face follow-up attendance in Cardiology from NHS reference costs 2018/19. In addition, patients in the TAVI arm

were assumed to have an electrocardiogram and echocardiogram, estimated to cost £139 and £76, respectively based on NHS reference costs 2018/19.

2.4 Health-related quality of life

The model estimates effectiveness in terms of quality adjusted life years (QALYs). These are estimated by combining life year estimates with quality of life (QoL) values associated with being in a particular health state. The QoL values applied in the model are shown in table 3. The QoL values were based on those used in the economic model developed by SHTG, in which QoL values from the EQ-5D values reported over time in the PARTNER 2 study for TAVI and SAVR.

Table 3: QoL values

Time (months)	SAVR	TAVI
Baseline	0.732	0.732
1 month	0.726	0.778
2 months	0.732	0.779
3 months	0.737	0.778
4 months	0.743	0.779
5 months	0.749	0.779
6 months	0.755	0.780
7 months	0.761	0.780
8 months	0.767	0.781
9 months	0.773	0.781
10 months	0.779	0.782
11 months	0.784	0.781
12 months	0.790	0.782
13 months	0.788	0.781
14 months	0.785	0.778
15 months	0.783	0.777
16 months	0.780	0.775
17 months	0.778	0.774
18 months	0.775	0.772
19 months	0.773	0.771
20 months	0.770	0.769
21 months	0.768	0.768
22 months	0.765	0.766
23 months	0.763	0.765
24 months	0.760	0.763
Subsequent months	0.760	0.760

Beyond the two year trial period, it was assumed that there would be no difference in QoL between strategies. Following the approach adopted in the SHTG analysis, the final QoL value reported in PARTNER 2 for the SAVR arm was applied to all subsequent cycles in both arms of the model.

It should be noted that many of the QoL differences between SAVR and TAVI were not statistically significant. The impact of only considering statistically significant differences in QoL was considered in sensitivity analysis.

3. Results

3.1 Base case results

The base case results of the analysis are shown in Table 4. 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.

Table 4. Base case results (presented on a per-patient basis)

Treatment	Cost		QALYs		ICER (cost per QALY)
	Total	Incremental	Total	Incremental	
SAVR	£19,880	-	4.27	-	-
TAVI	£29,025	£9,145	4.36	0.10	£94,512

3.2 Deterministic sensitivity analysis results

A series of deterministic sensitivity analyses were conducted, whereby an input parameter is changed, the model is re-run and the new cost-effectiveness result is recorded. This is a useful way of estimating uncertainty and determining the key drivers of the model result. The results of the deterministic sensitivity analyses are presented in Table 5.

It can be seen that the results of the analysis are relatively insensitive to changes in the majority of input parameters. In the majority of scenarios, the conclusion of the base case analysis remains unchanged with TAVI found to be more costly and more effective than SAVR but with ICERs above a threshold of £20,000 per QALY, indicating that it is not cost-effective.

The notable exceptions were the analysis in which the cost of SAVR was estimated based upon values reported in the economic analysis by HIQA. TAVI became cost-effective in the scenario where HIQA values were used for TAVI and SAVR and in another scenario where HIQA values were only used for SAVR (with base case values for TAVI). In the scenario where both HIQA values were used, TAVI was found to be dominant (i.e. less costly and more effective). In the scenario, where HIQA values were only used for SAVR, TAVI was found to be more effective and more costly but with an ICER below £20,000 per QALY indicating that is cost-effective.

These results demonstrate the importance of the procedure costs applied in the analysis. The analysis showing the impact of an alternative estimate for the cost of SAVR is of particular importance as it suggests that TAVI has the potential to be cost-effective if the NHS reference cost for SAVR was found to underestimate the true cost.

Table 5. Deterministic sensitivity analysis results

Modelled scenario	ICER result (cost per QALY)
Base case	£94,512
Baseline age = 70	£70,497
Baseline age = 75	£78,266
Baseline age = 80	£89,996
Baseline age = 85	£105,551
General mortality after 2 years with no multiplier	£91,115
Mortality multiplier = 1.1	£93,409
Mortality multiplier = 1.2	£95,587
Only statistically significant differences in complications included	£508,239
TAVI valve cost based on WHSCC cost for Cardiff	Not cost-effective*
TAVI valve cost based on WHSCC cost for Swansea	Not cost-effective*
SAVR cost based on WHSCC estimate	Not cost-effective*

