Healthcare Improvement Scotland | SHTG Advice on health technologies

Evidence Note
Number 91 May 2019

In response to enquiry from the National Planning Board

Transcatheter aortic valve implantation (TAVI) for the treatment of patients with severe symptomatic aortic stenosis at intermediate surgical risk.

What is an evidence note?

Evidence notes are rapid reviews of the evidence surrounding health technologies that are under consideration by decision makers within NHSScotland. They are intended to provide information quickly to support time-sensitive decisions. Information is available to the topic referrer within a 6-month period and the process of peer review and final publication of the associated advice is usually complete within 6–12 months. Evidence notes are not comprehensive systematic reviews. They are based on the best evidence that Healthcare Improvement Scotland could identify and retrieve within the time available. The evidence notes are subject to peer review. Evidence notes do not make recommendations for NHSScotland, however the Scottish Health Technologies Group (SHTG) produces an Advice Statement to accompany all Evidence Notes.

The health technology, clinical effectiveness and safety sections of this evidence note are adapted from a European Network for Health Technology Assessment (EUnetHTA) review of transcatheter aortic valve implantation (TAVI) for the treatment of patients at intermediate surgical risk. Published in December 2018, the review was developed using the HTA Core Model® for Rapid Relative Effectiveness Assessment as part of the EUnetHTA WP5 Joint Action 3 programme[1].

Key findings

Clinical effectiveness and safety

- In a meta-analysis of outcomes from RCTs (PARTNER 2 and SURTAVI) with follow-up of 2 years, transcatheter aortic valve implantation (TAVI) was non-inferior to surgical aortic valve replacement (SAVR) in terms of all cause or cardiac mortality.

- Rates of stroke and disabling stroke were not statistically significantly different between TAVI and SAVR, but TAVI patients had a shorter length of hospital stay.
- The strength of evidence as judged by the meta-analysis authors varied by outcome but was generally greater for measures at 30 days compared with 2-year outcomes where there was less certainty around the findings.
- There was no evidence of a difference between procedures in the degree of symptom improvement or the rates of major vascular complications.
- Adverse event profiles differed between the two procedures.
    - Patients undergoing TAVI had a lower rate of new atrial fibrillation and reduced rates of acute kidney injury.
    - TAVI patients had a higher rate of paravalvular regurgitation at 30 days/discharge and increased rates of aortic valve re-intervention.
- Across the two studies there were inconsistencies in findings for:
    - Life threatening or disabling bleeding.
    - Rates of new permanent pacemaker implantation.
- Health related quality of life improvements at 30 days are greater with transfemoral (TF) TAVI than with SAVR.
- Based on current evidence it is not possible to compare outcomes from different TAVI access routes with SAVR, nor is it possible to compare effectiveness of different TAVI systems in the same population.
- Data from longer term follow up are awaited.

Cost effectiveness

- The conclusions of five economic evaluations which used data from either the PARTNER 2 or SURTAVI trials were equivocal.
    - Two evaluations found TAVI to be both cost saving and more effective than SAVR. However, their underlying propensity matching technique is subject to confounding factors and the omission of several key details makes verification of respective models challenging.
    - Three evaluations reported moderate uncertainty with regards to the cost-effectiveness of TAVI.
    - The key areas of uncertainty were the methodology used to calculate procedural costs, the cost of the device itself, length of ICU stay and the durability of TAVI valves. There does appear to be clarity regarding TF TAVI being the most cost-effective access route relative to SAVR.

- Based on the results of a de-novo cost-utility analysis for Scotland, TAVI at list price is unlikely to be a cost-effective option in Scotland for patients with severe aortic stenosis who are at intermediate surgical risk. This patient population matches those in the PARTNER II and SURTAVI trials. This conclusion was robust under an extensive range of scenarios and sensitivity analyses.
- The cost-effectiveness of TAVI in patients undertaking the procedure via transfemoral access is considerably more favourable than for transthoracic access but is still associated with high incremental cost effectiveness ratios (ICERs) that are unlikely to offer good value for money for NHSScotland. The TAVI valve cost is an important driver of the results, with the base case ICER falling to more acceptable levels subject to a reduction in TAVI valve price.

Patient experience and decision making

- There is evidence from three qualitative studies of patients undergoing TAVI procedures to suggest that:
    - Patients' experiences prior to undergoing TAVI vary. While some patients are hopeful that they have access to a treatment option that could improve their lives, others are more fearful about facing death due to weak health. In this regard, pre-TAVI consultation in relation to managing expectations about undergoing the procedure and the recovery process is seen as important by patients.
    - Patients experience different levels of improvement after TAVI. Some patients experience reductions in symptom burden (such as less pain, fatigue and shortness of breath) which lead to improvements in quality of life (e.g. ability to stay independent or take part in social activities). Some patients, however, may continue to experience health issues following TAVI related to comorbidities or frailty.
    - Support for family caregivers should be an important consideration when developing care pathways for TAVI patients, particularly relating to adequate information about the post-procedure recovery process.
- There is evidence from three qualitative studies of patients' decision-making around undergoing TAVI to suggest that:
    - Among the most common factors influencing the decision-making process are patients' expectations that TAVI will improve their quality of life and wellbeing, reduce symptoms and extend their lives. Trust in healthcare professionals and the information provided before the procedure are other important factors.

- Some patients are unsure about the benefits or effects of undergoing TAVI and require more information and support in the decision-making process.
- 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.

Definitions

Aortic stenosis (AS): an obstruction of normal blood flow across the aortic valve caused by calcification, which may have a degenerative, rheumatic or congenital aetiology.

Surgical aortic valve replacement (SAVR): open-heart surgery to replace the diseased aortic valve. Use of a mechanical prosthetic valve is the current standard treatment for patients with severe symptomatic AS who are well enough to undergo surgery.

Transcatheter aortic valve implantation (TAVI): a minimally invasive procedure in which a bioprosthetic replacement aortic valve is delivered inside a catheter, either percutaneously through the vascular system or directly through an incision in the chest.

Literature searches

The European Network for Health Technology Assessment (EUnetHTA) developed search strategies for efficacy and safety outcomes including registry data. All search strategies were developed by an information specialist. The searches were performed on 26 and 27 June 2017.

The following sources of information were searched: Cochrane Library, Centre for Research and Dissemination (CRD), Embase, and Medline, and Medline Pub status ahead of print. In addition to the systematic search, a manual search of selected members of the International Network of Agencies for Health Technology Assessment (INAHTA) home pages was also performed.

Searches to identify ongoing studies were conducted in the following information sources: ICTRP and Clinicaltrials.gov.

Healthcare Improvement Scotland conducted additional searches during 2018 to ensure that the evidence included in this review was as comprehensive as possible.

A systematic search of the economics literature was carried out between the 20 and 22 November 2018 for cost effectiveness studies relating to the use of TAVI in intermediate

and low surgical risk patients. Medline, Medline in process, Embase, Web of Science, Cochrane and the Centre for Reviews and Dissemination were searched.

A systematic search for patient experience literature was carried out between 26 and 29 November 2018 for qualitative research around the TAVI procedure. Medline, Medline in process, Embase and Web of Science were searched.

A systematic search of the volumes and outcomes literature was carried out between 29 November and 4 December 2018 to identify journal articles, HTAs, economic studies and reviews capturing the relationship between the volume of TAVI procedures and outcomes. Medline, Medline in process, Embase, Cochrane and the Centre for Reviews and Dissemination were searched.

Key websites were searched for guidelines, policy documents, qualitative studies, economic studies, patient experiences.

Concepts used in the searches included: Transcatheter aortic valve implantation (TAVI), volume and outcome, low risk/intermediate patients, patient experience/views, costs, surgical valve replacement (SAVR). A full list of resources searched and terms used are available on request.

Introduction

For patients with severe symptomatic aortic stenosis, surgical aortic valve replacement (SAVR) is the reference treatment where surgical risk is low. For those assessed by a heart team as being at increased surgical risk transcatheter aortic valve implantation (TAVI) is an alternative procedure[2].

SAVR 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).

TAVI involves the insertion of a prosthetic valve, which functionally replaces the damaged aortic valve, using fluoroscopic and echographically guided minimally invasive procedures. 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) route is the most common, whereas the others are performed when the anatomy of the patient precludes access via the TF route. These approaches are the subclavian/ transaxillary (S/T) approach, the transapical (TA) approach, and the transaortic (TAo) approach.

Data from randomised controlled trials (RCTs) in elderly patients at who are at high surgical risk indicate that TAVI is non-inferior or superior to SAVR2. This is reflected in SHTG advice on the use of TAVI in patients who are inoperable or at high surgical risk[3, 4].

This evidence review examines the evidence comparing outcomes of TAVI and SAVR in patients with severe aortic stenosis who are at intermediate surgical risk.

Health technology description

There are several TAVI systems commercially available. For intermediate operative risk devices from two manufactures are available.

Edwards SAPIEN TAVI systems are manufactured by Edwards Lifesciences (www.edwards.com) and are available in both the USA and Europe for use outside clinical trials. The Edwards SAPIEN prostheses are balloon expandable and comprise a cobalt-chromium frame and bovine pericardium transcatheter heart valves. The S-XT and S3 systems are improvements to the original Cribier and Edwards SAPIEN devices. Between the S-XT and the S3, there are differences in the stent-frame design of the two systems. S3 offers a high radial strength, and the S3 also has an additional outer polyethylene terephthalate cuff to improve paravalvular leak sealing. Both S-XT and S3 are available in four diameter sizes: 20 mm, 23 mm, 26 mm, and 29 mm, although S-XT 20 mm is only available for TF use. The European Medical Device Risk Class for Edwards S3 is Risk Class III[1].

The CoreValve Evolut R/PRO systems are manufactured by Medtronic (www.medtronic.com) and received CE mark and FDA approval for treating patients with severe aortic stenosis who are at high or extreme risk for surgery, as well as intermediate risk for open-heart surgery as determined by a heart team. The Medtronic CoreValve Evolut R/PRO systems are recapturable transcatheter aortic valve implantation systems that includes the CoreValve Evolut R/PRO transcatheter aortic valve, the EnVeo R/PRO delivery catheter system, and the EnVeo™ R/PRO loading system. The Medtronic bioprosthesis comprises a self-expandable nitinol frame, supra annular design with a porcine pericardial tissue heart valve. All systems can be delivered via TF or alternative access routes, such as S/T or TAo. Evolut R/PRO valves are provided with a specific anticalcification treatment; they can be recaptured and repositioned if needed. The Evolut PRO valve has an outer wrap that adds surface area contact between the valve and the native aortic annulus to further improve valve sealing performance. Evolut R is available in four annulus diameter sizes (23 mm, 26 mm, 29 mm, and 34 mm). Evolut Pro is available in three annulus sizes: 23 mm, 26 mm, and 29 mm. The European Medical Device Risk Class for Evolut R/PRO is Risk Class III[a].

[1] https://www.gov.uk/guidance/medical-devices-conformity-assessment-and-the-ce-mark

Epidemiology and surgical risk assessment

AS is the most common native heart valve disease in adults in Europe[5]. In most cases, the aetiology is degenerative; hence it is most often seen in older people, increasing with age due to degenerative calcification[5, 6]. The key diagnostic tool for AS and its severity is echocardiography[2]. Most people with mild to moderate AS are asymptomatic whereas patients with severe AS are likely to develop symptoms associated with narrowing of the valve and overload of the left ventricle, including syncope, exercise-induced angina, dyspnoea and congestive heart failure. The prevalence of severe symptomatic AS is around 3% in those aged over 75 years but this rises steeply with age[7]. Consequently, due to an ageing population, the prevalence will increase over the following decades. The prevalence of all valvular diseases, including AS, has been predicted to double by 2046[8]. Without intervention, patients with severe symptomatic AS have a poor prognosis with an average survival of 2–3 years[9] and survival rates of only 15–50% at 5 years[10]. It has been estimated that more than one third of elderly patients with severe symptomatic AS in Europe are not referred for surgical AVR[6]. Patients who are not referred for surgery are more likely to be older than those who are referred, and more likely to have left ventricular dysfunction and multiple comorbidities[6].

The patient group of interest for this evidence review are those with severe symptomatic AS who are assessed as being at intermediate surgical risk.

The most commonly used surgical risk algorithms include STS Predicted Risk of Mortality (STS-PROM), logistic EuroSCORE and EuroSCORE II. 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. 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[2] as shown in Table 1.

To estimate the overall risk for each individual patient, and to stratify patients to receive either palliative medical treatment (no valve replacement), medical treatment with reassessment on follow-up, SAVR, or TAVI, the surgical risk scores are used alongside an assessment of frailty as well as major organ complications (not covered by the scores). A specialised heart team normally conducts this assessment process.

Table 1: Surgical risk for 30-day mortality in patient stratification for SAVR and TAVI

Scoring system	Surgical risk for 30-day mortality	
	Intermediate	Low
STS-PROM or EuroSCORE II	4-8%	<4%

A model calculation, which assumed the overall prevalence of aortic stenosis (AS) among people aged >60 to be 4.5%, suggested that 7.5 million people in Europe are likely to have AS[11]. 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 patients in Europe are eligible for open-heart surgery. The calculated proportion of these patients with intermediate surgical risk is approximately 28.9%, resulting in an estimate of 252,500 patients. The study went on to estimate that the number of UK patients aged ≥75 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)[11].

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

At present within NHSScotland, TAVI is offered to patients considered unsuitable for surgery (inoperable) or patients considered to be at high surgical risk as assessed by scoring systems and clinical parameters[3, 4].

The number of TAVI procedures performed in Scotland has been increasing since the service was introduced in 2012. It is estimated that 318 procedures were carried out in the financial year 2018/19 and, based on current criteria for TAVI provision applied to demographic changes, it is estimated that in the financial year 2019/20 there will be 322 cases performed (95% CI 288 to 359). This gives an annualised TAVI rate per million population of 58.92 which is lower than the 2017 UK TAVI rate of 61 TAVI procedures per million population (S Robb, Information Consultant, ISD Scotland. Personal Communication, 11 Jan 2019).

Clinical effectiveness

Guidelines

NICE interventional procedures guidance (IPG) states that[12]: 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.

The IPG 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.

European guidelines 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[2].

Randomised Controlled Trials

The EUnetHTA review identified two RCTs[13, 14]. 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.

PARTNER 2 cohort A trial[13]

Patient eligibility criteria for the trial included: severe aortic valve stenosis and intermediate surgical risk according to an STS score of at least 4% with an (not prespecified) upper limit of 8%. Patients with an STS score <4% could also be included if there were coexisting conditions not represented in the STS risk score algorithm. Patients included in the trial had a mean STS score of 5.8±2.1 for the TAVI group and 5.8±1.8 for the SAVR group. The mean age of patients in the trial was 82 years.

The trial stratified 2,032 patients into cohorts according to access route (transfemoral (TF) or transthoracic [including TA and TAo]) and then randomised in a 1:1 ratio to TAVI or SAVR. There were 1,011 patients in the TAVI arm (775 TF, 236 transthoracic) and 1,021 in the SAVR arm. Ninety-four patients (17 (1.7%) in the TAVI group and 77 (7.6%) in the SAVR group) withdrew from the study mainly owing to a decision after randomisation not to undergo surgery. It is unclear whether differences in withdrawal between the two groups might have created an imbalance in the prognostic characteristics of the two groups. Patients assigned to TAVI received an Edwards balloon-expandable SAPIEN XT heart valve.

Primary outcome was composite of death from any cause or disabling stroke at 24 months. 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 the TF 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. The study was not powered for analysis of this subgroup.

SURTAVI trial

Patient eligibility criteria for the trial included: symptomatic severe AS and intermediate surgical risk according to an STS score of 3%–15% and factors such as co-existing illness, frailty and disability. Patients included in the trial had a mean STS score of 4.5±1.6. The mean age of patients in the trial was 80 years.

In the trial, 1,746 patients were randomised (879 to the TAVI group and 867 to the SAVR group). TAVI was not attempted in 15 patients (1.7%) and SAVR was not attempted in 71 patients (8.2%). There were no differences identified in the baseline characteristics of those who were allocated to SAVR and received surgery and those who did not. Most patients in the TAVI group were treated transfemorally (93.6%). The choice of implant and access route was decided after randomisation. In the SURTAVI trial, 84% of the patients in the TAVI group received CoreValve self-expanding valves, whereas the remaining 16% received the Evolut R self-expanding valves.

Primary outcome was composite of death from any cause or disabling stroke at 24 months. 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).

EUnetHTA meta-analysis

EUnetHTA conducted meta-analyses of outcomes from the two identified studies. 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. 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 a Bayesian statistical method interim analysis after 1 year. 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 included:

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

Key findings are summarised in Table 2 alongside the interpretation of evidence certainty using the GRADE evidence rating scale (https://www.bmj.com/content/336/7650/924):

- 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.

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).

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).

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).

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

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), 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.

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 2: summary of clinical effectiveness findings of EUnetHTA meta-analyses[1]

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 II 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.			Not assessed

	In the SURTAVI trial effective AV orifice areas were significantly greater in the TAVI arm at all-time points of follow up.	
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)

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. 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[14].

In the PARTNER II 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 TF TAVI, whilst for patients eligible for TF TAVI receiving SAVR it was 3.2 (95% CI 1.3 to 5.5, n=551)[15]. 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 TF 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.

Safety

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

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

Key findings from the EUnetHTA report are summarised in Table 3 alongside the interpretation of evidence certainty using the GRADE evidence rating scale.

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).

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)

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).

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% CrI −0.1 to 5.9). Data were not pooled because the heterogeneity was high (I^2 = 99%).

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).

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).

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%).

Parvalvular 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).

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: summary of safety findings of EUnetHTA meta-analysis[1]

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*$^
New atrial fibrillation 30 day	204/1890 11%	641/1888 34%	0.32 (95% CI 0.27 to 0.37) p<0.0001	Moderate*
Life-threatening or disabling bleeding	In the PARTNER 2 trial, life-threatening or disabling bleeding at 30-day follow-up occurred in 10% of the TAVI group compared with 43% of patients in the SAVR group. (RR 0.24, 95% CI 0.20–0.29, p<0.001). In the SURTAVI trial, there was no evidence of differences between the two treatments at 30-day, 1- year, and 2-year follow-up in terms of life-threatening or disabling bleeding			Very low*∞$
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*$^
Major vascular complications 30 days ◊	131/1890 6.9%	59/1888 3.1%	3.03 (95% CI 0.79 to 11.67) p=0.11	Low*$

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 (I^2 = 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.

Observational studies

The EUnetHTA review included two observational studies that provided data on safety[16, 17].

A German registry study (n=763), examined risk of post-operative delirium (POD) and risk of in-hospital mortality[16]. 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 TF 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 TF 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[17]. 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[17]

	Risk of stroke at 1-year		
Subgroup STS PROM	**TAVI**	**SAVR**	**Hazard Ratio**
≥3% and <5%	3.8% n=1,953	3.3% n=1,850	1.06 (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)

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.

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 will 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.

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.

Association between procedure volumes and outcomes

Guidelines

A 2008 position statement from the British Cardiovascular Intervention Society (BCIS) and the Society of Cardiothoracic Surgeons (SCTS) noted that[18]:

> "… 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 h day/7 day week surgical and cardiological care[19].

