National Institute for Health and Care Excellence

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Heart valve disease presenting in adults: investigation and management

Cost-utility analysis: Transcatheter intervention for patients who have operable aortic stenosis

NICE guideline NG208

Economic analysis report

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Final

This analysis was developed by the National Guideline Centre

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1 Introduction

Aortic valve replacement is the treatment of choice when dealing with aortic stenosis. Surgical aortic valve replacement (SAVR) is the most used treatment to replace the aortic valve. However, SAVR may not always be suitable when the person is inoperable or is at a high operative risk. In these cases, transcatheter aortic valve implantation (TAVI) is a viable alternative, where the new valve is delivered through a blood vessel and an open-heart surgery is not needed.

Despite there being economic evidence for those who are operable the conclusions regarding the cost effectiveness of TAVI was highly variable (from TAVI being dominant to being dominated). Therefore, given this uncertainty, an economic evaluation of TAVI was considered of high priority and a decision model analysis was undertaken.

According to the Society for Cardiothoracic Surgery in Great Britain & Ireland there were almost 6,000 isolated first-time aortic valve replacement operations. There may be a large resource impact given the high cost of the interventions. NHS Reference Costs lists a complex single heart valve replacement or repair to cost between £12,600-£17,600, a standard single heart valve replacement or repair to cost £10,700-£13,900 and a transfemoral transcatheter aortic valve implantation (TAVI) to cost between £5,000-£6,000. It should be noted that the cost for TAVI do not include the cost of the TAVI device, which will significantly increase the NHS cost. The TAVI device cost is reimbursed separately under the NHSE High-Cost Tariff Excluded Devices Programme at an average price across the volume of £17,500 (Source: NHS Supply Chain). This price seems to be considerably higher than the price other countries purchase the latest generation TAVI valves. For instance, Edwards Lifescience's Sapien 3 is purchased in France at a price of £12,000[28].

At present, those who carry a low or intermediate surgical risk receive a surgical intervention over a transcatheter one. Therefore, if the committee recommend the use of transcatheter interventions for those with a low or intermediate surgical risk, there will be a large change in current practice and a potentially a large resource impact. The latest surgical audit shows that around 5,000 of patients receiving surgery are of a lower surgical risk [14].

2 Methods

2.1 Model overview

A cost-utility analysis was undertaken where quality-adjusted life years (QALYs) and costs from a current UK NHS and personal social services perspective were considered. The analysis followed the standard assumptions of the NICE reference case for interventions with health outcomes in an NHS setting including discounting at 3.5% for costs and health effects[31]. An incremental analysis was undertaken.

2.1.1 Comparators

The following comparators were included in the analysis:

- Standard (surgical) aortic valve replacement (SAVR) with biological valves
- Transcatheter aortic valve implantation (TAVI)

2.1.2 Population

Adults with operable aortic stenosis (non-bicuspid) requiring intervention

The model was run separately for several subpopulations that are determined by surgical risk category.

The risks were defined as following:

- Low surgical risk: STS or EuroSCORE 2 lower than 4
- Intermediate surgical risk: STS or EuroSCORE 2 between 4 and 8
- High surgical risk: STS or EuroSCORE 2 higher than 8

There was a discussion about the opportunity of conducting an additional stratification analysis by age groups, but the committee ultimately decided to limit the stratification to risk groups only. The committee acknowledged that risks and age are not independent variables and that the surgical risk is highly affected by the age of the patient. Moreover, NICE usually recommends avoiding age stratification although stratification by operative risk is generally accepted. Hence, it was decided to stratify by risk only using the average age of people at each risk group as the staring age.

2.1.3 Time horizon

A time horizon of 15 years was chosen to fully capture the long-term costs and benefits derived from using a TAVI compared with surgery in the base case scenario. However, it was recognized that extrapolation of the data used over a longer time horizon would be tenuous. Therefore different time horizons were tested in the sensitivity analysis: 5, 10, 15 and 30 years.