Modelled scenario	ICER result (cost per QALY)
TAVI and SAVR ICU LOS based on SHTG estimates	£109,116
No ICU LOS following TAVI	£65,306
TAVI cost based on HIQA estimate	£80,853
SAVR cost based on HIQA estimate	£9,392
TAVI and SAVR costs based on HIQA estimates	Dominant
No QoL differences after one month	£110,451
HIQA QALY estimates for TAVI and SAVR	£157,675
TAVI: transcatheter aortic valve implantation; SAVR: surgical aortic valve replacement; WHSCC: Welsh Health Specialised Services Committee; ICU: intensive care unit; LOS: length of stay; SHTG: Scottish Health Technologies Group; HIQA: Health Information and Quality Authority; QoL: quality of life; ICER: incremental cost-effectiveness ratio; QALY: quality adjusted life year; *ICER results not reported because scenario is based upon commercial in confidence data	

3.3 Threshold analysis results

A key area of uncertainty in the analysis is the cost of the TAVI valve. Therefore this aspect was further explored in a threshold analysis, in which the TAVI valve cost required for TAVI to be cost-effective was estimated. It was found that TAVI became cost-effective (ICER below £20,000) with a TAVI valve cost of £7,752.

3.4 Probabilistic sensitivity analysis results

Probabilistic sensitivity analysis (PSA) was conducted to assess the combined parameter uncertainty in the model. In this analysis, the mean values that were utilised in the base case were replaced with values drawn from distributions around the mean values. The results of 10,000 runs of the PSA are shown using ICER scatterplots and cost-effectiveness acceptability curves (CEAC). The ICER scatter plots show the incremental costs and QALYs associated with each of the 10,000 runs of the PSA along with the mean result. The CEAC graphs show the probability of each strategy being considered cost-effective at the various cost-effectiveness thresholds on the x axis.

Figure 2 shows the ICER scatterplot for TAVI in comparison to SAVR. It can be seen that all of the results reside in the top half of the graph- indicating that TAVI is always more costly than SAVR. The results appear to be roughly split in half between those that reside in the north-east quadrant (indicating that TAVI is more costly and more effective than SAVR) and those that reside in the north-west quadrant (indicating that TAVI is more costly and less effective than SAVR).

Figure 2. ICER scatterplot for TAVI in comparison to SAVR

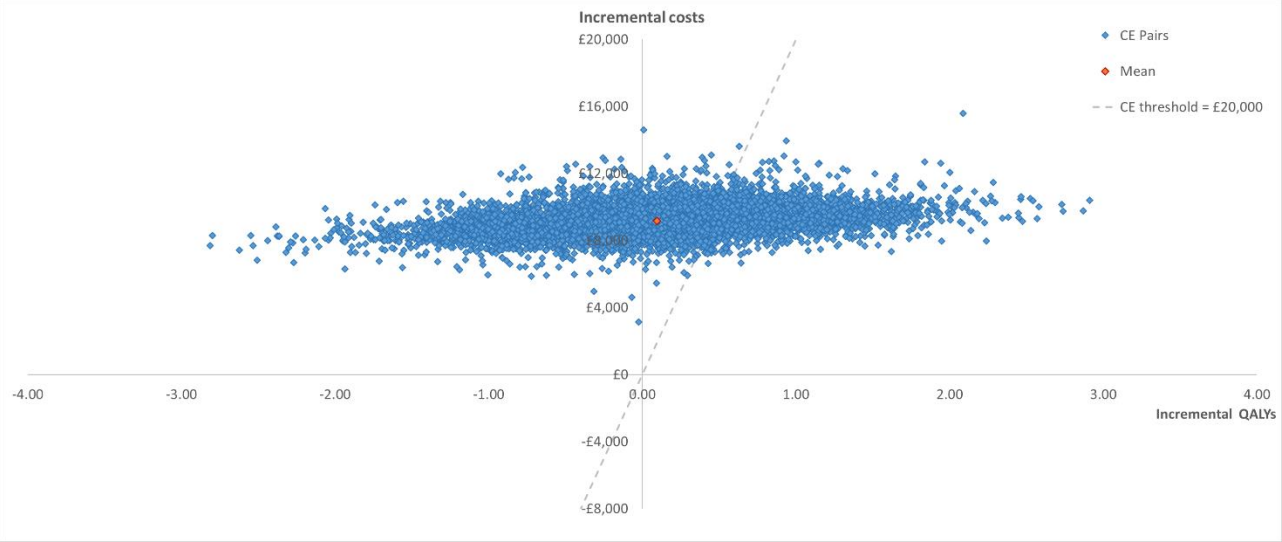


Figure 3 shows the CEACs for TAVI and SAVR. It can be seen that initially SAVR has a higher probability of being cost-effective but this decreases as the cost-effectiveness threshold increases and eventually TAVI becomes the preferred strategy. At a threshold of £20,000 per QALY, TAVI was found to have a 27% probability of being cost-effective while SAVR was found to have a 73% probability of being cost-effective.

Figure 3. CEACs for TAVI and SAVR