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[20].

Primary studies

Six potentially relevant studies were excluded on the basis that they analysed information from administrative databases[21-26]. 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[27-30]. A variety of methodologies were described and a range of short term outcome measures explored. Parameters of each study are outlined in Table 5.

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) [30]. 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* 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 TF 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-TF 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[27]. The maturity of the TAVI programme at each centre was not identified. The association between annual number of TF 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* 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 center were not significantly different than at a low and intermediate volume centre for patients having TAVI by alternate access (non-TF) 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[25]. Balancing the clinical significance of differences in outcome with geographic access to TAVI was highlighted in a US discussion paper[31] and the statistical challenges of assessing the quality of procedures at low annual volume (<50) centres also requires consideration[20].

Table 5: parameters of volume outcome studies

Study Details	Centres/Procedures Data period	Volume definitions (Annual)	Outcomes
Wassef 2018[30] 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 2017[28] US Transcatheter Valve Registry	395/42,988 2011-2015	Cumulative volume as a continuous variable	In-hospital outcomes Mortality Vascular complications Bleeding Stroke
Bestehorn[27] 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 2017[29] 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)

Patient and social aspects

Studies relevant to the patient and social aspects section of the 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.

Patients' experiences of undergoing TAVI

Three primary studies were identified that looked at patients' experiences of undergoing TAVI[32-34]. Study characteristics are presented in Table 6.

Study quality was assessed using the Quality of Reporting Tool (QuaRT)[35]. 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[33] 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[32] 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[33] 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[34] 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 6: Qualitative studies exploring patients' experiences of undergoing TAVI

Study	Aim	Patients characteristics (N, mean age)	Follow-up	Country	Data collection & analysis methods	Quality
Baumbusch (2018)[32]	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. Qualitative description	Good
Olsson (2018)[33]	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 (2017)[34]	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

Patients' decision-making about undergoing TAVI

Three primary studies were identified that looked at patients' decision-making around undergoing TAVI. Study characteristics are presented in Table 7.

Study quality was assessed using the Quality of Reporting Tool (QuaRT)[35]. 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[36] 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[37] 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 members 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[38] 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 7: Patients' decision-making about undergoing TAVI

Study	Aim	Patients characteristics (N, mean age)	Country	Data collection & analysis methods	Quality
Lauck (2016)[36]	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 (2016)[37]	Describe the decision making process about undergoing TAVI treatment	N=24 (15 men; 9 women) Mean age=80.7	Sweden	Interviews	Good
Skaar (2017)[38]	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

Cost effectiveness

Published literature

The literature search identified five economic evaluations that assessed the cost-effectiveness of TAVI for intermediate risk surgical patients with AS who are eligible for SAVR. Evaluations were carried out from a US[39], French[40], Canadian[41, 42] and Japanese[43] perspective, but none from a UK perspective.

The key source of clinical-effectiveness evidence used to underpin the evaluations were the two industry sponsored RCTs assessing the non-inferiority of balloon or self-expandable TAVI to SAVR in intermediate risk patients with AS. Four studies used the PARTNER-2[13] trial results and one study used the SURTAVI[14] trial results.

It is worth noting that the PARTNER-2 trial was conducted using second generation SAPIEN-XT valves, which do not have a CE mark for intermediate risk patients with AS. Only two studies reported on the cost-effectiveness of the third generation SAPIEN 3 valves, which do have a CE mark for use in intermediate risk patients with AS. Similarly, only 16% of patients randomised to the TAVI arm of the SURTAVI trial received second generation Evolut-R valves with CE certification for use in intermediate risk patients with AS.

The economic evaluation by Baron *et al* (2018) presented an analysis of SAPIEN XT versus SAVR, based on the randomised PARTNER-2A trial, and a separate analysis of SAPIEN 3, by propensity matching 1,077 patients from the PARTNER-S3i Registry with the surgical arm of the randomised trial[39]. The registry used identical inclusion and exclusion criteria to the trial, and a pre-specified propensity score was employed to adjust for differences between the groups.

A Markov model was used to synthesise the costs and outcomes data available up to 24 months, which were then extrapolated to the lifetime horizon. Projected long-term survival was estimated using calibrated US life tables for the surgical group and an empirically derived hazard ratio for the TAVI group. The hazard ratio used for the base case analysis was 1.0, which implies no further benefit from TAVI on mortality beyond 24 months; however, it also implies no increased mortality from longer-term adverse events following TAVI. Utility values for health states were based on QoL data collected through the EQ-5D questionnaire administered to all patients up to 24 months, but were not presented in the publication and could not be verified. Both procedural and non-procedural index admission resource use and costs were included in the analysis. Procedure costs were derived using a micro-costing approach based on procedure duration, resource use and intra procedural complications recorded by the study centres. Non-procedural index costs and follow-up resource use and costs were derived by linking patients with US Medicare claims data. For the 22% of the XT-TAVI cohort and 23% of S3-TAVI cohort who could not be linked, these costs were estimated using regression models. TAVI device costs were estimated to be $32,500 (£25,000).

The base case results of the model found TAVI to be economically dominant compared with SAVR; TAVI was projected to reduce total lifetime costs by $8,000 (£6,200) and $9,700 (£7,700) with an increase of 0.15 and 0.27 incremental quality adjusted life years (QALY) for the SAPIEN XT and SAPIEN 3 valves respectively. Although procedural costs were $20,000 (£15,500) higher with TAVI than SAVR due to the higher costs of the valve, total cost differences for index admission were much lower due to reductions in length of stay with TAVI. Follow-up costs were also lower in TAVI compared with SAVR due to significant reductions in hospital days and rehabilitation within the first six months following the procedure. TAVI using SAPIEN 3 was associated with a significantly lower two-year mortality rate and greater projected life expectancy compared with SAVR, whereas these differences were not significant in the case of SAPIEN-XT.

Results were not sensitive to variations in discount rate, paravalvular regurgitation associated excess mortality, or the TAVI valve cost, although the latter was only tested up to

an upper limit of $35,000 (£27,000). However, the model was sensitive to hazard ratios for late-mortality and follow-up costs associated with TAVI. No sensitivity analysis on utility values was reported.

The conclusions of this study were similar to those of the evaluation by Goodall *et al* (2018)[40], which also assessed the cost-effectiveness of TAVI (with the SAPIEN 3 valve) compared with SAVR by propensity matching patients from the PARTNER-S3i Registry with the surgical arm of the randomised trial. Whilst data on survival, clinical event rates and quality of life were all derived from the trial, all index admission and follow-up costs used in the analysis were from the French public reimbursement tariff. The TAVI device costs were not presented in the publication and its impact was not tested in the sensitivity analysis.

TAVI was found to be economically dominant to SAVR with lifetime costs projected to be lower by €439 (£386) alongside an increase of 0.41 QALYs. Compared with the results of Baron et al (2018), the incremental QALYs gained with TAVI were higher but the total lifetime savings associated with TAVI were much lower; largely because the index admission costs for TAVI were higher than SAVR. Hence, the savings achieved by TAVI were the result of reductions in rehabilitation and post-discharge complications. Sensitivity analysis found the least favourable scenario for TAVI (in terms of the difference in admission costs) to have an incremental cost effectiveness ratio (ICER) of €18,000 (£15,800).

Whilst both these studies report promising results, the retrospective propensity matched analysis for the third-generation SAPIEN-3 valves can be subject to confounding factors which could potentially have biased results in favour of TAVI. It was unclear whether Goodall *et al* (2018) propensity matched based solely on mortality and opted to use un-adjusted PARTNER-2 data for complications; which seems to favour TAVI. Another limitation was use of the as-treated trial population only in the economic analysis by Baron *et al* (2018). Given that a relatively higher proportion of patients randomized to SAVR did not undergo the procedure compared to those randomised to TAVI, this may have confounded the results as one may expect higher risk patients to have withdrawn from TAVI. Further, both studies were industry funded and lack the transparency needed to facilitate external verification. Specific details regarding model structure and parameter inputs that one might generally expect to be presented when reporting economic evaluations were omitted.

In contrast, non-industry funded studies present less promising results. Kodera *et al* (2018)[43] used clinical effectiveness data from the PARTNER 2 trial and from the national registry to model cost-effectiveness of TAVI (using SAPIEN XT valve) within the Japanese public payer context. Compared with SAVR, TAVI was more expensive by ¥1,723,516 (£12,100) and generated an additional 0.22 QALYs. The resulting ICER of ¥7,523,821 (£52,800) per QALY exceeded the local cost-effectiveness threshold.

The results of two cost-utility analyses, conducted from the Canadian health care system payer's perspective, also suggest moderate uncertainty with regards to the cost-effectiveness of TAVI[41, 42]. Both of these studies were undertaken by the same research

team and utilised identical model structures but based their analysis on clinical efficacy data derived from different trials. The cost-effectiveness of two different types of devices relative to SAVR, the self-expandable TAVI (used in the SURTAVI trial) and the balloon-expandable TAVI (used in the PARTNER 2 trial), could therefore be examined.

Model parameters informed by trial data included 30-day outcomes, 2-year outcomes and length of stay (ICU and ward). Specific QoL data from trials were unavailable to authors at the time, hence estimates for short and long term health states were obtained from previous trials of respective TAVI systems in the high risk population. The cost inputs for both models were very similar and obtained either from the same sources in the literature or from the Ontario Schedule of Benefits. TAVI device costs were estimated to be $22,000 (£12,900) for the self-expandable device and $24,000 (£14,000) for the balloon-expandable device.

Base case results of both models found that TAVI was more expensive but also more effective than SAVR. Relative to SAVR, self-expandable TAVI was associated with higher total lifetime costs of $11,305 (£6,600) and was more effective by 0.15 QALYs; yielding an ICER of $76,736 (£44,900) per QALY. Balloon-expandable TAVI was associated with higher total lifetime costs of $10,548 (£6,200) and was more effective by 0.23 QALYs; yielding an ICER of $46,083 (£27,000) per QALY. The variation in absolute value of the ICERs was attributed to increased re-hospitalisation and complication rates arising from significant differences in permanent pacemaker implantation in patients receiving a self-expandable TAVI valve.

Hence, in contrast to self-expandable TAVI, the ICER for balloon-expandable TAVI was below the conventional Canadian cost-effectiveness threshold. However, deterministic sensitivity analysis found the cost of the TAVI valve and length of ICU stay to be drivers of cost-effectiveness in both models. The balloon-expandable SAPIENT XT valve was no longer cost effective with a relatively small increase in cost of $1100 (£644) or if length of ICU stay increased by 0.3 days. Probabilistic sensitivity analysis found that parameter inputs were associated with a moderate to high degree of uncertainty; TAVI was the preferred option in only 53% of the simulations at the conventional cost-effectiveness threshold. This was likely due to the models being informed by single trials which were non-inferiority studies by design.

The equivocal findings of these economic evaluations reveal uncertainty around the index admission costs associated with TAVI. Whilst real-world linked cost data indicate that TAVI is associated with cost savings, tariff-based projections suggest that any savings would largely be negated by high device costs. However, savings in admission costs would appear to be plausible considering a combination of factors including iterative improvements in TAVI devices, delivery systems, operator experience and application of early discharge algorithms.

There is further uncertainty regarding the durability of TAVI valves stemming from a gap in evidence[44]. None of the economic models accounted for the probability of longer-term valve failure and post-TAVI valve replacement.

There does however appear to be some consensus between evaluations. Stratified analyses within individual studies found the cost-effectiveness of TAVI to be contingent on the type of access route. In the US based study index admission costs and cumulative two year costs with transthoracic TAVI were significantly higher compared with SAVR and also generated lower QALYs. This was in sharp contrast to the economic dominance of TF TAVI. Similarly, scenario analysis in the Canadian studies found the ICER of a TF only cohort to be lower than that of a combined cohort (transfemoral and transapical access) versus SAVR.

De-novo cost-utility analysis of TAVI versus SAVR in severe AS patients at intermediate risk. A Scottish perspective.

A cost-utility analysis from a Scottish perspective was conducted in order to inform decision-making around use of TAVI in the intermediate surgical risk population. An extensive report of this analysis is presented in Appendix 1.

Methodology

In the baseline analysis, all primary clinical endpoints were derived from the full intention to treat (ITT) population in PARTNER II which compared TAVI using the Sapien XT valve with SAVR in intermediate risk patients. Beyond the two year trial follow-up it was assumed that the risk of complications in the two procedure arms was the same. Mortality post-trial follow-up was informed by general population mortality adjusted for the age and gender distribution which was up-scaled by an adjustment hazard ratio of 1.15 to reflect the heightened risk of mortality in patients with severe AS undergoing aortic valve replacement at intermediate risk. The model cohort demographics were based on the PARTNER II population, which informed the mean starting age of the model cohort, gender distribution, as well as the distribution of access modality (transfemoral/transthoracic).

The impact of using alternative clinical data was explored in further scenario analyses. Clinical endpoints from the following studies comparing TAVI with SAVR in intermediate risk patients were tested: PARTNER II ITT transfemoral population; PARTNER II ITT transthoracic population; PARTNER II as-treated population; PARTNER S3i registry study (as-treated population) comparing SAPIEN 3 with the surgical arm in PARTNER II; PARTNER S3i as-treated transfemoral population; SURTAVI ITT population; and SURTAVI modified-ITT population.

All costs applied in the model were derived from UK data and are detailed in Table 8. Aggregated procedure costs were derived from local Scottish data including the following components: theatre, radiology, laboratory, other treatments and inpatient costs. Subsequent length of stay (LoS) costs in various units linked to each procedure were also included. The reference cost of the TAVI procedure excludes the cost of the valve. Data on

valve costs were provided by Scottish National Procurement which included a range of different valve brands and various price rebates for bulk purchases. Complication costs were derived from a mix of NHS Reference Costs and clinical expert opinion. Differential follow-up costs were also applied at every twelve months in both procedure arms based on clinical expert opinion.

The QoL utilities used in the model were derived from EQ-5D values reported in the PARTNER II study according to time and intervention. No difference in utilities was assumed between treatment arms beyond two years and, in the absence of age-specific utility values for this patient population, and the last utility derived in the SAVR arm was applied to all subsequent cycles. No additional disutilities from complications were applied in the model, as the effects of these were already captured by the population derived utility values. In an alternative scenario analysis, between-group-differences in utilities reported across the trial follow-up that were not statistically significant were assumed to be zero.

Base case results

Base case results using clinical data from Partner II ITT cohort are presented in Table 8, showing a modest QALY gain (0.13) with TAVI versus SAVR over the patient lifetime and a considerable increase in cost (£12,945) mainly owing to the cost of the TAVI valve, resulting in a high ICER.

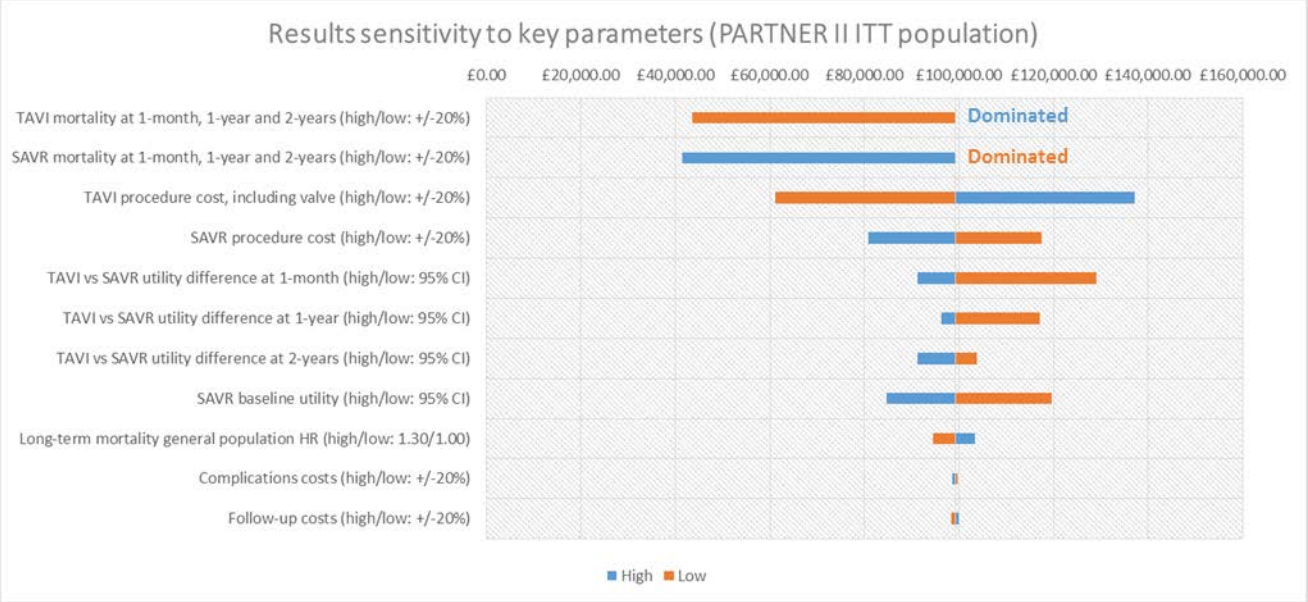
Table 8: Base case results (per patient, discounted, PARTNER II ITT population)

	TAVI	SAVR	Incremental
Procedure cost (including TAVI valve)[a]	[redacted]	[redacted]	£12,713.07
Complications and follow-up cost[a]	[redacted]	[redacted]	£231.49
Total cost	£34,995.93	£22,051.37	£12,944.56
Lys	5.28	5.11	0.17
QALYs	3.93	3.80	0.13
ICER (£/LY)	-	-	£76,929.11
ICER(£/QALY)	-	-	**£98,965.02**

[a] commercial in confidence cost data provided by National Procurement

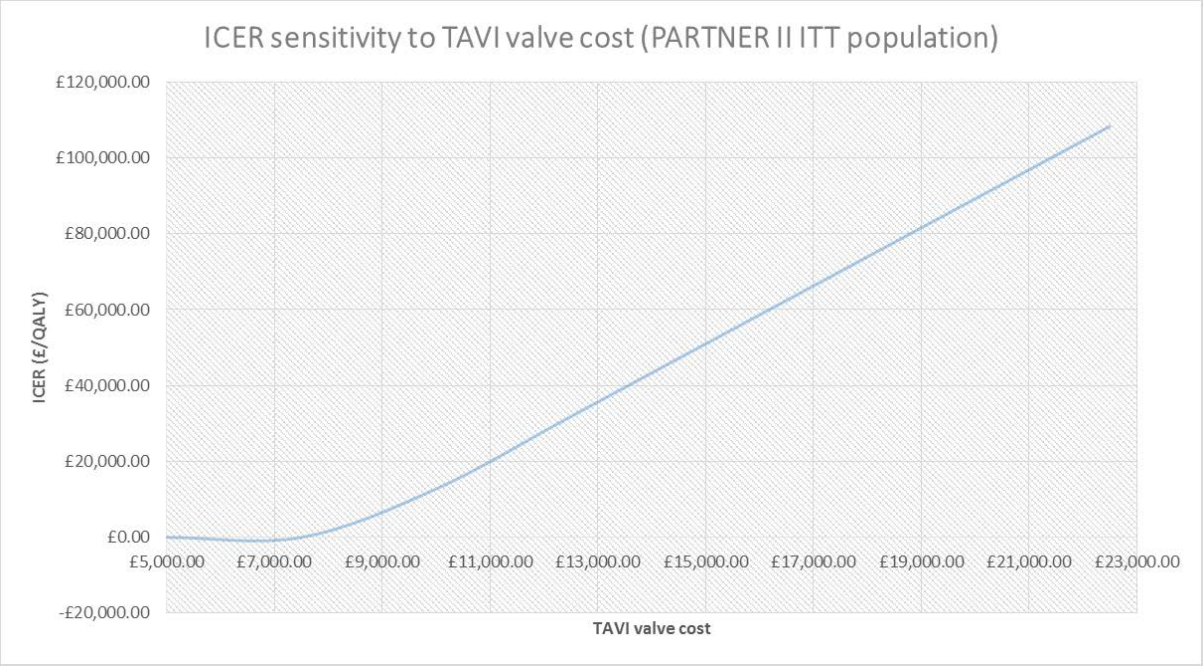
The sensitivity of the base case results to key model inputs is explored in the one-way deterministic sensitivity analysis reported in Figure 1. All model inputs were varied across their 95% CI or across a pre-defined range. The base case results seem to be most sensible to procedure costs and trial reported between-group differences in health utility scores.