2.1.4 Deviations from NICE reference case

No deviations from the NICE reference case were taken.

2.2 Approach to modelling

The model is structured in two parts:

- A **decision tree** was used to calculate the proportion of people that fall into the different post-procedural outcomes (up to 30 days). The 30 days decision tree model reflects the immediate period following the intervention when several post-procedural consequences can occur. The decision tree was used to determine the outcomes of re-interventions as well. Further details on the decision tree model can be found in section 2.2.1.
- A **Markov model** was used to estimate the longer-term outcomes and costs.

2.2.1 Model structure

2.2.1.1 Post-procedural consequences decision tree

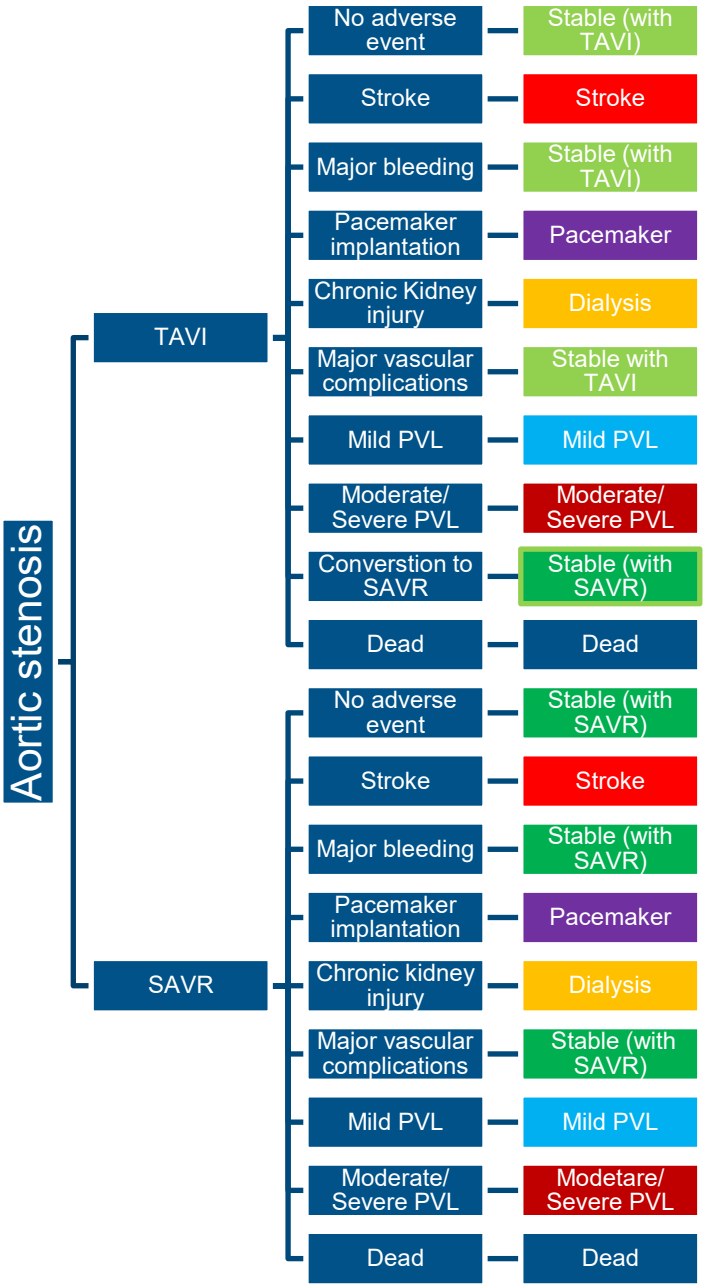
The decision tree reflects the initial month following the intervention when people in the intervention arm receive the transcatheter procedure (TAVI). Hence, the model captures the costs and loss of utility associated with several intervention consequences or complication. Following the review of the literature and the discussion with the committee, it was agreed to include the following post-procedural outcomes in the decision tree model:

- Stroke
- Major bleeding
- Pacemaker implantation
- Chronic kidney injury (Dialysis)
- Vascular complication
- Mild PVL
- Moderate/ Severe PVL
- Conversion to SAVR (only in the TAVI arm)
- Intervention-related mortality

There are multiple other possible outcomes for people that undergo these kinds of surgeries, such as patient prosthesis mismatch and atrial fibrillation (AF). However, there was some uncertainty amongst the committee regarding the inclusion of these outcomes. Atrial fibrillation developed during the intervention is known to cause short term costs and outcomes but the committee noted that it is a periprocedural outcome only and does not have an effect in the long term. In the base case scenario, the short-term costs of these complications are expected to be already captured in the HRG hospital stay cost in the base case scenario,

Figure 1 shows the structure of the decision tree model. There are seven final states patients can end up at the end of the 30 days period: stable (with SAVR or TAVI), stroke, pacemaker, dialysis, mild paravalvular leak, moderate/severe paravalvular leak and dead. Major bleeding and vascular complication are assumed to be only temporary states and, as such, result only in a temporary loss of utility. If a TAVI procedure is converted to SAVR, people move to the 'stable with SAVR' state even though they are in the TAVI arm, where they experience a higher mortality[11] and different costs and utility. Stroke, pacemaker, dialysis and PVL (both mild or moderate/severe) are assumed to cause costs and affect quality of life and survival in the long term and were, hence, modelled as Markov states.

Figure 1: Decision tree model structure



2.2.1.2 Long-term outcomes Markov model

A yearly cycle length was chosen to account for the changes in patients experience after an intervention.

The Markov model was developed to represent long-term outcomes and estimate costs and consequence of the population. Costs and outcomes were collected at each cycle for a period of 15 years after which the majority of the cohort was dead.

Following the discussion among the committee, it was agreed to include 8 health states:

- Stable (with TAVI or SAVR)
- Stable (with re-intervention)
- Stroke
- Post-stroke
- Dialysis
- Pacemaker
- Mild PVL
- Moderate/ Severe PVL
- Re-intervention

Figure 2 illustrates the structure of the Markov model. Each patient starts in the state defined by the corresponding ending state of the decision tree model and was then simulated for 15 repeated cycles representing 15 years of time.

Those who are alive and experienced no adverse event or experienced one of the short-term outcomes such as major bleeding, vascular complications, enter the Markov model in the stable state.

People in the stable, mild or moderate PVL and pacemaker states are at risk of reintervention, which has a yearly probability of occurring. People undergoing reintervention move to a new decision tree model simulating the outcomes of the new intervention (which can be a new TAVI or SAVR). At the beginning of the next cycle, people who underwent reintervention re-enter the model in the state defined by the ending state of the reintervention decision tree model. It is possible, therefore, for people in the stable state to experience stroke or dialysis and to transit to one of these states as a result of the complication experienced during the reintervention. People who are stable after the reintervention moved to “stable with reintervention” state. This state is essentially a group of tunnel states that were added to “reset” the probability of needing an additional reintervention and to avoid that some patients undergo multiple subsequent reinterventions at late cycles.