Figure 1: One-way sensitivity analysis results



The effect of the TAVI valve cost on the base case ICER is further investigated in Figure 2 and shows this input to be a big driver of the cost-effectiveness of TAVI versus SAVR in the model. It can be estimated that for valve prices lower than £12,000 the cost-effectiveness of TAVI looks more favourable.

Figure 2: Device cost sensitivity



Scenario analysis

Table 9 reports results for various scenario analyses which use different clinical inputs from alternative studies.

Table 9: Scenario analyses

Scenario	Base case assumption	New scenario assumption	ICER new scenario
Baseline (PARTNER II ITT population)	-	-	£98,965.02
PARTNER II transfemoral ITT population	Clinical outcomes for the model derived from PARTNER II ITT population	Clinical outcomes for the model derived from PARTNER II transfemoral ITT population	£56,249.58
PARTNER II transthoracic ITT population	Clinical outcomes for the model derived from PARTNER II ITT population	Clinical outcomes for the model derived from PARTNER II transthoracic ITT population	Dominated
PARTNER II as-treated population	Clinical outcomes for the model derived from PARTNER II ITT population	Clinical outcomes for the model derived from PARTNER II as-treated population	£84,830.58
Partner S3i as-treated population	Clinical outcomes for the model derived from PARTNER II ITT population	Clinical outcomes for the model derived from Partner S3i as-treated population	£38,974.72
Partner S3i as-treated transfemoral population	Clinical outcomes for the model derived from PARTNER II ITT population	Clinical outcomes for the model derived from Partner S3i as-treated	£37,908.62

		transfemoral population	
SURTAVI ITT population	Clinical outcomes for the model derived from PARTNER II ITT population	Clinical outcomes for the model derived from SURTAVI ITT population	£686,222.40
SURTAVI modified-ITT population	Clinical outcomes for the model derived from PARTNER II ITT population	Clinical outcomes for the model derived from SURTAVI modified-ITT population	£321,262.17
Assume no difference in utilities past 1-month follow-up	Utilises all between-group-differences observed across the 2-year follow-up in PARTNER II	Utilises only the statistically significant between-group-difference observed at 1-month follow-up in PARTNER II	£95,166.82
Assume no difference in probability of major/life-threatening bleeding	Substantial difference in major/life-threatening bleeding in favour of TAVI observed in PARTNER II	Utilises the same probability for this complication in both arms informed by the rate observed in the TAVI arm of the trial	£101,567.27
Only including complications which significantly differed between treatment arms in the	Including all absolute rates for all complications observed in the trial	Where no statistically significant difference between treatment arms was observed, the same rate observed in TAVI applies in both arms	£265,662.10
Only including complications which significantly differed	Including all absolute rates for all	Where no statistically significant	£98,412.27

between treatment arms in the (except death from any cause or disabling stroke)	complications observed in the trial	difference between treatment arms was observed (except death from any cause or disabling stroke), the same rate observed in TAVI applies in both arms	
Bottom-up approach to costing procedure	Using top-down tariffs to cost procedures	Bottom-up approach	
Shorter time horizon	15 years; 10 years; 5 years	20 years	£101,407.72; £114,095.08; £168,435.72
Different discount rate	0%; 7%	3.5%	£82,816.71; £116,856.14

Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) was run by randomly sampling 1,000 sets of model inputs and results. All these simulations are plotted in the cost-effectiveness plane in Figure 3. This shows that most of the simulations fall below commonly accepted cost-effectiveness thresholds for decision making, with TAVI being cost-effective versus SAVR in 38.9% and 26.9% of the simulations at the £30,000/QALY and £20,000/QALY thresholds respectively. TAVI was dominated by SAVR in 34.5% of the simulations. Cost-effectiveness acceptability curves were also plotted based on these analyses, shown in Figure 4. Each curve illustrates the probability of TAVI being cost-effective versus SAVR at various levels of cost-effectiveness threshold under alternative scenarios. As an example, a relatively lower probability of TAVI being cost-effective can be observed in the transthoracic population compared to the alternative populations.

Figure 3

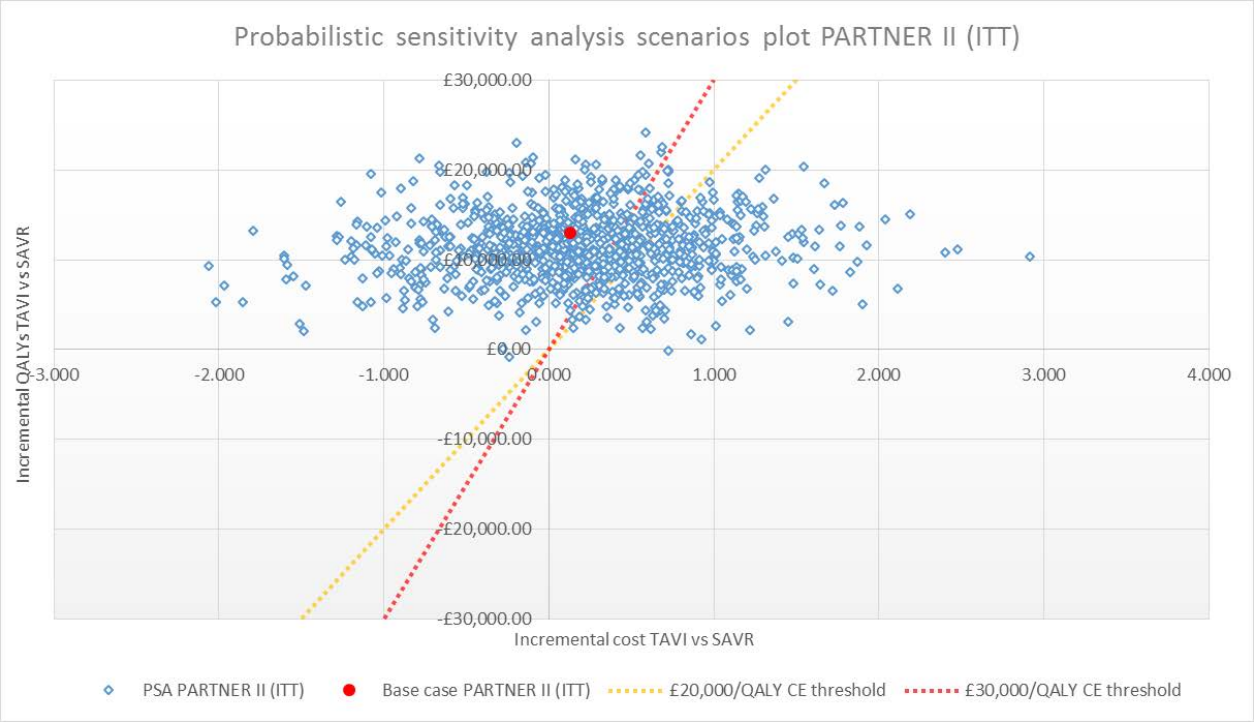
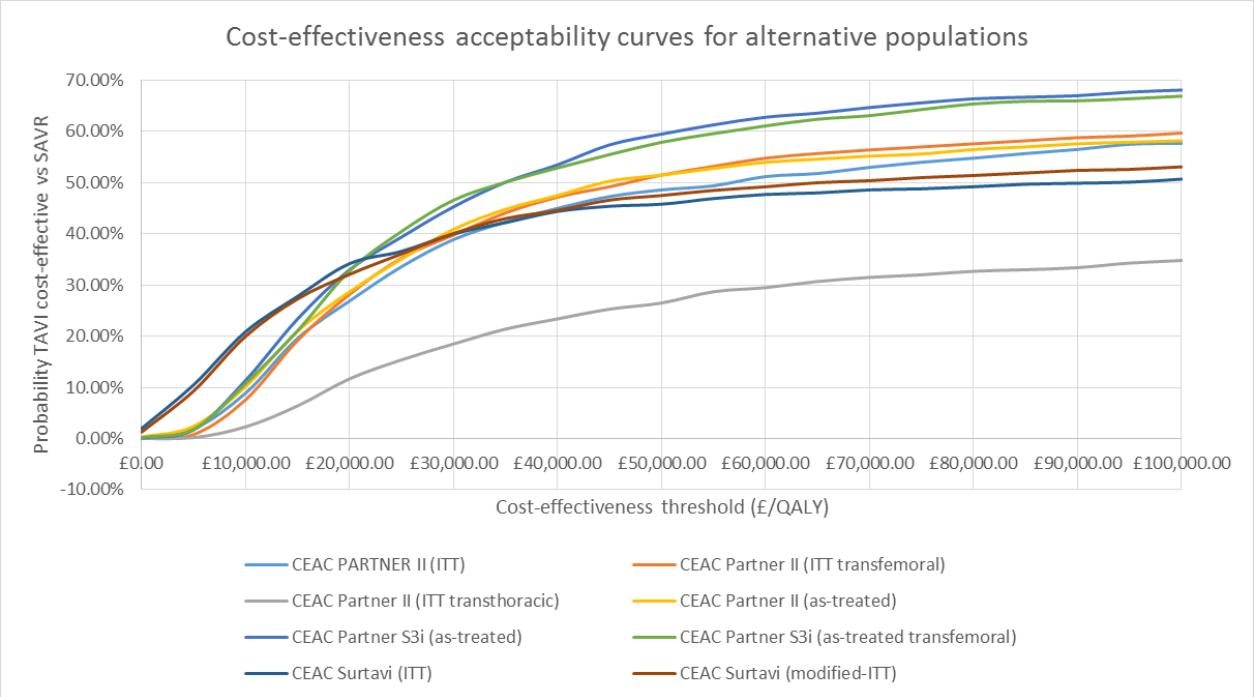


Figure 4



Discussion

The economic modelling presented here has explored the cost-effectiveness of TAVI versus SAVR in patients with severe AS with an intermediate STS risk score from a Scottish

perspective. The analyses utilise clinical data and utilities from the pivotal trials conducted in this population, which have then been combined with Scottish specific costs. TAVI was generally associated with high ICERs and low probabilities of being cost-effective against SAVR. The generalisability of these results may be limited by the risk profile and patient characteristics of the non-Scottish patient cohorts that were used to derive the model inputs. TAVI may still be a cost-effective option in patients that would classify as intermediate risk based on their STS score but which are considered frail and have other comorbidities not captured in the trial populations.

One caveat surrounding the analysis is that the top-down estimates of procedures costs are derived from a heterogenous mix of patient risk groups and hence may not accurately reflect the true cost in the intermediate group. Similarly, the reference costs used for complications were averaged across a mix of patients with varying comorbidities or underlying causes for developing complications. However, variations to these costs were tested in the sensitivity analyses, and it did not affect the conclusions.

Further caveats are as follows. The PARTNER II trial was powered for the ITT and as-treated analysis, but not powered for transfemoral/transthoracic subgroup stratification. Utility scores were derived from the EQ-5D data collected within PARTNER II, which may affect generalisability to the UK. All QoL scales apart from the KCCQ-OS score within PARTNER II were secondary end points, and baseline EQ-5D health status was only available in 1,833 of 2,032 randomised patients, with proportionally more returns in the TAVI group. Although inevitable, treatment arms were not blinded, which could have influenced patient-reported health status during follow-up**.** There was a modest amount of missing health status data at 2 years (15.7% for SAVR; 11.9% for TAVR). While missing data could have contributed to responder bias, there was no difference in baseline characteristics between patients with and without available health status data at 2 years, thereby suggesting that the effect of responder bias is likely minimal.

Conclusion

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 unclear: stroke, acute kidney injury, new permanent pacemaker, major vascular complications, aortic valve reintervention, and life threatening and/or disabling bleeding.

Trail follow-up only extends to 2 years and so longer-term outcomes are awaited. The short follow-up period also leads to uncertainty surrounding the durability of the valves in an

intermediate risk population who are likely to have a longer life expectancy than the high risk/inoperable population.

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 (<40 or <50 per year) should be avoided.

Based on the published cost effectiveness literature, it is unclear whether TAVI would be a cost-effective alternative to SAVR in intermediate risk patients. Considering the insignificant differences in mortality outcomes between the two, the economic case for TAVI is likely to hinge on procedural costs (including the cost of the device) and the magnitude by which local TAVI provision impacts upon length of hospital stay.

Based on the results of a de-novo cost-utility analysis for Scotland, TAVI is unlikely to be a cost-effective option in Scotland for patients with severe AS who are at intermediate surgical risk. This patient population matches those in the PARTNER II and SURTAVI trials. This conclusion was robust under an extensive range of scenarios and sensitivity analyses. The cost-effectiveness of TAVI in patients undertaking the procedure via transfemoral access is considerably more favourable than for transthoracic access but is still associated with high ICERs that are unlikely to offer good value for money for NHSScotland. The TAVI valve cost is an important driver of the results, with the base case ICER falling to more acceptable levels for valve costs lower than £12,000 (£15,000 in the transfemoral population), but still subject to the underlying uncertainty.

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.

Equality and diversity

Healthcare Improvement Scotland is committed to equality and diversity in respect of the nine equality groups defined by age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion, sex, and sexual orientation.

References can be accessed via the internet (where addresses are provided), via the NHS Knowledge Network www.knowledge.scot.nhs.uk, or by contacting your local library and information service.

A glossary of commonly used terms in Health Technology Assessment is available from htaglossary.net.

Acknowledgements

Healthcare Improvement Scotland and SHTG invited the following individuals and organisations to peer review the draft evidence note:

- **Dr Philip Adamson,** Consultant Cardiologist, Royal Infirmary of Edinburgh
- **Sophie Barnett,** Manufacturer – Medtronic **UK**
- **Dr Paul Broadhurst,** Consultant Cardiologist, Aberdeen Royal Infirmary
- **Andrew Champion,** Assistant Director, Evidence Evaluation, Welsh Health Specialised Services Committee
- **Dr Nick Cruden,** Consultant Cardiologist, Royal Infirmary of Edinburgh
- **Claire Duxbury,** Manufacturer - Boston Scientific Ltd
- **Richard Forsyth,** Patient Organisation - British Heart Foundation
- **Nick Hartshorne-Evans,** Patient Organisation – Pumping Marvellous Foundation
- **Dr Mitchell Lindsay,** Consultant Cardiologist, Golden Jubilee National Hospital

Declarations of interest were sought from all peer reviewers. All contributions from peer reviewers were considered by the group. However the peer reviewers had no role in authorship or editorial control and the views expressed are those of Healthcare Improvement Scotland.

Healthcare Improvement Scotland development team

- Lorna Thompson and Nikolina Angelova, Health Services Researchers
- Paul Herbert, Information Scientist
- Lucian Gaianu and Rohan Deogaonkar, Health Economist
- Caroline Foulkes, Communications and Publications Co-ordinator
- Paula O'Brien, Project Team Member
- Members of the SHTG evidence review committee

References

1. Abraha I, Chiarolla E, Corio M, Gillespie F, Migliore A, Cerbo M *et al*. Transcatheter aortic valve implantation (TAVI) in patients at intermediate surgical risk. Rapid assessment of other (non-pharmaceuticals) health technologies using the HTA Core Model for Rapid Relative Effectiveness Assessment. EUnetHTA Project ID: OTCA06 2018.
2. Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ*, et al.* 2017 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J. 2017;38(36):2739-91.
3. Healthcare Improvement Scotland. Transcatheter aortic valve implantation (TAVI) for severe symptomatic aortic stenosis in adults at high surgical risk. 2017 [cited 4 April 2019]; Available from: http://www.healthcareimprovementscotland.org/our_work/technologies_and_medicines/topics_assessed/shtg_001-17.aspx
4. Healthcare Improvement Scotland. Transcatheter aortic valve implantation (TAVI) for severe symptomatic aortic stenosis in adults who are not eligible for surgery. 2014 . Available on request from: shtg.hcis@nhs.net
5. Iung B, Baron G, Butchart EG, Delahaye F, Gohlke-Barwolf C, Levang OW*, et al.* A prospective survey of patients with valvular heart disease in Europe: The Euro heart survey on salvular heart disease. Eur Heart J. 2003;24(13):1231-43.
6. Iung B, Cachier A, Baron G, Messika-Zeitoun D, Delahaye F, Tornos P*, et al.* Decision-making in elderly patients with severe aortic stenosis: why are so many denied surgery? Eur Heart J. 2005;26(24):2714-20.
7. Osnabrugge RL, Mylotte D, Head SJ, Van Mieghem NM, Nkomo VT, LeReun CM*, et al.* Aortic stenosis in the elderly: disease prevalence and number of candidates for transcatheter aortic valve replacement: a meta-analysis and modeling study. J Am Coll Cardiol. 2013;62(11):1002-12.
8. d'Arcy JL, Coffey S, Loudon MA, Kennedy A, Pearson-Stuttard J, Birks J*, et al.* Large-scale community echocardiographic screening reveals a major burden of undiagnosed valvular heart disease in older people: the OxVALVE Population Cohort Study. Eur Heart J. 2016;37(47):3515-22.
9. Sethi S, Daniel T, Howell J, Griffin C. A commissioning framework for transcatheter aortic valve implantation (TAVI) for severe symptomatic aortic stenosis. 2009 [cited 4 April 2019); Available from: http://bcis.org.uk/wp-content/uploads/2016/12/TAVI-National-Commissioning-Framework-FINAL-160309.pdf.
10. Vahanian A, Alfieri O, Andreotti F, Antunes MJ, Baron-Esquivias G, Baumgartner H*, et al.* 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). Eur J Cardiothorac Surg. 2012;42(4):S1-44.
11. De Sciscio P, Brubert J, De Sciscio M, Serrani M, Stasiak J, Moggridge GD. Quantifying the shift toward transcatheter aortic valve replacement in low-risk patients: A meta-analysis. Circ Cardiovasc Qual Outcomes. 2017;10(6) e003287.
12. NICE. Transcatheter aortic valve implantation for aortic stenosis. IPG586 2017 [cited 4 April 2019]; Available from: https://www.nice.org.uk/guidance/ipg586
13. Leon MB, Smith CR, Mack MJ, Makkar RR, Svensson LG, Kodali SK*, et al.* Transcatheter or surgical aortic-valve replacement in intermediate-risk patients. N Engl J Med. 2016;374(17):1609-20.
14. Reardon MJ, Van Mieghem NM, Popma JJ, Kleiman NS, Sondergaard L, Mumtaz M*, et al.* Surgical or transcatheter aortic-valve replacement in intermediate-risk patients. N Engl J Med. 2017;376(14):1321-31.

15. Baron SJ, Arnold SV, Wang K, Magnuson EA, Chinnakondepali K, Makkar R*, et al.* 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 Cardiol. 2017;2(8):837-45.
16. Bestehorn K, Bestehorn M, Fleck E. 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. 2015;31(12):2157-63.
17. Brennan JM, Thomas L, Cohen DJ, Shahian D, Wang A, Mack MJ*, et al.* Transcatheter versus surgical aortic valve replacement: propensity-matched comparison. J Am Coll Cardiol. 2017;70(4):439-50.
18. British Cardiovascular Intervention Society (BCIS) and the Society of Cardiothoracic Surgeons (SCTS). Transcatheter Aortic Valve Implantation (TAVI). A position statement. 2008.[cited 4 April 2019]; Available from: http://www.bcis.org.uk/wp-content/uploads/2016/12/BCIS-SCTS-position-statement.pdf
19. Pagano D, Kappetein AP, Sousa-Uva M, Beyersdorf F, Klautz R, Mohr F*, et al.* EACTS clinical statement: guidance for the provision of adult cardiac surgery. Eur J Cardiothorac Surg. 2016;50(6):1006-9.
20. 20. Bavaria JE, Tommaso CL, Brindis RG, Carroll JD, Deeb GM, Feldman TE*, et al.* 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, the American College of Cardiology, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons. Ann Thorac Surg. 2019; 107(2):650-684.
21. Badheka AO, Patel NJ, Panaich SS, Patel SV, Jhamnani S, Singh V*, et al.* Effect of hospital volume on outcomes of transcatheter aortic valve implantation. Am J Cardiol. 2015;116(4):587-94.
22. de Biasi AR, Paul S, Nasar A, Girardi LN, Salemi A. National analysis of short-term outcomes and volume-outcome relationships for transcatheter aortic valve replacement in the era of commercialization. Cardiology. 2016;133(1):58-68.
23. Kim LK, Minutello RM, Feldman DN, Swaminathan RV, Bergman G, Singh H*, et al.* Association between transcatheter aortic valve implantation volume and outcomes in the United States. Am J Cardiol. 2015;116(12):1910-5.
24. Khera S, Kolte D, Gupta T, Goldsweig A, Velagapudi P, Kalra A*, et al.* Association between hospital volume and 30-day readmissions following transcatheter aortic valve replacement. JAMA Cardiol. 2017;2(7):732-41.
25. Kaier K, Oettinger V, Reinecke H, Schmoor C, Frankenstein L, Vach W*, et al.* Volume-outcome relationship in transcatheter aortic valve implantations in Germany 2008-2014: a secondary data analysis of electronic health records. BMJ Open. 2018;8(7):e020204.
26. Ando T, Adegbala O, Villablanca PA, Shokr M, Akintoye E, Briasoulis A*, et al.* Failure to rescue, hospital volume, and in-hospital mortality after transcatheter aortic valve implantation. Am J Cardiol. 2018;122(5):828-32.
27. Bestehorn K, Eggebrecht H, Fleck E, Bestehorn M, Mehta RH, Kuck KH. Volume-outcome relationship with transfemoral transcatheter aortic valve implantation (TAVI): insights from the compulsory German Quality Assurance Registry on Aortic Valve Replacement (AQUA). EuroIntervention. 2017;13(8):914-20.
28. Carroll JD, Vemulapalli S, Dai D, Matsouaka R, Blackstone E, Edwards F*, et al.* Procedural experience for transcatheter aortic valve replacement and relation to outcomes: The STS/ACC TVT Registry. J Am Coll Cardiol. 2017;70(1):29-41.

29. Verma DR, Pershad Y, Lazkani M, Fang K, Morris M, Pershad A. Volume-outcome relationships for transcatheter aortic valve replacement-risk-adjusted and volume stratified analysis of TAVR outcomes. Indian Heart J. 2017;69(6):700-6.
30. Wassef AWA, Rodes-Cabau J, Liu Y, Webb JG, Barbanti M, Munoz-Garcia AJ*, et al.* The learning curve and annual procedure volume standards for optimum outcomes of transcatheter aortic valve replacement: findings from an international registry. JACC Cardiovasc Interv. 2018;11(17):1669-79.
31. Rogers T, Khan JM, Edelman JJ, Waksman R. Summary of the 2018 Medicare Evidence Development & Coverage Advisory Committee (MEDCAC) for transcatheter aortic valve replacement. Cardiovasc Revasc Med. 2018; 19(8):964-70.
32. Baumbusch J, Lauck SB, Achtem L, O'Shea T, Wu S, Banner D. Understanding experiences of undergoing transcatheter aortic valve implantation: one-year follow-up. Eur J Cardiovasc Nurs. 2018;17(3):280-8.
33. Olsson K, Naslund U, Nilsson J, Hornsten A. Patients' experiences of the transcatheter aortic valve implantation trajectory: A grounded theory study. Nurs Open. 2018;5(2):149-57.
34. Astin F, Horrocks J, McLenachan J, Blackman DJ, Stephenson J, Closs SJ. The impact of transcatheter aortic valve implantation on quality of life: A mixed methods study. Heart Lung. 2017;46(6):432-8.
35. Carroll C, Booth A, Lloyd-Jones M. Should we exclude inadequately reported studies from aualitative systematic reviews? An evaluation of sensitivity analyses in two case study reviews. Qual Health Res. 2012;22(10):1425-34.
36. Lauck SB, Baumbusch J, Achtem L, Forman JM, Carroll SL, Cheung A*, et al.* Factors influencing the decision of older adults to be assessed for transcatheter aortic valve implantation: An exploratory study. Eur J Cardiovasc Nurs. 2016;15(7):486-94.
37. Olsson K, Naslund U, Nilsson J, Hornsten A. Patients' decision making about undergoing transcatheter aortic valve implantation for severe aortic stenosis. J Cardiovasc Nurs. 2016;31(6):523-8.
38. Skaar E, Ranhoff AH, Nordrehaug JE, Forman DE, Schaufel MA. Conditions for autonomous choice: A qualitative study of older adults? experience of decision-making in TAVR. J of Geriatr Cardiol. 2017;14(1):42-8.
39. Baron SJ, Wang K, House JA, Magnuson EA, Reynolds MR, Makkar R*, et al.* Cost-effectiveness of transcatheter vs. surgical aortic valve replacement in patients with severe aortic stenosis at intermediate risk:Results from the PARTNER 2 Trial. Circulation. 2019 ;139(7):877-88.
40. Goodall G, Lamotte M, Ramos M, Maunoury F, Pejchalova B, de Pouvourville G. Cost-effectiveness analysis of the SAPIEN 3 TAVI valve compared with surgery in intermediate-risk patients. J Med Econ. 2019;22(4):289-96.
41. Tam DY, Hughes A, Fremes SE, Youn S, Hancock-Howard RL, Coyte PC*, et al.* A cost-utility analysis of transcatheter versus surgical aortic valve replacement for the treatment of aortic stenosis in the population with intermediate surgical risk. J Thorac Cardiovasc Surg. 2018;155(5):1978-88.
42. Tam DY, Hughes A, Wijeysundera HC, Fremes SE. Cost-effectiveness of self-expandable transcatheter aortic valves in intermediate-risk patients. Ann Thorac Surg. 2018;106(3):676-83.
43. Kodera S, Kiyosue A, Ando J, Komuro I. Cost effectiveness of transcatheter aortic valve implantation in patients with aortic stenosis in Japan. J Cardiol. 2018;71(3):223-9.
44. Salaun E, Clavel MA, Rodes-Cabau J, Pibarot P. Bioprosthetic aortic valve durability in the era of transcatheter aortic valve implantation. Heart. 2018;104(16):1323-32.

Appendix 1: A cost-utility analysis of TAVI versus SAVR in intermediate risk patients with severe aortic stenosis from a Scottish perspective

Introduction

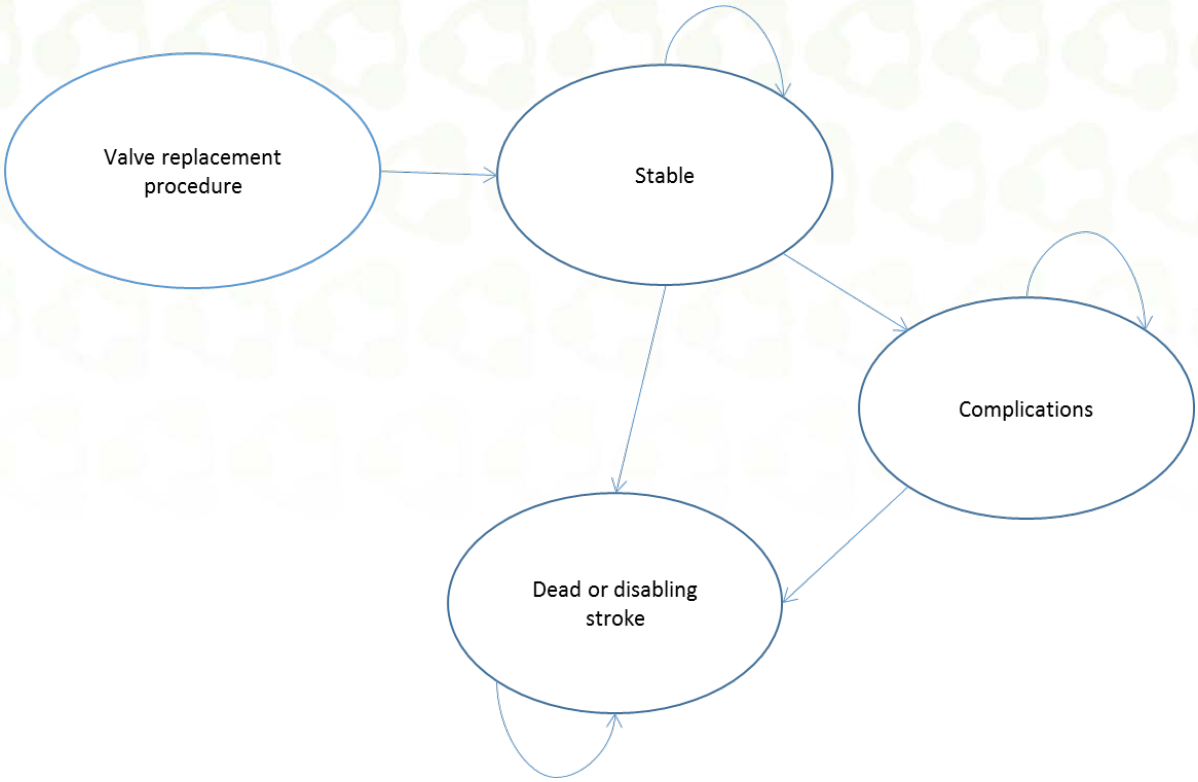
Transcatheter aortic valve implantation (TAVI) has been shown to be non-inferior to surgical aortic valve replacement (SAVR) in the intermediate risk population classified using the Society of Thoracic Surgeons (STS) score in two recent large non-inferiority randomised clinical trials (RCTs)[1, 2]. However, the cost-effectiveness of TAVI in this population is unclear, with a range of economic evaluations reaching different results and conclusions[3-7], and with limited generalisability to the Scottish setting.

A comprehensive understanding of the clinical and economic implications of TAVI is necessary to enable appropriate funding decisions. Therefore, a cost-utility analysis from a Scottish perspective was conducted in order to inform decision-making around extending the availability of TAVI to the intermediate surgical risk population.

Model description

A cost-utility analysis was conducted using a probabilistic Markov model, which tracks a cohort of patients as they move through a series of four main health states across a lifetime horizon in discrete time cycles of one month. The model structure is depicted in Figure A1. All patients start in the 'Valve replacement procedure' health state where they undertake either TAVI or SAVR. Patients transition to and between the other three states ('Stable', 'Complications', or 'Death or disabling stroke') as they develop various complications, suffer a disabling stroke episode, or die. Transition probabilities are derived based on the published clinical data comparing TAVI with SAVR in intermediate risk patients, combined with general population mortality and a mortality adjustment factors specific to patients with severe aortic stenosis. Complications are assumed to be resolved within the cycle they occur.

Figure A1: Markov model structure



Patients derive health benefit (utility) within these health states which depends on the procedure undertaken. Patients also incur costs for the underlying procedure, as they develop various complications, or for routine follow-up. 'Death' and 'Disabling stroke' are absorbing states in the model within which patients do not incur any health utility and hence are pooled together, the only difference being that 'Disabling stroke' is associated with healthcare resource use and cost while 'Death' is not. The model tracks the total costs and health benefits accrued by patients in both procedure arms over their lifetime and estimates discounted incremental costs, life-years, quality adjusted-life years (QALYs) and incremental cost-effectiveness ratios (ICERs), using the standard 3.5% Treasury discount rate.

The structural uncertainty in the model is explored through a series of scenario analyses. First order parameter uncertainty is explored through a series of deterministic sensitivity analyses. Whereas the joint parameter uncertainty is explored through a series of probabilistic sensitivity analyses using second-order Monte Carlo simulations.

Clinical data (mortality and complications)

In the baseline analysis, all primary clinical endpoints were derived from the full intention-to-treat (ITT) population in PARTNER II which compared TAVI using the Sapien XT valve with SAVR in intermediate risk patients[1].

Clinical endpoints such as all-cause mortality, stroke, re-interventions and other complications are reported at follow-ups of 30 days, one year and two years in the trial.

Data corresponding to the first follow-up time point were used to derive transition probabilities during the first model cycle following the TAVI or SAVR procedure. The latter two follow-up time points were used to derive adjusted one-cycle probabilities that were applied in the model up to that respective follow-up. This approach assumes a uniform risk across the specified follow-up, i.e. a patient is as likely to develop stroke at three months as they are at eleven months from the intervention, with all these risks being informed by the observed risk at the one-year trial follow-up. The resulting transition probabilities derived from the PARTNER II full ITT population clinical endpoints are reported in Table A1.

Table A1: One-month cycle transition probabilities at 30-days, up to 1 year, and up to 2 years (%, derived from K-M estimates from PARTNER II full ITT population)

	At 30 days		Up to 1 year		Up to 2 years	
	TAVI	**SAVR**	**TAVI**	**SAVR**	**TAVI**	**SAVR**
Death from any cause or disabling stroke	6.2%	7.9%	0.9%	0.9%	0.5%	0.5%
Disabling stroke	3.2%	4.3%	0.2%	0.1%	0.1%	0.1%
Transient ischemic attack (TIA)	0.9%	0.4%	0.1%	0.1%	0.1%	0.0%
Non-disabling stroke	2.3%	1.8%	0.1%	0.1%	0.0%	0.0%
Myocardial infarction (MI)	1.2%	1.9%	0.1%	0.1%	0.1%	0.1%
Major vascular complication	7.9%	5.0%	0.0%	0.0%	0.0%	0.0%
Life-threatening or disabling bleeding	10.5%	43.4%	0.5%	0.3%	0.2%	0.2%
Acute kidney injury (stage III)	1.3%	3.1%	0.2%	0.2%	0.0%	0.1%
New atrial fibrillation	9.1%	26.4%	0.1%	0.1%	0.1%	0.0%
New permanent peacemaker	8.5%	6.8%	0.1%	0.2%	0.2%	0.1%
Endocarditis	0.0%	0.0%	0.1%	0.1%	0.0%	0.0%
Aortic-valve re-intervention	0.4%	0.0%	0.1%	0.0%	0.0%	0.0%
Coronary obstruction	0.4%	0.6%	0.0%	0.0%	0.0%	0.0%

Beyond the two year trial follow-up it was assumed that the risk of complications in both procedure arms was zero. Mortality post-trial follow-up was informed by general population

mortality adjusted for the age and gender distribution which was up-scaled by an adjustment hazard ratio of 1.15 to reflect the heightened risk of mortality in patients with severe aortic stenosis undertaking aortic valve replacement at intermediate risk[8]. The model cohort demographics were based on the PARTNER II population, which informed the mean starting age of the model cohort, gender distribution, as well as the distribution of access modality (transfemoral/transthoracic).

The impact of using alternative clinical data was explored in further scenario analyses which utilised clinical endpoints from the following studies comparing TAVI with SAVR in intermediate risk patients: PARTNER II ITT transfemoral population[1]; PARTNER II ITT transthoracic population[1]; PARTNER II as-treated population[1]; PARTNER S3i registry study (as-treated population) comparing Sapiens 3 with the surgical arm in PARTNER II[9]; PARTNER S3i as-treated transfemoral population[9]; SURTAVI ITT population[2]; and the SURTAVI modified-ITT population[2]. The transition probabilities derived from the clinical endpoints reported in these studies are detailed in Annex 1.

Costs and quality of life

All costs applied in the model were derived from UK data and are detailed in Table A2. Aggregated procedure costs were derived from local Scottish data including the following components: theatre, radiology, laboratory, other treatments and inpatient day. Additional costs associated to the subsequent length of stay (LoS) in various unit types linked to each procedure were also added. The reference cost of the TAVI procedure excludes the cost of the valve. Data on valve costs were provided by Scottish National Procurement which included a range of different valve brands and various price rebates for bulk purchases. The valve cost utilised in the base-case analysis was the balloon-expandable Sapiens valve without a rebate. A range of price rebates applies for bulk orders, the maximum rebate being reached for orders of [redacted] valves, quantity which may be considered to be in line with Scottish TAVI population projections. Complication costs were derived from a mix of NHS Reference Costs and clinical expert opinion. Differential follow-up costs were also applied at every twelve months in both procedure arms based on clinical expert opinion.