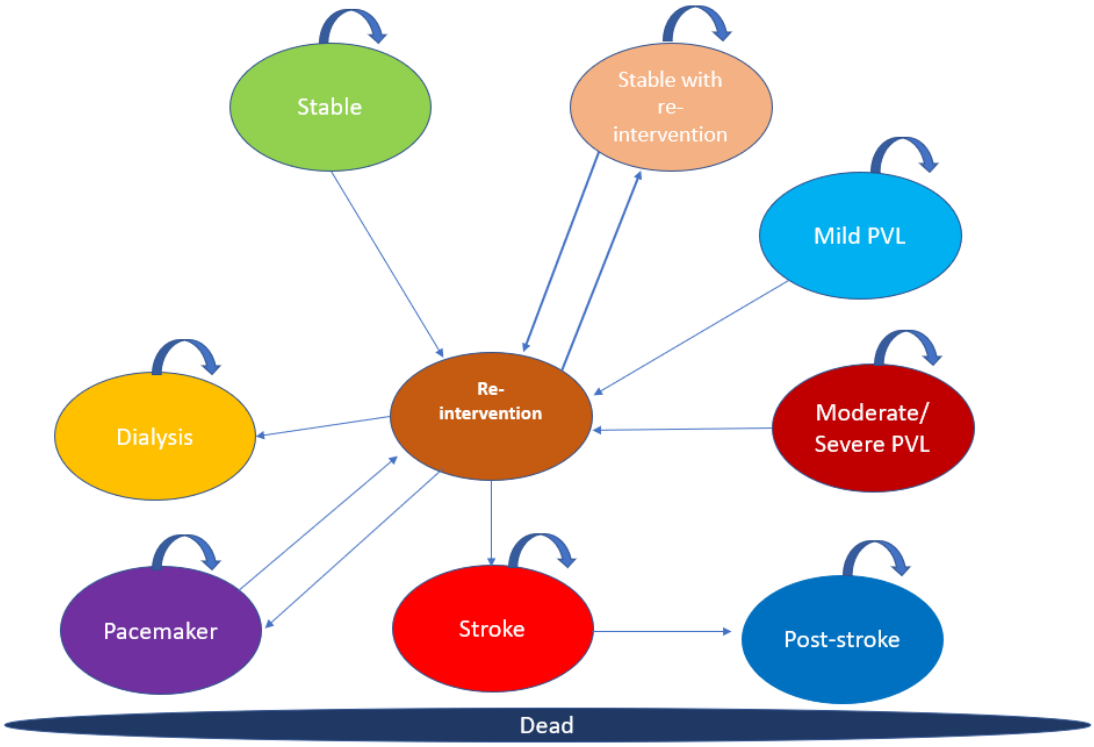
It was assumed that dialysis, stroke and post-stroke are long-term states and that, consequently, it is not possible to transit out of them (although it is always possible to move to the dead state). This is a clear simplification of reality and was done for modelling purpose. Stroke is a tunnel state implying that people remain in this state for one cycle only before moving to the next state (post-stroke or dead).

A half-cycle correction was applied to the Markov model, which assumes that events occurred halfway through the cycle (at 6 months).

Key simplifying assumptions:

- People who have had stroke or dialysis cannot undergo re-intervention.
- People cannot have multiple morbidities meaning that once a person transits to a state (stroke, pacemaker and dialysis), they cannot move to another one.
- Dialysis and post-stroke are long-term states and can only transit to dead.

Figure 2: Markov model structure



All states can transit to dead

2.2.2 Uncertainty

The model was built probabilistically to take account of the uncertainty around input parameter point estimates. A probability distribution was defined for each model input parameter. When the model was run, a value for each input was randomly selected simultaneously from its respective probability distribution; mean costs and mean QALYs were calculated using these values. The model was run repeatedly – 5,000 times for the base case - and results were summarised.

The way in which distributions are defined reflects the nature of the data, so for example event probabilities were given a beta distribution, which is bounded by 0 and 1, reflecting that the probability of an event occurring cannot be less than 0 or greater than 1. All of the variables that were probabilistic in the model and their distributional parameters are detailed in Table 1 and in the relevant input summary tables in section 2.3.1. Probability distributions in the analysis were parameterised using error estimates from data sources.

Table 1: Description of the type and properties of distributions used in the probabilistic sensitivity analysis