Table A2: Costs utilised in the analysis

	Estimate	Source
Procedure cost (top-down)		
TAVI using Transfemoral Approach	£10,141	Local Scottish PLICS data
Inpatient day	*£941*	Local Scottish PLICS data
Laboratory	*£105*	Local Scottish PLICS data

Other treatments	*£1,426*	Local Scottish PLICS data
Radiology	*£229*	Local Scottish PLICS data
Theatre	*£1,591*	Local Scottish PLICS data
Additional 3 x days LoS cardiology unit	*£5,850*	ISD data and expert opinion; based on cardiology stay in Edinburgh royal Infirmary or Golden Jubilee
TAVI using Other Approach	£12,091	Local Scottish PLICS data
Inpatient day	*£941*	Local Scottish PLICS data
Laboratory	*£105*	Local Scottish PLICS data
Other treatments	*£1,426*	Local Scottish PLICS data
Radiology	*£229*	Local Scottish PLICS data
Theatre	*£1,591*	Local Scottish PLICS data
Additional 4 x days LoS cardiology unit	*£7,800*	ISD data and expert opinion; based on cardiology stay in Edinburgh royal Infirmary or Golden Jubilee
SAVR	£19,165	Local Scottish PLICS data
Inpatient day	*£913*	Local Scottish PLICS data
Laboratory	*£86*	Local Scottish PLICS data
Other treatments	*£654*	Local Scottish PLICS data
Radiology	*£138*	Local Scottish PLICS data
Theatre	*£5,408*	Local Scottish PLICS data
Additional 1 x days LoS ICU	*£2,217*	ISD data and expert opinion
Additional 4 x days LoS cardiology unit	*£7,800*	ISD data and expert opinion; based on cardiology stay in Edinburgh royal Infirmary or Golden Jubilee

TAVI valve cost		
Sapien (Edwards)	[redacted]	Scottish National Procurement
Sapien (max rebate)	[redacted]	Scottish National Procurement
Sapien XT (Edwards)	[redacted]	Scottish National Procurement
Sapien XT (max rebate)	[redacted]	Scottish National Procurement
Sapien 3 (Edwards)	[redacted]	Scottish National Procurement
Sapien 3 (max rebate)	[redacted]	Scottish National Procurement
Sapien 3 Ultra (Edwards)	[redacted]	Scottish National Procurement
Sapien 3 Ultra (max rebate)	[redacted]	Scottish National Procurement
Centera (Edwards)	[redacted]	Scottish National Procurement
Centera (max rebate)	[redacted]	Scottish National Procurement
Evolut Pro (Medtronic)	[redacted]	Scottish National Procurement
Evolut R (Medtronic)	[redacted]	Scottish National Procurement
Portico (Abbott)	[redacted]	Scottish National Procurement
Allegra (NVT)	[redacted]	Scottish National Procurement

Acurate (Boston Scientific)	[redacted]	Scottish National Procurement
Lotus (Boston Scientific)	[redacted]	Scottish National Procurement
Complications costs		
Disabling stroke	£5,470	NHS Reference Costs 2017/2018
Transient ischemic attack (TIA)	£1,180	NHS Reference Costs 2017/2018
Non-disabling stroke	£2,214	NHS Reference Costs 2017/2018
Myocardial infarction (MI)	£1,665	NHS Reference Costs 2017/2018
Major vascular complication	£2,500	Expert opinion
Life-threatening or disabling bleeding	£1,000	Expert opinion
Acute kidney injury	£3,165	NHS Reference Costs 2017/2018
New atrial fibrillation	£500	Expert opinion
New permanent peacemaker	£3,947	NHS Reference Costs 2017/2018
Endocarditis	£3,935	NHS Reference Costs 2017/2018
Aortic-valve reintervention	£3,000	Expert opinion
Coronary obstruction	£1,000	Expert opinion
Follow-up costs		

TAVI follow-up	£317	Expert opinion
SAVR follow-up	£218	Expert opinion

The quality of life utilities used in the model were derived from EQ-5D values reported in the PARTNER II study according to time and intervention[10]. The trial reported baseline utilities in both arms, as well as change from baseline and between-group-differences at one month, one year and two years. In the surgical arm of the model, patients start with the baseline utility which changes over time as informed by the change from baseline reported in the trial. It is assumed the change occurs uniformly across time, i.e. the change from baseline utility to the utility reported at one year occurs in equal increments accrued at each model cycle. In the TAVI arm of the model, utility is informed by applying the between-group-differences reported in the trial to the utilities in the SAVR arm, assuming again that any changes occur uniformly across time. The resulting utilities at each model cycle in both arms are reported in Table A3.

Table A3: Health utility scores accrued at each cycle by each treatment arm in the model

Model cycle	**SAVR**	**Incremental TAVI vs SAVR**
T0	0.732	-
1st month	0.726	0.052
2nd month	0.732	0.047
3rd month	0.737	0.041
4th month	0.743	0.036
5th month	0.749	0.030
6th month	0.755	0.025
7th month	0.761	0.019
8th month	0.767	0.014
9th month	0.773	0.008
10th month	0.779	0.003
11th month	0.784	-0.003

12th month	0.790	-0.008
13th month	0.788	-0.007
14th month	0.785	-0.007
15th month	0.783	-0.006
16th month	0.780	-0.005
17th month	0.778	-0.004
18th month	0.775	-0.003
19th month	0.773	-0.002
20th month	0.770	-0.001
21st month	0.768	0.000
22nd month	0.765	0.001
23rd month	0.763	0.002
24th month	0.760	0.003
Post-24th month	0.732	0.000

No difference in utilities between arms was assumed past the two years trial follow-up and, in the absence of age-specific utility values for this patient population, the last utility derived in the SAVR arm was applied to all subsequent cycles. No additional disutilities were applied in the model due to complications as the effects of these were already captured by the population derived utility values. The trial reported modest differences in health utility scores which were often non-significant. In an alternative scenario analysis, between-group-differences in utilities reported across the trial follow-up that were not statistically significant were assumed to be zero.

Results

Base case

Base case results using clinical data from Partner II ITT cohort are presented in Table A4, showing a modest QALY gain (0.13) with TAVI versus SAVR over the patient lifetime at the expense of a considerable increase in cost (£12,945), resulting in a high incremental cost effectiveness ratio (ICER).

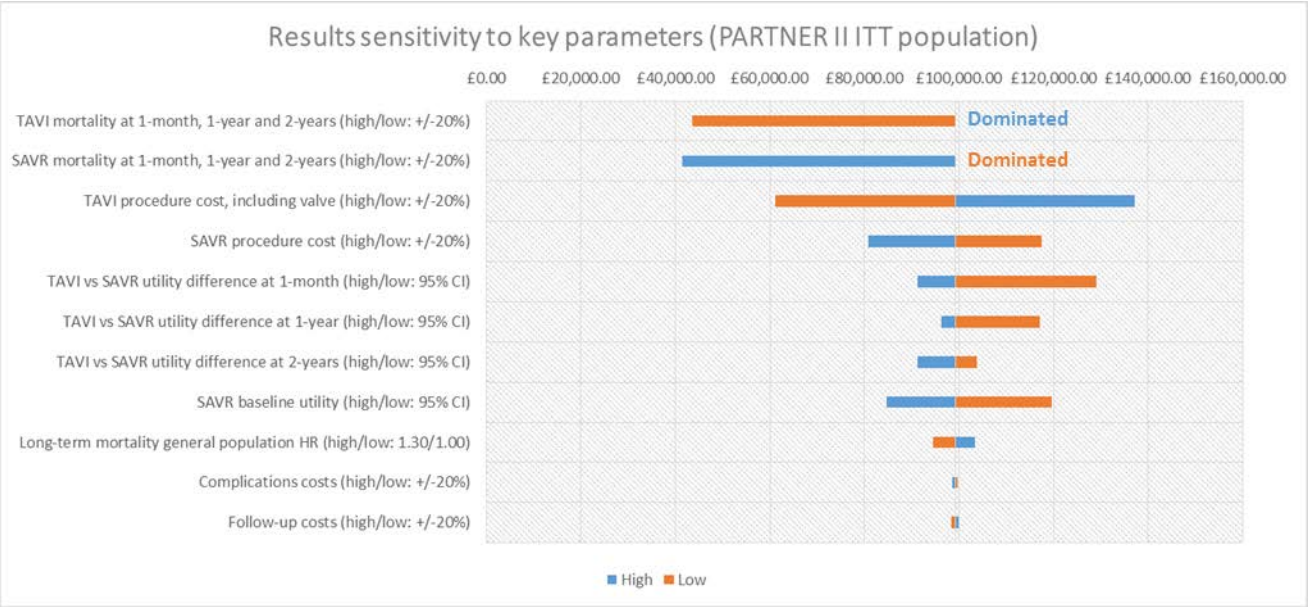
Table A4: Base case results (per patient, discounted, PARTNER II ITT population)

	TAVI	SAVR	Incremental
Procedure cost (including TAVI valve)	[redacted]	[redacted]	£12,713.07
Complications and follow-up cost	[redacted]	[redacted]	£231.49
Total cost	£34,995.93	£22,051.37	£12,944.56
Life Years	5.28	5.11	0.17
QALYs	3.93	3.80	0.13
ICER (£/LY)	-	-	£76,929.11
ICER(£/QALY)	-	-	**£98,965.02**

Deterministic sensitivity analysis

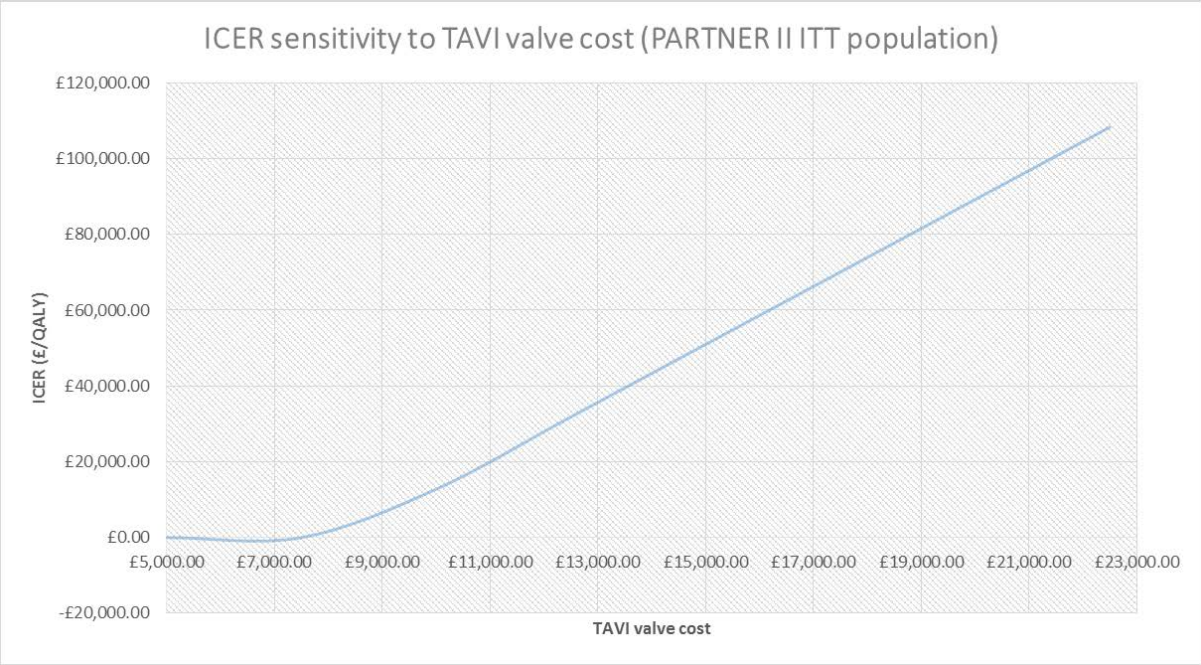
The sensitivity of the base case results to key model inputs is explored in the one-way deterministic sensitivity analysis reported in Figure A2. All model inputs were varied across their 95% CI or across a pre-defined range. The base case results seem to be most sensitive to procedure costs and trial reported mortality and between-group-differences in health utility scores.

Figure A2: One-way sensitivity analysis results



The effect of the TAVI valve cost on the base case ICER is further investigated in Figure A3 and shows this input to be a big driver of the cost-effectiveness of TAVI versus SAVR in the model. It can be seen that for valve prices lower than £12,000 the cost-effectiveness of TAVI looks more favourable.

Figure A3



Scenario analysis

Table A5 reports results for various scenario analyses which use different clinical inputs from alternative studies.

Table A5: Scenario analyses

Scenario	Base case assumption	New scenario assumption	ICER new scenario
Alternative populations			
Baseline (PARTNER II ITT population)			£98,965.02
PARTNER II transfemoral ITT population	Clinical outcomes for the model derived from PARTNER II ITT population	Clinical outcomes for the model derived from PARTNER II	£56,444.34

		transfemoral ITT population	
PARTNER II transthoracic ITT population	Clinical outcomes for the model derived from PARTNER II ITT population	Clinical outcomes for the model derived from PARTNER II transthoracic ITT population	Dominated
PARTNER II as-treated population	Clinical outcomes for the model derived from PARTNER II ITT population	Clinical outcomes for the model derived from PARTNER II as-treated population	£84,692.48
Partner S3i as-treated population	Clinical outcomes for the model derived from PARTNER II ITT population	Clinical outcomes for the model derived from Partner S3i as-treated population	£38,950.08
Partner S3i as-treated transfemoral population	Clinical outcomes for the model derived from PARTNER II ITT population	Clinical outcomes for the model derived from Partner S3i as-treated transfemoral population	£37,984.69
SURTAVI ITT population	Clinical outcomes for the model derived from PARTNER II ITT population with Sapien valve cost	Clinical outcomes for the model derived from SURTAVI ITT population with Medtronic Evolut R valve cost	£333,929.69
SURTAVI modified-ITT population	Clinical outcomes for the model derived from PARTNER II ITT population with Sapien valve cost	Clinical outcomes for the model derived from SURTAVI modified-ITT population with	£167,080.23

		Medtronic Evolut R valve cost	
Partner II ITT population			
Maximum TAVI valve price rebate	Utilises TAVI Sapiens valve price without a rebate	Applies maximum rebate to valve price (for quantities of [redacted] valves)	£68,192.70
NHS Reference Costs	Local PLICS data combined with LoS utilised to derive procedure costs	Procedure costs derived from NHS Reference Costs 2017/18	£98,965.02
Assume no difference in utilities past 1-month follow-up	Utilises all between-group-differences observed across the 2-year follow-up in PARTNER II	Utilising only the statistically significant between-group-difference observed at 1-month follow-up in PARTNER II	£95,498.51
Assume no difference in probability of major/life-threatening bleeding	Very large difference in major/life-threatening bleeding in favour of TAVI observed in PARTNER II	Utilising the same probability for this complication in both arms informed by the rate observed in the TAVI arm of the trial	£101,368.56
Only including complications which significantly differed between treatment arms in PARTNER II	Including all absolute rates for all complications observed in the trial	Where no statistically significant difference between treatment arms was observed, the same rate observed in TAVI	£265,662.10

		applies in both arms	
Only including complications which significantly differed between treatment arms in PARTNER II (except death from any cause or disabling stroke)	Including all absolute rates for all complications observed in the trial	Where no statistically significant difference between treatment arms was observed (except death from any cause or disabling stroke), the same rate observed in TAVI applies in both arms	£98,412.27
Shorter time horizon	15 years; 10 years; 5 years	20 years	£101,204.46; £113,865.80; £168,093.58
Different discount rate	0%; 7%	3.5%	£82,655.26; £116,615.75

Probabilistic sensitivity analysis (PSA)

A PSA was conducted to explore the joint parameter uncertainty in the model. Various probability distributions were assigned to all clinical, cost and utility inputs in the model as detailed in Annex 2. The parameters of the probability distributions were derived using the method of moments where possible, or assumed otherwise. A simulation was run by randomly sampling 1,000 set of model inputs and results. All these simulations are plotted in the cost-effectiveness plane in Figure A4. This shows that most of the simulations fall below commonly accepted cost-effectiveness thresholds for decision making, with TAVI being cost-effective versus SAVR in only 38.9% and 26.9% of the simulations at the £30,000/QALY and £20,000/QALY thresholds respectively. Moreover, TAVI was dominated by SAVR in 34.5% of the simulations. Separate PSA simulations were also run individually for the other scenarios explored that utilised alternative clinical inputs from PARTNER II subgroups, PARTNER S3i and SURTAVI, which are reported in Annex 3. Cost-effectiveness acceptability curves were also plotted based on these analyses as can be seen in Figure A5. These illustrate the probability of TAVI being cost-effective versus SAVR at various levels of the cost-effectiveness threshold under alternative scenarios.

Figure A4

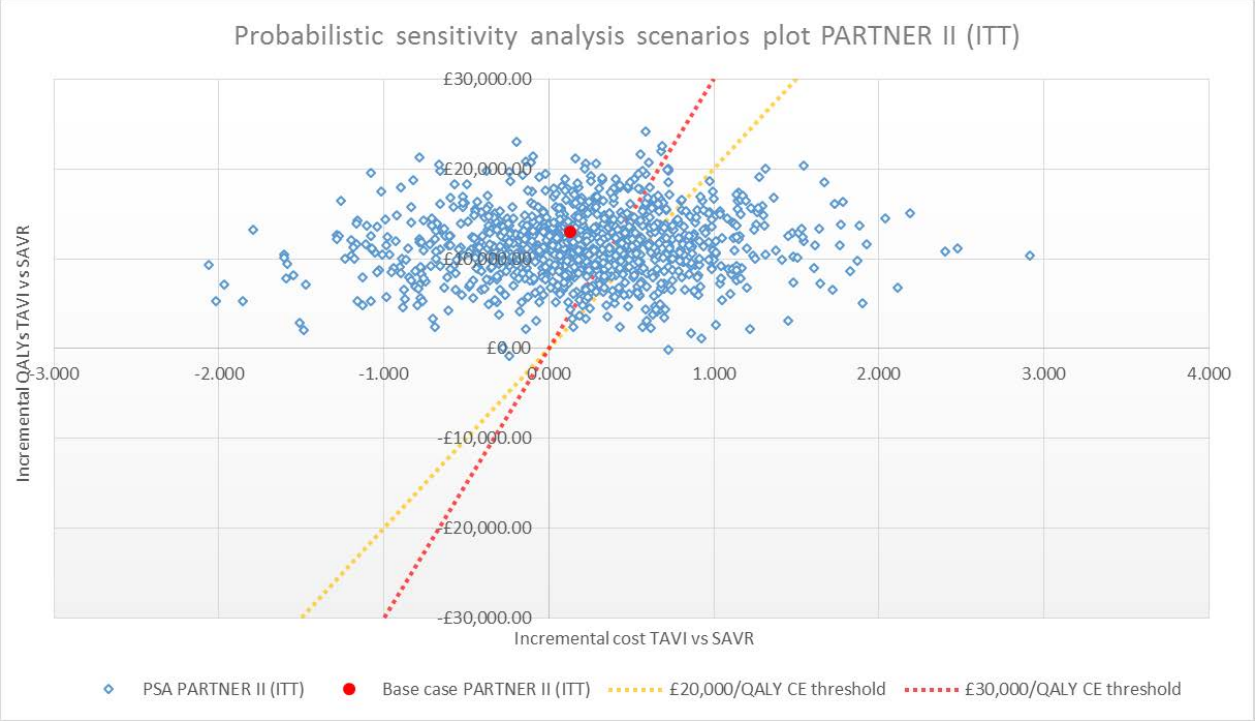
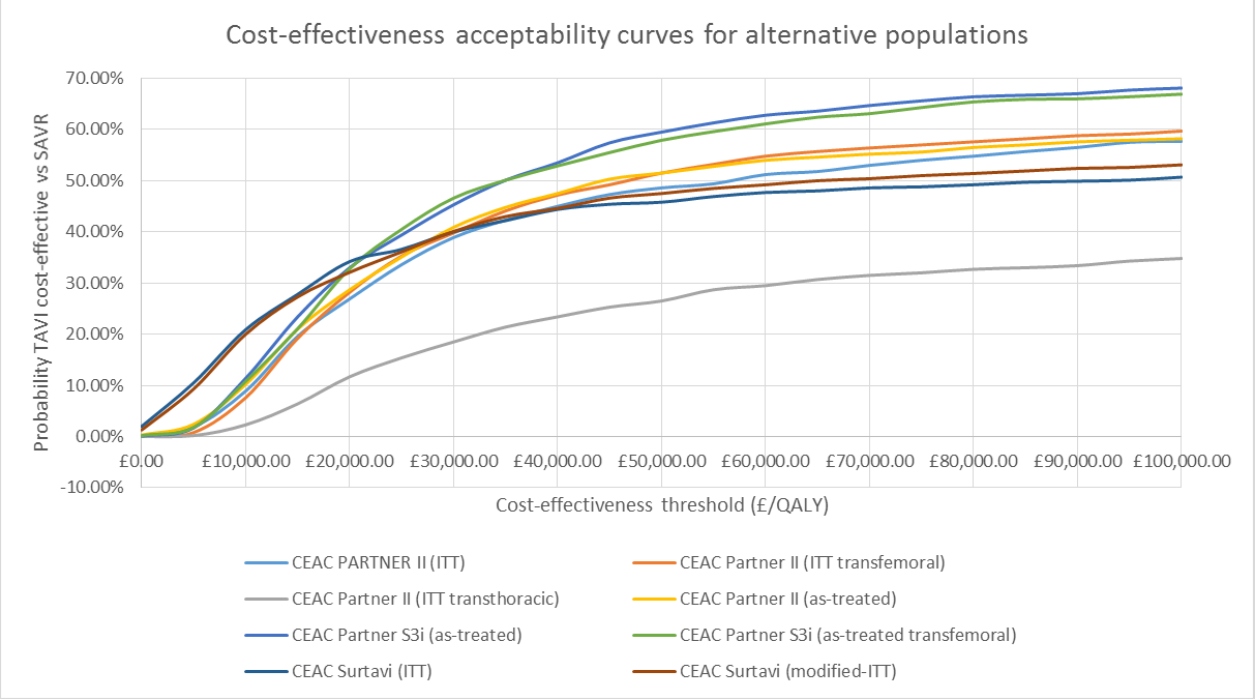


Figure A5



Discussion

This analysis explored the cost-effectiveness of TAVI versus SAVR in patients with severe aortic stenosis with an intermediate STS risk score from a Scottish perspective, utilising clinical data and utilities from the pivotal trials conducted in this population combined with

Scottish specific costs. TAVI was generally associated with high ICERs and low probabilities of being cost-effective against SAVR. The generalizability of these results is limited by the risk profile and patient characteristics of the study cohorts utilised to derive the model inputs for this analysis. TAVI may still be a cost-effective option in patients that would classify as intermediate risk based on their STS score but which are considered frail and have other comorbidities not captured in the trial populations.