Parameter	Type of distribution	Properties of distribution
Baseline risks	Beta	Bounded between 0 and 1. As the sample size and the number of events were specified alpha and beta values were calculated as follows: • Alpha = (number of patients hospitalised) Beta = (number of patients) − (number of patients hospitalised)
Hazard ratios Odds ratios Risk ratios	Lognormal	The natural log of the mean and standard error was calculated as follows: • Mean = ln (mean cost) − $SE^2/2$ • SE = [ln (upper 95% CI) − ln (lower 95% CI)]/ (1.96×2) $\sqrt{\ln \frac{SE^2 + mean^2}{mean^2}}$ This formula includes a correction to ensure the mean generated in the probabilistic analysis will be the same as the reported mean.[4]
Utilities	Beta	Bounded between 0 and 1. Derived from mean and its standard error, using the method of moments. Alpha and Beta values were calculated as follows: Alpha = $mean^2 \times [(1-mean)/SE^2] - mean$ Beta = alpha×[(1−mean)/mean]
Utility decrements	Gamma	Bounded at 0, positively skewed. Derived from mean and its standard error. Alpha and beta values were calculated as follows: • Alpha = $(mean/SE)^2$ • Beta = SE^2/Mean

Abbreviations: 95% CI = 95% confidence interval; SE = standard error; SMR = standardised mortality ratio.

The following variables were left deterministic (that is, they were not varied in the probabilistic analysis):

- The cost-effectiveness threshold
- Health state costs (based on analyses that use unit costs from UK national sources)
- Mortality probabilities for general population (based on UK national data)
- Reintervention rates after SAVR (based on Rodriguez-Gabella 2018[45])
- Utility score in the general population (based on the paper from Ara 2010[2])
- Relative mortality after TAVI (based on the study of Martin 2017[27])

2.2.3 Sensitivity analyses

Various deterministic sensitivity analyses were undertaken to test the robustness of model assumptions. In these, one or more inputs were changed, and the analysis rerun to evaluate the impact on results and whether conclusions on which intervention should be recommended would change. Details of the sensitivity analyses undertaken can be found in methods section 2.5.

2.3 Model inputs

2.3.1 Summary table of model inputs

Model inputs were based on clinical evidence identified in the systematic review undertaken for the guideline, supplemented by additional data sources as required. Model inputs were validated with clinical members of the guideline committee. A summary of the model inputs used in the base-case (primary) analysis is provided in Table 2. More details about sources, calculations and rationale for selection can be found in the sections following this summary table.

Table 2: Overview of parameters and parameter distributions used in the model

Input	Data	Source	Probability distribution
Comparators	• Standard (surgical) aortic valve replacement (SAVR) with biological valves • Transcatheter aortic valve implantation (TAVI)		n/a
Population	Adults with operable aortic stenosis (non-bicuspid) requiring intervention		n/a
Perspective	UK NHS & PSS	NICE reference case[31]	n/a
Time horizon	15 years		n/a
Discount rate	Costs: 3.5% Outcomes: 3.5%	NICE reference case[31]	n/a
Cohort settings			
Cohort size	1000		n/a
Start age	Low risk: 75 Intermediate risk: 80 High risk: 81	Carroll 2020[8]	Normal
Percentage of patients that are male at start	54%	UK TAVI audit 2020[22, 23]	n/a
Decision tree baseline probabilities (TAVI)			
Conversion to SAVR	0.0055	UK TAVI audit 2020[23]	Beta
Stroke	0.021	UK TAVI audit 2020[23]	Beta
Major bleeding	0.023	UK TAVI audit 2020[23]	Beta
Pacemaker implantation	0.097	UK TAVI audit 2020[23]	Beta
Vascular complications	0.023	UK TAVI audit 2020[23]	Beta

Input	Data	Source	Probability distribution
Chronic kidney injury requiring RRT	0.015	Calibrated from Ferro 2017[11]	Beta
Mild PVL	Low risk: 0.258 Intermediate risk: 0.258 High risk: 0.291	Herrmann 2016 [15] Wendler 2017 [53]	Dirichlet
Moderate Severe PVL	0.027	Herrmann 2016 [15] Wendler 2017 [53]	Dirichlet
30 days mortality risk (SAVR)			
Low risk	0.007	NACSA[14]	Beta
Intermediate risk	0.023	NACSA[14]	Beta
High risk	0.056	NACSA[14]	Beta
Markov model transition probabilities			
Reintervention rate after SAVR	1 year: 1.40% 2 years: 1.94% 3 years: 1.94% 4 years: 1.94% 5 years: 1.99% 6 years: 2.53% 7 years: 3.58% 8 years: 3.95% 9 years: 4.48% 10 years: 5.54% 11 years: 7.81% 12 years: 10.08% 13 years: 12.70%	Rodriguez-Gabella 2018[45]	n/a
Reintervention type	**TAVI arm:** • 76% TAVI • 24% SAVR **SAVR arm:** • 17% TAVI • 83% SAVR	Pibarot 2020 [41]	n/a
Rehospitalisation	First year: 0.09 Second year (and beyond): 0.03	PARTNER 2[20] PARTNER 3[19] Evolut[42]	Beta
Pacemaker hospitalisation risk ratio	1.18	Faroux 2020[10]	Log-normal
Mortality			
General population mortality		ONS Life Tables 2016-2018[39]	n/a
TAVI relative survival in intermediate risk	1 year: 91.7% 2 years: 89%	Martin 2017[27]	n/a

Input	Data	Source	Probability distribution
patients (compared to general survival)	3 years: 85.5% Extrapolated for the subsequent years assuming cumulative excess hazard increasing at a constant rate		
Intermediate vs low risk mortality hazard ratio	1.6	Barbash 2015[3]	Log-normal
High vs low risk mortality hazard ratio	2.7	Barbash 2015[3]	Log-normal
Dialysis mortality hazard ratio 1 year	2.81	Calibrated from Ferro 2017[11]	Log-normal
Pacemaker mortality risk ratio	1.17	Faroux 2020[10]	Log-normal
Mild PVL mortality hazard ratio	Base case: 1 Scenario analysis: 1.23	Makkar 2020[26]	Log-normal
Moderate/severe PVL mortality hazard ratio	2.44	Makkar 2020[26]	Log-normal
Stroke (OR)	3.21	Myat 2020[29]	Log-normal
Post-stroke (OR)	1.58	Myat 2020[29] calculated using the same ratio of Bronnum-Hansen 2001[7]	Log-normal
Decision tree relative treatment effects (TAVI vs SAVR)			
Stroke risk ratio	0.83	PARTNER 2[20] PARTNER 3[19] Evolut[42]	Log-normal
Major Bleed risk ratio	0.24		Log-normal
Pacemaker Implantation risk ratio	1.81		Log-normal
Vascular complication risk ratio	1.46		Log-normal
Kidney Injury risk ratio	0.37		Log-normal
Mortality 30 days risk ratio	0.81		Log-normal
Mild PVL	6.71		Log-normal
Moderate/severe PVL	10.82		Log-normal
Markov model relative treatment effects (TAVI vs SAVR)			

Input	Data	Source	Probability distribution
All-cause mortality risk ratio	1 year: 0.91 2 years: 0.97	PARTNER 2[20] PARTNER 3[19] Evolut[42]	Log-normal
Reintervention risk ratio	Base case: 1.87 Scenario analysis: 1.08	PARTNER 2[20] PARTNER 3[19] Evolut[42]	Log-normal
Hospitalisation	1 year: 0.73 Beyond 1 year: 1.91	PARTNER 2[20] PARTNER 3[19] Evolut[42]	Log-normal
Health-related quality of life (utilities)			
Markov Model 1 Year Utilities			
High risk			
TAVI first year	0.70	Gleason 2018[12]	Beta
TAVI >1 year	0.72	Gleason 2018[12]	Beta
SAVR first year	0.65	Gleason 2018[12]	Beta
SAVR >1 year	0.72	Gleason 2018[12]	Beta
Intermediate risk			
TAVI first year	0.80	Baron 2018[6]	Beta
TAVI >1 year	0.80	Baron 2018[6]	Beta
SAVR first year	0.78	Baron 2018[6]	Beta
SAVR >1 year	0.80	Baron 2018[6]	Beta
Low risk			
TAVI first year	0.87	Baron 2019[5]	Beta
TAVI >1 year	0.87	Baron 2019[5]	Beta
SAVR first year	0.86	Baron 2019[5]	Beta
SAVR >1 year	0.87	Baron 2019[5]	Beta
Decision Tree Utility Decrements			
Major bleeding	0.45	Kaier 2016[16]	Gamma
Vascular complications	0.01	Kaier 2016[16]	Gamma
Pacemaker	0.00	Assumption	
Major bleeding duration	45 days	Kaier 2016[16]	n/a
Vascular complications duration	30 days	Assumption	n/a
Waiting time before a reintervention	6 months	Expert opinion	n/a
Markov Model Utility Decrements			