It is important to recognise that the observed health status and complications results apply only to surviving patients at each time interval. If a new treatment results in a survival benefit compared with the alternative, it may paradoxically appear to result in worse long-term health status and complications than the alternative strategy owing to differential attrition of the sickest patients in the alternative treatment arm.

One caveat of the analysis is that the top-down estimates of the procedures costs are likely to have been derived from a heterogeneous mix of patient risk groups and hence may not accurately reflect the true cost in the intermediate group. These costs were varied in the sensitivity analysis and the uncertainty surrounding the estimates would have been captured in the probabilistic sensitivity analysis, but did not have an important impact on the results. Similarly, the reference costs used for complications are averaged across a mix of patients with varying comorbidities or underlying causes for developing the complications.

The PARTNER II trial was powered for the ITT and as-treated analysis, but not powered for transfemoral/transthoracic stratification. Utility scores were derived from the EQ-5D data collected within PARTNER II possibly utilising a US tariff, hence the utility scores may slightly differ if the UK tariff is used. All quality of life scales (apart from the KCCQ-OS score) from PARTNER II were considered secondary endpoints, and baseline EQ-5D health status was only available for 1,833 of 2,032 randomised patients; missing health status data at two years was 15.7% for SAVR and 11.9% for TAVR. Whilst missing data could have contributed to responder bias, there was no difference in baseline characteristics between patients with and without available health status data at 2 years, thereby suggesting that the effect of responder bias is likely minimal. Further, the trial was not blinded, which could have influenced patient-reported health status during follow-up.

The probabilistic sensitivity analyses did not account for the covariance and ordering between model inputs. This has the tendency to produce high cost-effectiveness likelihood as the variation across the many independent parameters of the model tends to cancel itself out, producing very little variation in effectiveness and underestimating the true uncertainty in the model. This is particularly important in situations with a large number of parameters and where the base case ICER is moderately close to the threshold.

Conclusion

Based on the results of this analysis, TAVI is unlikely to be a cost-effective option in Scotland in a population of patients with severe aortic stenosis, classified as intermediate risk based on the STS score, and which match the populations in the PARTNER II and SURTAVI trials. This conclusion was robust under an extensive range of scenarios and sensitivity analyses. The cost-effectiveness of TAVI in patients undertaking the procedure via transfemoral access is considerably more favourable than for transthoracic access but is still associated with high ICERs that are unlikely to offer good value for money for NHSScotland. The TAVI valve cost is a big driver of the cost-effectiveness of the procedure, with the base case ICER falling to more acceptable levels for valve costs lower than £12,000, but still subject to the underlying uncertainty.

References

1. Leon MB, Smith CR, Mack MJ, Makkar RR, Svensson LG, Kodali SK, et al. Transcatheter or surgical aortic-valve replacement in intermediate-risk patients. N Engl J Med. 2016;374(17):1609-20.
2. Reardon MJ, Van Mieghem NM, Popma JJ, Kleiman NS, Sondergaard L, Mumtaz M, et al. Surgical or transcatheter aortic-valve replacement in intermediate-risk patients. N Engl J Med. 2017;376(14):1321-31.
3. Goodall G, Lamotte M, Ramos M, Maunoury F, Pejchalova B, de Pouvourville G. Cost-effectiveness analysis of the SAPIEN 3 TAVI valve compared with surgery in intermediate-risk patients. J Med Econ. 2019;22(4):289-96.
4. Kodera S, Kiyosue A, Ando J, Komuro I. Cost effectiveness of transcatheter aortic valve implantation in patients with aortic stenosis in Japan. J Cardiol. 2018;71(3):223-9.
5. Baron SJ, Wang K, House JA, Magnuson EA, Reynolds MR, Makkar R, et al. Cost-effectiveness of transcatheter vs. surgical aortic valve replacement in patients with severe aortic stenosis at intermediate risk:Results from the PARTNER 2 Trial. Circulation. 2019 ;139(7):877-88.
6. Tam DY, Hughes A, Wijeysundera HC, Fremes SE. Cost-effectiveness of self-expandable transcatheter aortic valves in intermediate-risk patients. Ann Thorac Surg. 2018;106(3):676-83.
7. Tam DY, Hughes A, Fremes SE, Youn S, Hancock-Howard RL, Coyte PC, et al. A cost-utility analysis of transcatheter versus surgical aortic valve replacement for the treatment of aortic stenosis in the population with intermediate surgical risk. J Thorac Cardiovasc Surg. 2018;155(5):1978-88.
8. Reynolds MR, Lei Y, Wang K, Chinnakondepalli K, Vilain KA, Magnuson EA*, et al.* Cost-effectiveness of transcatheter aortic valve replacement with a self-expanding prosthesis versus surgical aortic valve replacement. J Am Coll of Cardiol. 2016;67(1):29-38.
9. Brennan JM, Thomas L, Cohen DJ, Shahian D, Wang A, Mack MJ, et al. Transcatheter versus surgical aortic valve replacement: propensity-matched comparison. J Am Coll Cardiol. 2017;70(4):439-50.
10. Baron SJ, Arnold SV, Wang K, Magnuson EA, Chinnakondepali K, Makkar R, et al. 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 Cardiol. 2017;2(8):837-45.

Annex 1: Clinical endpoints for alternative study populations

Table A6: One-month cycle transition probabilities at 30-days, up to 1 year, and up to 2 years (%, derived from K-M estimates from PARTNER II transfemoral ITT population)

	At 30 days		Up to 1 year		Up to 2 years	
	TAVI	**SAVR**	**TAVI**	**SAVR**	**TAVI**	**SAVR**
Death from any cause or disabling stroke	4.9%	7.7%	0.7%	0.8%	0.4%	0.5%
Disabling stroke	2.3%	4.2%	0.2%	0.2%	0.1%	0.1%
Transient ischemic attack (TIA)	0.9%	0.3%	0.2%	0.1%	0.1%	0.0%
Non-disabling stroke	1.8%	2.1%	0.1%	0.1%	0.0%	0.0%
Myocardial infarction (MI)	0.6%	1.8%	0.1%	0.1%	0.1%	0.1%
Major vascular complication	8.5%	3.9%	0.0%	0.0%	0.0%	0.0%
Life-threatening or disabling bleeding	6.7%	41.4%	0.4%	0.3%	0.2%	0.2%
Acute kidney injury (stage III)	0.5%	3.0%	0.2%	0.2%	0.0%	0.1%
New atrial fibrillation	4.9%	26.7%	0.1%	0.1%	0.1%	0.0%
New permanent peacemaker	8.1%	7.1%	0.1%	0.2%	0.2%	0.1%
Endocarditis	0.0%	0.0%	0.1%	0.1%	0.1%	0.0%
Aortic-valve re-intervention	0.4%	0.0%	0.1%	0.1%	0.0%	0.0%
Coronary obstruction	0.1%	0.6%	0.0%	0.0%	0.0%	0.0%

Table A7: One-month cycle transition probabilities at 30-days, up to 1 year, and up to 2 years (%, derived from K-M estimates from PARTNER II transthoracic ITT population)

	At 30 days		Up to 1 year		Up to 2 years	
	TAVI	**SAVR**	**TAVI**	**SAVR**	**TAVI**	**SAVR**

Death from any cause or disabling stroke	10.2%	8.7%	1.3%	1.0%	0.6%	0.5%
Disabling stroke	6.0%	4.5%	0.1%	0.0%	0.1%	0.1%
Transient ischemic attack (TIA)	0.9%	0.8%	0.1%	0.1%	0.1%	0.1%
Non-disabling stroke	3.8%	0.8%	0.0%	0.1%	0.0%	0.1%
Myocardial infarction (MI)	3.0%	2.1%	0.1%	0.0%	0.1%	0.1%
Major vascular complication	5.9%	8.6%	0.1%	0.0%	0.1%	0.0%
Life-threatening or disabling bleeding	22.6%	49.8%	0.8%	0.5%	0.1%	0.3%
Acute kidney injury (stage III)	3.9%	3.4%	0.3%	0.1%	0.1%	0.1%
New atrial fibrillation	22.8%	25.4%	0.1%	0.1%	0.0%	0.0%
New permanent peacemaker	9.9%	5.9%	0.1%	0.1%	0.2%	0.2%
Endocarditis	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Aortic-valve re-intervention	0.4%	0.0%	0.1%	0.0%	0.1%	0.0%
Coronary obstruction	1.3%	0.4%	0.0%	0.0%	0.0%	0.0%

Table A8: One-month cycle transition probabilities at 30-days, up to 1 year, and up to 2 years (%, derived from K-M estimates from PARTNER II as-treated population)

	At 30 days		**Up to 1 year**		**Up to 2 years**	
	TAVI	**SAVR**	**TAVI**	**SAVR**	**TAVI**	**SAVR**
Death from any cause or disabling stroke	5.7%	8.0%	0.8%	0.9%	0.5%	0.5%
Disabling stroke	3.2%	4.4%	0.2%	0.1%	0.1%	0.1%
Transient ischemic attack (TIA)	0.9%	0.4%	0.1%	0.1%	0.1%	0.0%
Non-disabling stroke	2.3%	1.7%	0.1%	0.1%	0.0%	0.0%
Myocardial infarction (MI)	1.1%	1.9%	0.1%	0.1%	0.1%	0.1%

Major vascular complication	8.1%	5.4%	0.0%	0.0%	0.0%	0.0%
Life-threatening or disabling bleeding	10.5%	46.9%	0.5%	0.3%	0.2%	0.2%
Acute kidney injury (stage III)	1.2%	3.3%	0.2%	0.2%	0.0%	0.1%
New atrial fibrillation	9.1%	28.3%	0.1%	0.1%	0.1%	0.0%
New permanent peacemaker	8.6%	7.3%	0.1%	0.2%	0.2%	0.1%
Endocarditis	0.0%	0.0%	0.1%	0.1%	0.0%	0.0%
Aortic-valve re-intervention	0.4%	0.0%	0.1%	0.0%	0.0%	0.0%
Coronary obstruction	0.4%	0.6%	0.0%	0.0%	0.0%	0.0%

Table A9: One-month cycle transition probabilities at 30-days, up to 1 year, and up to 2 years (%, derived from K-M estimates from Partner S3i as-treated population)

	At 30 days		**Up to 1 year**		**Up to 2 years**	
	TAVI	**SAVR**	**TAVI**	**SAVR**	**TAVI**	**SAVR**
Death from any cause or disabling stroke	2.0%	8.0%	0.6%	0.9%	0.6%	0.6%
Disabling stroke	1.0%	4.4%	0.1%	0.1%	0.0%	0.0%
Transient ischemic attack (TIA)	0.4%	0.4%	0.1%	0.1%	0.0%	0.0%
Non-disabling stroke	1.7%	1.7%	0.1%	0.1%	0.0%	0.0%
Myocardial infarction (MI)	0.3%	1.9%	0.0%	0.1%	0.0%	0.0%
Major vascular complication	6.1%	5.4%	0.0%	0.0%	0.0%	0.0%
Life-threatening or disabling bleeding	4.6%	46.7%	0.0%	0.0%	0.0%	0.0%
Acute kidney injury (stage III)	0.5%	3.3%	0.0%	0.0%	0.0%	0.0%
New atrial fibrillation	5.0%	28.3%	0.1%	0.1%	0.0%	0.0%
New permanent peacemaker	10.2%	7.3%	0.2%	0.2%	0.0%	0.0%
Endocarditis	0.2%	0.0%	0.1%	0.1%	0.0%	0.0%

Aortic-valve re-intervention	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%
Coronary obstruction	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%

Table A10: One-month cycle transition probabilities at 30-days, up to 1 year, and up to 2 years (%, derived from K-M estimates from Partner S3i as-treated transfemoral population)

	At 30 days		Up to 1 year		Up to 2 years	
	TAVI	**SAVR**	**TAVI**	**SAVR**	**TAVI**	**SAVR**
Death from any cause or disabling stroke	1.7%	7.5%	0.5%	0.9%	0.6%	0.6%
Disabling stroke	0.7%	4.2%	0.1%	0.2%	0.0%	0.0%
Transient ischemic attack (TIA)	0.4%	0.3%	0.1%	0.1%	0.0%	0.0%
Non-disabling stroke	1.8%	2.1%	0.1%	0.1%	0.0%	0.0%
Myocardial infarction (MI)	0.3%	1.8%	0.1%	0.1%	0.0%	0.0%
Major vascular complication	6.4%	4.2%	0.0%	0.0%	0.0%	0.0%
Life-threatening or disabling bleeding	3.6%	44.2%	0.0%	0.0%	0.0%	0.0%
Acute kidney injury (stage III)	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
New atrial fibrillation	3.2%	28.5%	0.1%	0.1%	0.0%	0.0%
New permanent peacemaker	10.5%	7.6%	0.2%	0.2%	0.0%	0.0%
Endocarditis	0.2%	0.0%	0.1%	0.1%	0.0%	0.0%
Aortic-valve re-intervention	0.1%	0.0%	0.1%	0.1%	0.0%	0.0%
Coronary obstruction	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%

Table A11: One-month cycle transition probabilities at 30-days, up to 1 year, and up to 2 years (%, derived from K-M estimates from SURTAVI ITT population)

	At 30 days		Up to 1 year		Up to 2 years	
	TAVI	**SAVR**	**TAVI**	**SAVR**	**TAVI**	**SAVR**

Death from any cause or disabling stroke	2.7%	3.2%	0.5%	0.5%	0.5%	0.5%
Disabling stroke	1.1%	2.2%	0.1%	0.1%	0.0%	0.1%
Transient ischemic attack (TIA)	0.9%	0.7%	0.2%	0.1%	0.1%	0.1%
Non-disabling stroke	1.6%	2.8%	0.2%	0.1%	0.0%	0.1%
Myocardial infarction (MI)	0.9%	0.7%	0.2%	0.1%	0.1%	0.1%
Major vascular complication	5.0%	6.1%	0.8%	0.7%	0.6%	0.6%
Life-threatening or disabling bleeding	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Acute kidney injury (stage III)	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
New atrial fibrillation	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
New permanent peacemaker	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Endocarditis	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Aortic-valve re-intervention	0.7%	0.2%	0.1%	0.0%	0.1%	0.0%
Coronary obstruction	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%

Table A12: One-month cycle transition probabilities at 30-days, up to 1 year, and up to 2 years (%, derived from K-M estimates from SURTAVI modified-ITT population)

	At 30 days		**Up to 1 year**		**Up to 2 years**	
	TAVI	**SAVR**	**TAVI**	**SAVR**	**TAVI**	**SAVR**
Death from any cause or disabling stroke	2.8%	3.9%	0.5%	0.5%	0.4%	0.5%
Disabling stroke	1.2%	2.5%	0.1%	0.1%	0.0%	0.1%
Transient ischemic attack (TIA)	1.5%	1.1%	0.2%	0.1%	0.1%	0.1%
Non-disabling stroke	2.2%	3.1%	0.1%	0.1%	0.1%	0.1%
Myocardial infarction (MI)	0.9%	1.0%	0.1%	0.1%	0.1%	0.1%

Major vascular complication	6.0%	1.1%	0.0%	0.0%	0.0%	0.0%
Life-threatening or disabling bleeding	12.2%	9.3%	0.0%	0.0%	0.0%	0.0%
Acute kidney injury (stage III)	1.7%	4.4%	0.0%	0.0%	0.0%	0.0%
New atrial fibrillation	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
New permanent peacemaker	25.9%	6.6%	0.0%	0.0%	0.0%	0.0%
Endocarditis	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Aortic-valve re-intervention	0.9%	0.2%	0.1%	0.0%	0.1%	0.0%
Coronary obstruction	0.2%	0.0%	0.0%	0.0%	0.0%	0.0%

Annex 2: Probability distributions assigned to model inputs and estimated probability parameters (PARTNER II ITT population)

Parameter	Sample mean	SE	Distribution	Alpha	Beta	Point estimate
TAVI Death from any cause or disabling stroke at 1m	2.70%	n/a	Beta	2.70	97.30	2.36%
TAVI Disabling stroke at 1m	1.10%	n/a	Beta	1.10	98.90	4.30%
TAVI Transient ischemic attack (TIA) at 1m	0.90%	n/a	Beta	0.90	99.10	1.33%
TAVI Non-disabling stroke at 1m	1.60%	n/a	Beta	1.60	98.40	1.22%
TAVI Myocardial infarction (MI) at 1m	0.90%	n/a	Beta	0.90	99.10	0.21%
TAVI Major vascular complication at 1m	5.00%	n/a	Beta	5.00	95.00	7.93%
TAVI Life-threatening or disabling bleeding at 1m	0.00%	n/a	Beta	1.00	99.00	0.81%
TAVI Acute kidney injury (stage III) at 1m	0.00%	n/a	Beta	1.00	99.00	0.53%
TAVI New atrial fibrillation at 1m	0.00%	n/a	Beta	1.00	99.00	4.64%
TAVI New permanent peacemaker at 1m	0.00%	n/a	Beta	1.00	99.00	1.94%
TAVI Endocarditis at 1m	0.00%	n/a	Beta	1.00	99.00	3.08%
TAVI Aortic-valve re-intervention at 1m	0.70%	n/a	Beta	0.70	99.30	0.57%
TAVI Coronary obstruction at 1m	0.00%	n/a	Beta	1.00	99.00	0.10%

SAVR Death from any cause or disabling stroke at 1m	3.20%	n/a	Beta	3.20	96.80	3.48%
SAVR Disabling stroke at 1m	2.20%	n/a	Beta	2.20	97.80	2.20%
SAVR Transient ischemic attack (TIA) at 1m	0.70%	n/a	Beta	0.70	99.30	0.02%
SAVR Non-disabling stroke at 1m	2.80%	n/a	Beta	2.80	97.20	2.92%
SAVR Myocardial infarction (MI) at 1m	0.70%	n/a	Beta	0.70	99.30	0.05%
SAVR Major vascular complication at 1m	6.10%	n/a	Beta	6.10	93.90	1.93%
SAVR Life-threatening or disabling bleeding at 1m	0.00%	n/a	Beta	1.00	99.00	1.05%
SAVR Acute kidney injury (stage III) at 1m	0.00%	n/a	Beta	1.00	99.00	2.62%
SAVR New atrial fibrillation at 1m	0.00%	n/a	Beta	1.00	99.00	1.43%
SAVR New permanent peacemaker at 1m	0.00%	n/a	Beta	1.00	99.00	1.44%
SAVR Endocarditis at 1m	0.00%	n/a	Beta	1.00	99.00	0.09%
SAVR Aortic-valve re-intervention at 1m	0.20%	n/a	Beta	0.20	99.80	0.04%
SAVR Coronary obstruction at 1m	0.00%	n/a	Beta	1.00	99.00	3.40%
TAVI Death from any cause or disabling stroke at 1y	0.54%	n/a	Beta	0.54	99.46	0.40%
TAVI Disabling stroke at 1y	0.10%	n/a	Beta	0.10	99.90	0.04%
TAVI Transient ischemic attack (TIA) at 1y	0.23%	n/a	Beta	0.23	99.77	0.24%

TAVI Non-disabling stroke at 1y	0.19%	n/a	Beta	0.19	99.81	0.87%
TAVI Myocardial infarction (MI) at 1y	0.23%	n/a	Beta	0.23	99.77	0.08%
TAVI Major vascular complication at 1y	0.84%	n/a	Beta	0.84	99.16	1.49%
TAVI Life-threatening or disabling bleeding at 1y	0.00%	n/a	Beta	1.00	99.00	2.58%
TAVI Acute kidney injury (stage III) at 1y	0.00%	n/a	Beta	1.00	99.00	0.60%
TAVI New atrial fibrillation at 1y	0.00%	n/a	Beta	1.00	99.00	0.19%
TAVI New permanent peacemaker at 1y	0.00%	n/a	Beta	1.00	99.00	0.30%
TAVI Endocarditis at 1y	0.00%	n/a	Beta	1.00	99.00	0.44%
TAVI Aortic-valve re-intervention at 1y	0.12%	n/a	Beta	0.12	99.88	0.00%
TAVI Coronary obstruction at 1y	0.00%	n/a	Beta	1.00	99.00	3.38%
SAVR Death from any cause or disabling stroke at 1y	0.54%	n/a	Beta	0.54	99.46	0.88%
SAVR Disabling stroke at 1y	0.14%	n/a	Beta	0.14	99.86	0.02%
SAVR Transient ischemic attack (TIA) at 1y	0.12%	n/a	Beta	0.12	99.88	0.00%
SAVR Non-disabling stroke at 1y	0.09%	n/a	Beta	0.09	99.91	0.00%
SAVR Myocardial infarction (MI) at 1y	0.12%	n/a	Beta	0.12	99.88	0.02%
SAVR Major vascular complication at 1y	0.67%	n/a	Beta	0.67	99.33	0.33%

SAVR Life-threatening or disabling bleeding at 1y	0.00%	n/a	Beta	1.00	99.00	0.07%
SAVR Acute kidney injury (stage III) at 1y	0.00%	n/a	Beta	1.00	99.00	0.84%
SAVR New atrial fibrillation at 1y	0.00%	n/a	Beta	1.00	99.00	2.44%
SAVR New permanent peacemaker at 1y	0.00%	n/a	Beta	1.00	99.00	1.13%
SAVR Endocarditis at 1y	0.00%	n/a	Beta	1.00	99.00	0.15%
SAVR Aortic-valve re-intervention at 1y	0.03%	n/a	Beta	0.03	99.97	0.00%
SAVR Coronary obstruction at 1y	0.00%	n/a	Beta	1.00	99.00	3.74%
TAVI Death from any cause or disabling stroke at 2y	0.46%	n/a	Beta	0.46	99.54	0.14%
TAVI Disabling stroke at 2y	0.03%	n/a	Beta	0.03	99.97	0.00%
TAVI Transient ischemic attack (TIA) at 2y	0.09%	n/a	Beta	0.09	99.91	0.00%
TAVI Non-disabling stroke at 2y	0.04%	n/a	Beta	0.04	99.96	0.00%
TAVI Myocardial infarction (MI) at 2y	0.09%	n/a	Beta	0.09	99.91	0.00%
TAVI Major vascular complication at 2y	0.56%	n/a	Beta	0.56	99.44	0.02%
TAVI Life-threatening or disabling bleeding at 2y	0.00%	n/a	Beta	1.00	99.00	2.77%
TAVI Acute kidney injury (stage III) at 2y	0.00%	n/a	Beta	1.00	99.00	1.45%
TAVI New atrial fibrillation at 2y	0.00%	n/a	Beta	1.00	99.00	0.62%

TAVI New permanent peacemaker at 2y	0.00%	n/a	Beta	1.00	99.00	2.62%
TAVI Endocarditis at 2y	0.00%	n/a	Beta	1.00	99.00	1.51%
TAVI Aortic-valve re-intervention at 2y	0.06%	n/a	Beta	0.06	99.94	0.00%
TAVI Coronary obstruction at 2y	0.00%	n/a	Beta	1.00	99.00	1.54%
SAVR Death from any cause or disabling stroke at 2y	0.50%	n/a	Beta	0.50	99.50	0.21%
SAVR Disabling stroke at 2y	0.08%	n/a	Beta	0.08	99.92	0.27%
SAVR Transient ischemic attack (TIA) at 2y	0.09%	n/a	Beta	0.09	99.91	0.00%
SAVR Non-disabling stroke at 2y	0.07%	n/a	Beta	0.07	99.93	0.00%
SAVR Myocardial infarction (MI) at 2y	0.09%	n/a	Beta	0.09	99.91	0.00%
SAVR Major vascular complication at 2y	0.58%	n/a	Beta	0.58	99.42	0.21%
SAVR Life-threatening or disabling bleeding at 2y	0.00%	n/a	Beta	1.00	99.00	1.32%
SAVR Acute kidney injury (stage III) at 2y	0.00%	n/a	Beta	1.00	99.00	0.39%
SAVR New atrial fibrillation at 2y	0.00%	n/a	Beta	1.00	99.00	0.29%
SAVR New permanent peacemaker at 2y	0.00%	n/a	Beta	1.00	99.00	0.11%
SAVR Endocarditis at 2y	0.00%	n/a	Beta	1.00	99.00	0.03%
SAVR Aortic-valve re-intervention at 2y	0.02%	n/a	Beta	0.02	99.98	0.00%

SAVR Coronary obstruction at 2y	0.00%	n/a	Beta	1.00	99.00	0.92%
Utility SAVR baseline transfemoral	0.73	0.007	Beta	3334.97	1233.48	0.730
Utility SAVR baseline transthoracic	0.74	0.012	Beta	1048.61	368.43	0.720
Utility SAVR baseline-change at 1m transfemoral	-0.002	0.008	Normal	n/a	n/a	0.010
Utility SAVR baseline-change at 1yr transfemoral	0.066	0.009	Normal	n/a	n/a	0.075
Utility SAVR baseline-change at 2yr transfemoral	0.037	0.009	Normal	n/a	n/a	0.040
Utility SAVR baseline-change at 1m transthoracic	-0.022	0.017	Normal	n/a	n/a	0.005
Utility SAVR baseline-change at 1yr transthoracic	0.032	0.015	Normal	n/a	n/a	0.008
Utility SAVR baseline-change at 2yr transthoracic	-0.001	0.017	Normal	n/a	n/a	0.019
Utility TAVI vs SAVR at 1m transfemoral	0.066	0.010	Normal	n/a	n/a	0.083
Utility TAVI vs SAVR at 1yr transfemoral	-0.011	0.010	Normal	n/a	n/a	-0.015
Utility TAVI vs SAVR at 2yr transfemoral	-0.002	0.011	Normal	n/a	n/a	0.016
Utility TAVI vs SAVR at 1m transthoracic	0.007	0.021	Normal	n/a	n/a	0.024
Utility TAVI vs SAVR at 1yr transthoracic	0.000	0.021	Normal	n/a	n/a	-0.035
Utility TAVI vs SAVR at 2yr transthoracic	0.018	0.024	Normal	n/a	n/a	0.051

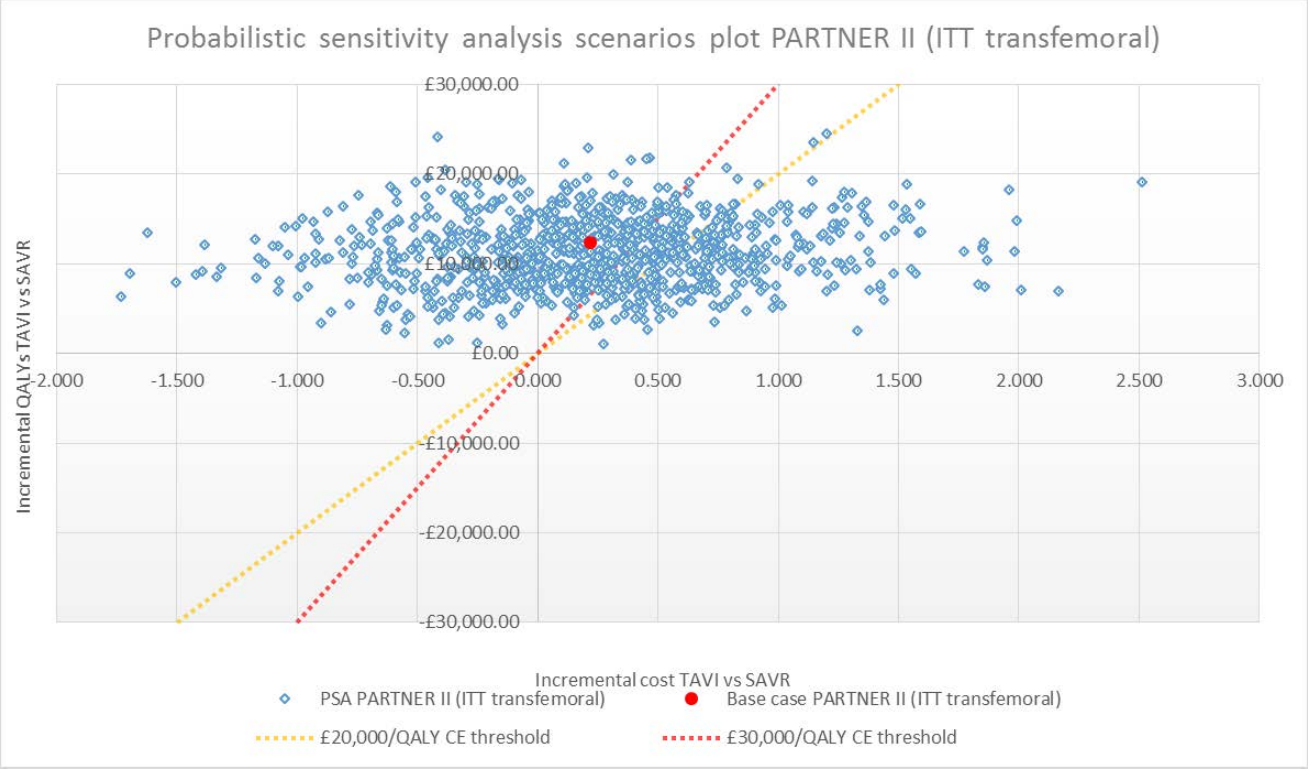
TAVI procedure cost including valve	£24,421.55	£1,792.89	Gamma	185.54	131.62	£26,825.88
SAVR procedure cost	£12,033.03	£3,008.26	Gamma	16.00	752.06	£13,461.77
Cost Disabling stroke	£5,470.00	£547.00	Gamma	100	54.7	£5,101.02
Cost Transient ischemic attack (TIA)	£1,180.00	£118.00	Gamma	100	11.8	£1,554.18
Cost Non-disabling stroke	£2,214.00	£221.40	Gamma	100	22.14	£1,975.10
Cost Myocardial infarction (MI)	£1,665.00	£166.50	Gamma	100	16.65	£1,477.07
Cost Major vascular complication	£1,000.00	£100.00	Gamma	100	10	£954.16
Cost Life-threatening or disabling bleeding	£1,000.00	£100.00	Gamma	100	10	£1,115.65
Cost Acute kidney injury	£3,165.00	£316.50	Gamma	100	31.65	£3,393.87
Cost New atrial fibrillation	£1,000.00	£100.00	Gamma	100	10	£936.17
Cost New permanent peacemaker	£3,947.00	£394.70	Gamma	100	39.47	£3,232.11
Cost Endocarditis	£3,935.00	£393.50	Gamma	100	39.35	£4,700.69
Cost Aortic-valve re-intervention	£1,000.00	£100.00	Gamma	100	10	£912.40
Cost Coronary obstruction	£1,000.00	£100.00	Gamma	100	10	£1,058.25
TAVI follow-up cost	£317	£31.70	Gamma	100	3.17	£283.74

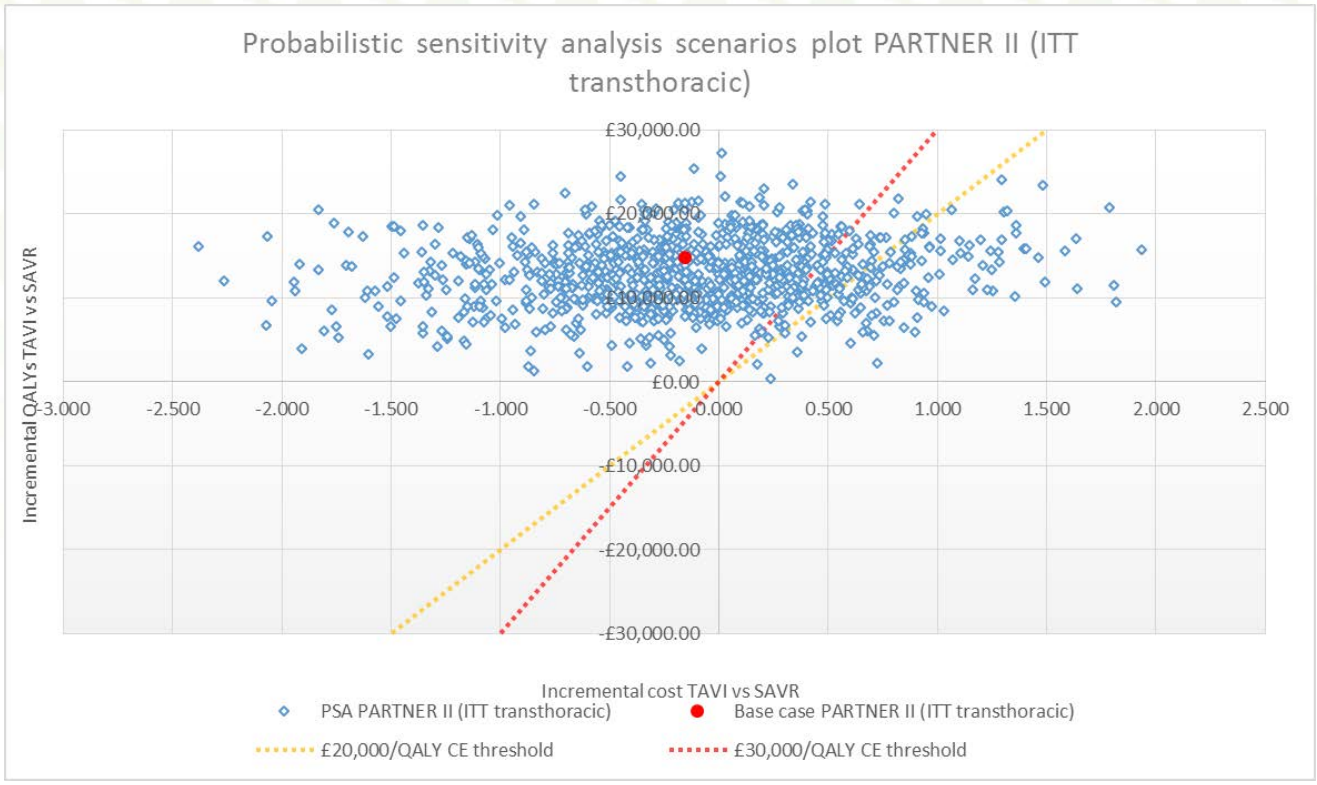
SAVR follow-up cost	£218	£21.80	Gamma	100	2.18	£228.42