Input	Data	Source	Probability distribution
Stroke	0.16	Luengo Fernandez 2013[24]	Gamma
Post-stroke	0.18	Luengo Fernandez 2013[24]	Gamma
Dialysis	0.18	Kaier 2016[16]	Gamma
Costs			
ICU			
ICU cost (per day)	£1,415	NHS Reference Costs 2018-2019[37]	n/a
TAVI mean ICU length of stay			
Low risk	0 days	UK TAVI Trial [52] - median	Log-normal
Intermediate risk	0 days	Assumption	Log-normal
High risk	0 days	Assumption	Log-normal
SAVR mean ICU length of stay			
Low risk	1 day	UK TAVI Trial [52] - median	Log-normal
Intermediate risk	1.55 days	UK TAVI Trial [52] – median- scaled using Reinöhl 2015[44]	Log-normal
High risk	1.88 days	UK TAVI Trial [52] – median - scaled using Reinöhl 2015[44]	Log-normal
Hospital ward			
SAVR bed day cost (per day)	£325	NHS Reference Costs 2017-2018[36]	n/a
TAVI bed day cost (per day)	£325	NHS Reference Costs 2017-2018[36]	n/a
TAVI mean hospital length of stay			
Low risk	3 days	UK TAVI Trial [52] - median	Log-normal
Intermediate risk	3.19 days	UK TAVI Trial [52] – median - scaled using Reinöhl 2015[44]	Log-normal
High risk	3.30 days	UK TAVI Trial [52] – median - scaled using Reinöhl 2015[44]	Log-normal
SAVR mean hospital length of stay			
Low risk	8.00 days	UK TAVI Trial [52] - median	Log-normal
Intermediate risk	10.58 days	UK TAVI Trial [52] – median - scaled using Reinöhl 2015[44]	Log-normal
High risk	12.10 days	UK TAVI Trial [52] – median - scaled using Reinöhl 2015[44]	Log-normal

Input	Data	Source	Probability distribution
Procedural cost (including LOS and ICU)			
TAVI (excluding valve)			
Low risk	£5,479	NHS Reference Costs 2018-2019[37]	n/a
Intermediate risk	£5,540	NHS Reference Costs 2018-2019[37]	n/a
High risk	£5,575	NHS Reference Costs 2018-2019[37]	n/a
SAVR (including valve)			
Low risk	£13,394	NHS Reference Costs 2018-2019[37]	n/a
Intermediate risk	£15,489	NHS Reference Costs 2018-2019[37]	n/a
High risk	£18,572	NHS Reference Costs 2018-2019[37]	n/a
Valve cost			
TAVI valve	£17,500	NHS Supply Chain. Average price under the NHSE High-Cost Tariff Excluded Devices programme	n/a
Home-rehabilitation costs	£982	National Audit of Intermediate Care 2017[30]	n/a
Intermediate care costs	£5,965	National Audit of Intermediate Care 2017[30]	n/a
Decision Tree Costs			
Major bleeding	Base case: £0 Scenario analysis: £1,972	NHS Reference Costs 2018-2019[37]	n/a
Vascular complications	Base case: £0 Scenario analysis: £1,826	NHS Reference Costs 2018-2019[37]	n/a
New pacemaker implantation	Base case: £0 Scenario analysis: £2,451	NHS Reference Costs 2018-2019[37]	n/a
1 Year Markov Model Costs			
Rehospitalisation	£2,275	NHS Reference Costs 2018-2019[37]	n/a
Stroke	£18,948	Xu 2018 SSNAPP project inflated to 2018-2019[54]	n/a
Post-stroke	£6,727	Xu 2018 SSNAPP project inflated to 2018-2019[54]	n/a
Dialysis	£37,893	NICE guideline NG107[34] and NHS Reference Costs 2018-2019[37]	n/a