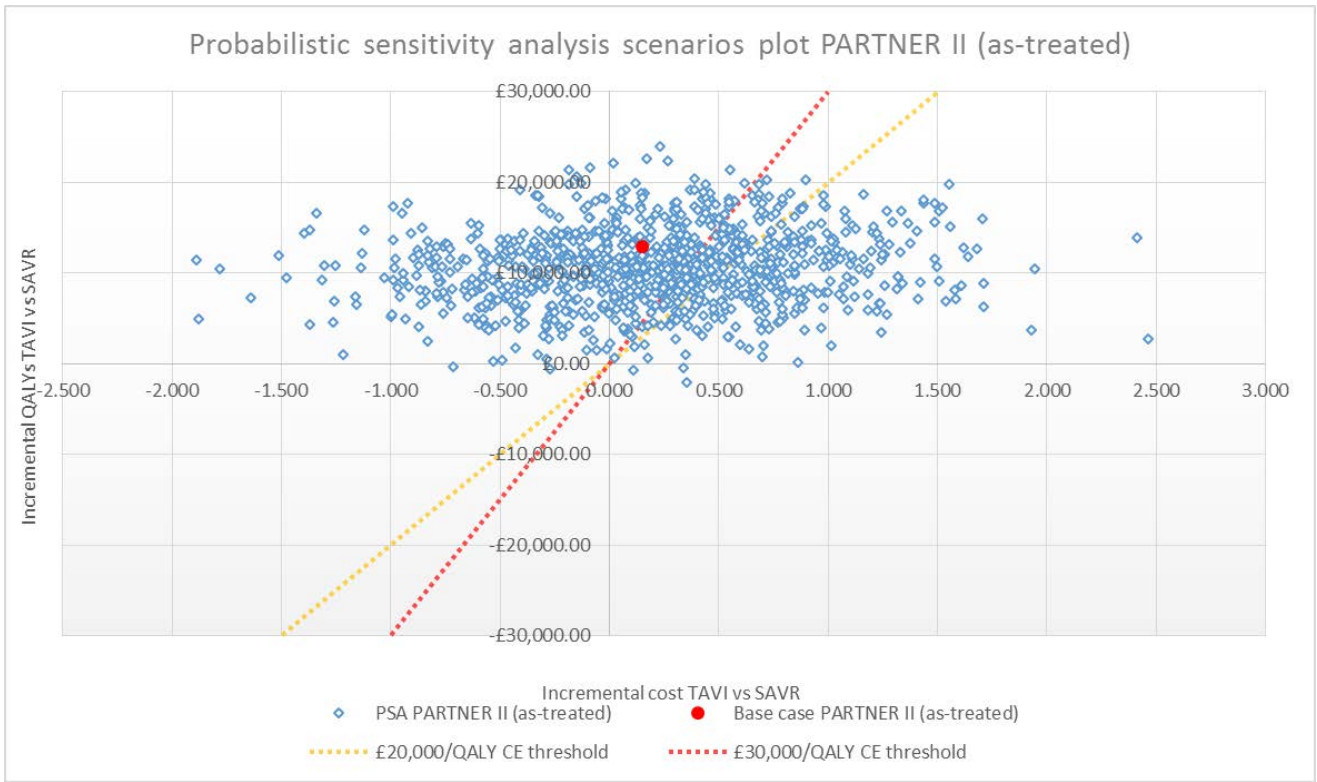
Annex 3: PSA analyses for alternative populations

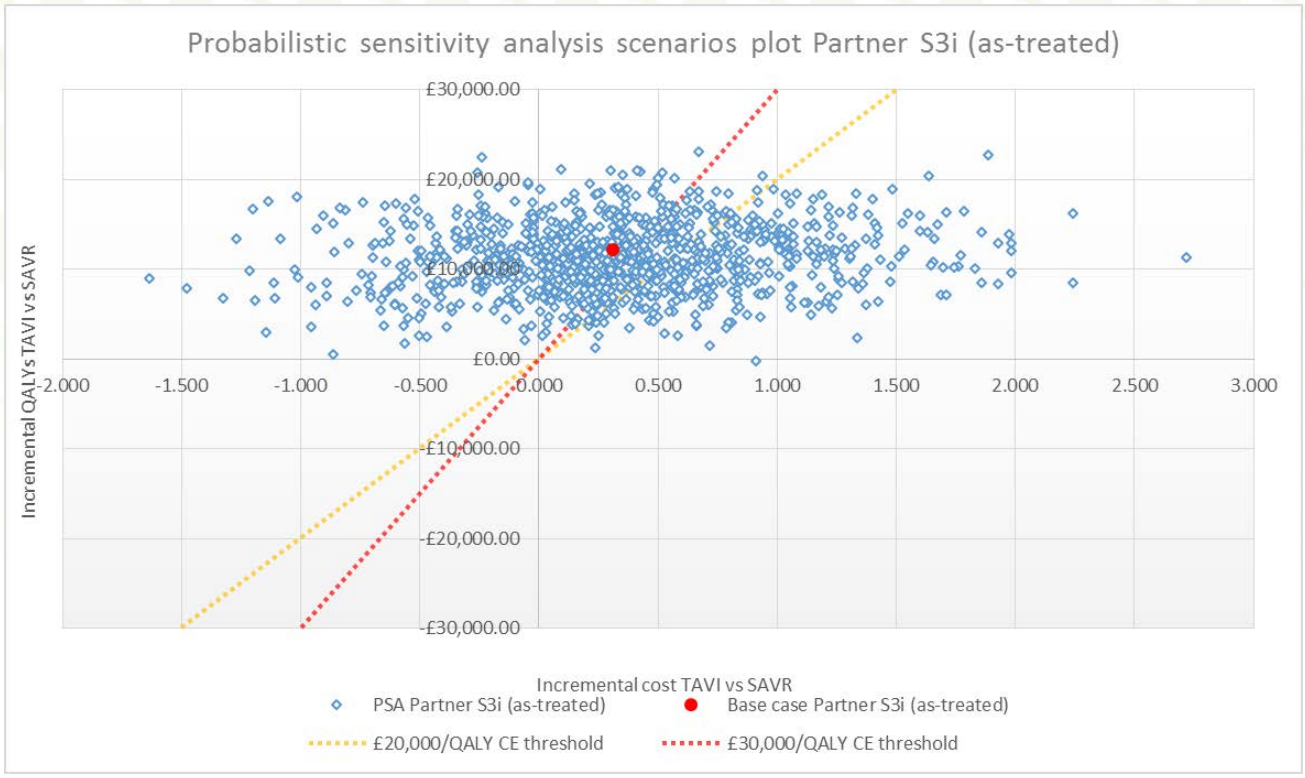
PSA scenarios summary

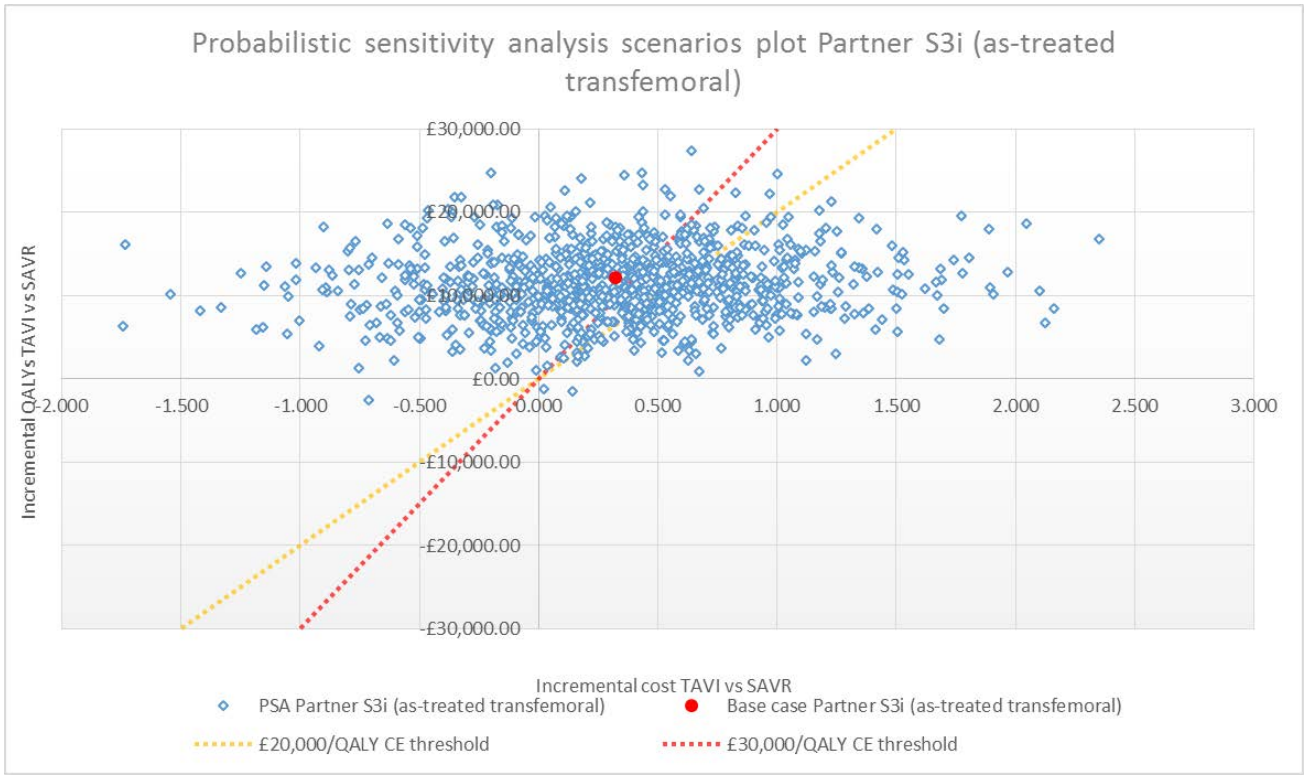
	Partner II (ITT transfemoral)	Partner II (ITT transthoracic)	Partner II (as-treated)	Partner S3i (as-treated)	Partner S3i (as-treated transfemoral)	Surtavi (ITT)	Surtavi (modified-ITT)
Probability CE at £30,000/QALY threshold	39.8%	18.5%	40.9%	45.3%	46.6%	40.0%	40.1%
Probability CE at £20,000/QALY threshold	28.2%	11.7%	28.7%	33.0%	32.8%	34.2%	32.1%
Probability dominating	0.0%	0.0%	0.3%	0.1%	0.2%	2.0%	1.3%
Probability dominated	32.2%	56.4%	35.7%	24.4%	26.0%	44.4%	41.8%

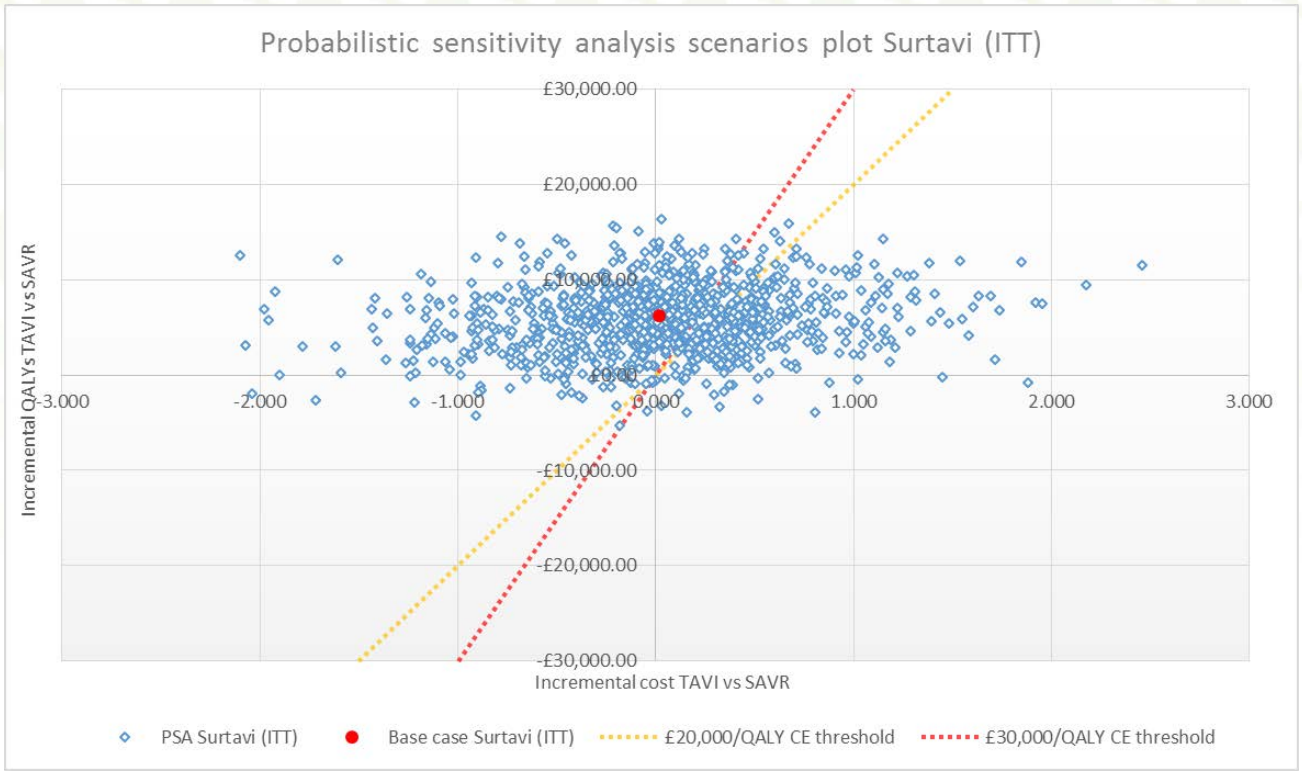


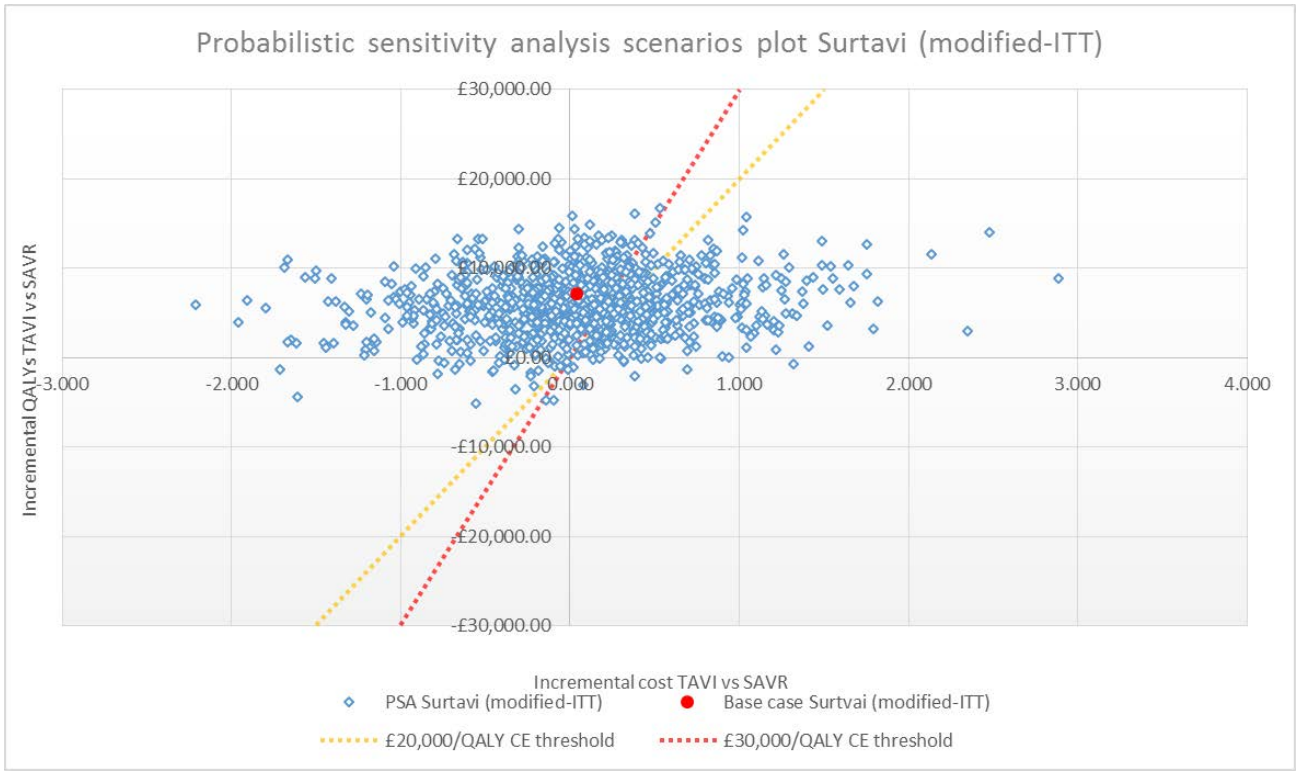

Probabilistic sensitivity analysis scenarios plot PARTNER II (ITT transthoracic)
£30,000.00
£20,000.00
£10,000.00
£0.00
-£10,000.00
-£20,000.00
-£30,000.00
-3.000
-2.500
-2.000
-1.500
-1.000
-0.500
0.000
0.500
1.000
1.500
2.000
2.500
Incremental QALYs TAVI vs SAVR
Incremental cost TAVI vs SAVR
PSA PARTNER II (ITT transthoracic)
Base case PARTNER II (ITT transthoracic)
£20,000/QALY CE threshold
£30,000/QALY CE threshold


Probabilistic sensitivity analysis scenarios plot PARTNER II (as-treated)
£30,000.00
£20,000.00
£10,000.00
£0.00
-£10,000.00
-£20,000.00
-£30,000.00
-2.500
-2.000
-1.500
-1.000
-0.500
0.000
0.500
1.000
1.500
2.000
2.500
3.000
Incremental QALYs TAVI vs SAVR
Incremental cost TAVI vs SAVR
PSA PARTNER II (as-treated)
Base case PARTNER II (as-treated)
£20,000/QALY CE threshold
£30,000/QALY CE threshold


Probabilistic sensitivity analysis scenarios plot Partner S3i (as-treated)
£30,000.00
£20,000.00
£10,000.00
£0.00
-£10,000.00
-£20,000.00
-£30,000.00
-2.000
-1.500
-1.000
-0.500
0.000
0.500
1.000
1.500
2.000
2.500
3.000
Incremental QALYs TAVI vs SAVR
Incremental cost TAVI vs SAVR
PSA Partner S3i (as-treated)
Base case Partner S3i (as-treated)
£20,000/QALY CE threshold
£30,000/QALY CE threshold


Probabilistic sensitivity analysis scenarios plot Partner S3i (as-treated transfemoral)
£30,000.00
£20,000.00
£10,000.00
£0.00
-£10,000.00
-£20,000.00
-£30,000.00
-2.000
-1.500
-1.000
-0.500
0.000
0.500
1.000
1.500
2.000
2.500
3.000
Incremental QALYs TAVI vs SAVR
Incremental cost TAVI vs SAVR
PSA Partner S3i (as-treated transfemoral)
Base case Partner S3i (as-treated transfemoral)
£20,000/QALY CE threshold
£30,000/QALY CE threshold


Probabilistic sensitivity analysis scenarios plot Surtavi (ITT)
£30,000.00
£20,000.00
£10,000.00
£0.00
-£10,000.00
-£20,000.00
-£30,000.00
-3.000
-2.000
-1.000
0.000
1.000
2.000
3.000
Incremental QALYs TAVI vs SAVR
Incremental cost TAVI vs SAVR
PSA Surtavi (ITT)
Base case Surtavi (ITT)
£20,000/QALY CE threshold
£30,000/QALY CE threshold


Probabilistic sensitivity analysis scenarios plot Surtavi (modified-ITT)
£30,000.00
£20,000.00
£10,000.00
£0.00
-£10,000.00
-£20,000.00
-£30,000.00
-3.000
-2.000
-1.000
0.000
1.000
2.000
3.000
4.000
Incremental QALYs TAVI vs SAVR
Incremental cost TAVI vs SAVR
PSA Surtavi (modified-ITT)
Base case Surtvai (modified-ITT)
£20,000/QALY CE threshold
£30,000/QALY CE threshold