Input	Data	Source	Probability distribution
PVL (echo + visit)	£250	NHS Reference Costs 2018-2019[37]	n/a

Abbreviations: TAVI = NHS = national health service; OR= odds ratio; PSS = personal social services; PVL = paravalvular leak; SAVR = surgical aortic valve replacement; and transcatheter aortic valve implantation.

2.3.2 Baseline probabilities

2.3.2.1 TAVI adverse events

The decision tree model was populated with the baseline probabilities of TAVI adverse events informed by the latest NICOR TAVI audit[23]. NICOR TAVI audit reports the outcomes collected in the UK TAVI registry so it represents the best source for contemporary outcomes of TAVI in the UK practice. However, it does not provide a stratified analysis by surgical risk group. Therefore, the baseline risks from the audit were applied to all TAVI patients regardless of the surgical risk group (see table 4).

Renal injury requiring renal replacement therapy was not reported in the audit but was instead extracted by a study from Ferro 2017[11] using data drawn from the UK TAVI registry. Ferro reported both the percentage of people needing RRT and their survival during the first 30 days. As most of the people with dialysis tend to die within the first 30 days, the number of those who died in the decision tree had to be subtracted to obtain the real number of people with dialysis entering the Markov model.

The probabilities of having mild or moderate/severe paravalvular leak(PVL) were extracted from two studies assessing the third generation Sapien 3 TAVI valve and, as such, are considered to reflect the performance of the latest valves. The rate of 2.7% is consistent with the rate reported from the UK TAVI registry and should therefore reflect UK practice as well.

Table 3: TAVI adverse events outcomes

Parameter	Value	Source
Conversion to SAVR	0.0055	UK TAVI audit 2020[23]
Stroke	0.021	UK TAVI audit 2020[23]
Major bleeding	0.023	UK TAVI audit 2020[23]
Pacemaker implantation	0.097	UK TAVI audit 2020[23]
Vascular complications	0.023	UK TAVI audit 2020[23]
Chronic kidney injury requiring renal replacement therapy	0.015	Calibrated from Ferro 2017[11]
Mild paravalvular leak (PVL)	Low risk: 0.258 Intermediate risk: 0.258 High risk: 0.291	Herrmann 2016 [15] Wendler 2017 [53]
Moderate or severe PVL	0.027	Herrmann 2016 [15] Wendler 2017 [53]

Mortality at 30 days was instead extracted from the latest audit on surgical aortic valve replacement (see section 2.3.4.1)

2.3.2.2 Hospitalisation after TAVI

The probability of requiring a hospitalisation after TAVI during one cycle was calculated using the trials included in the meta-analysis. It was noted that the probability is higher during the first year (9%) but lower in the second year (3%), therefore two different probabilities were used for the first and the following years (see table 4). It was assumed that beyond the second year, people would have the same probability of being hospitalised they had at year 2.

Table 4: Hospitalisation transition probabilities (TAVI)

Parameter	Value	Source
First year	0.09	PARTNER 2[20] PARTNER 3[19] Evolut[42]
Beyond year 1	0.03	PARTNER 2[20] PARTNER 3[19] Evolut[42]

As the model applies a relative risk to the probability of hospitalisation for those who have a pacemaker, double counting had to be addressed to avoid the overestimation of the number of hospitalisations predicted by the model. The probability of requiring a hospitalisation if not exposed to the higher risk of a pacemaker was calculated through the following equation, which is an adaptation from equation 3.6 on page 49 of the Applied Methods of Cost-Effectiveness Analysis in Health Care handbook:

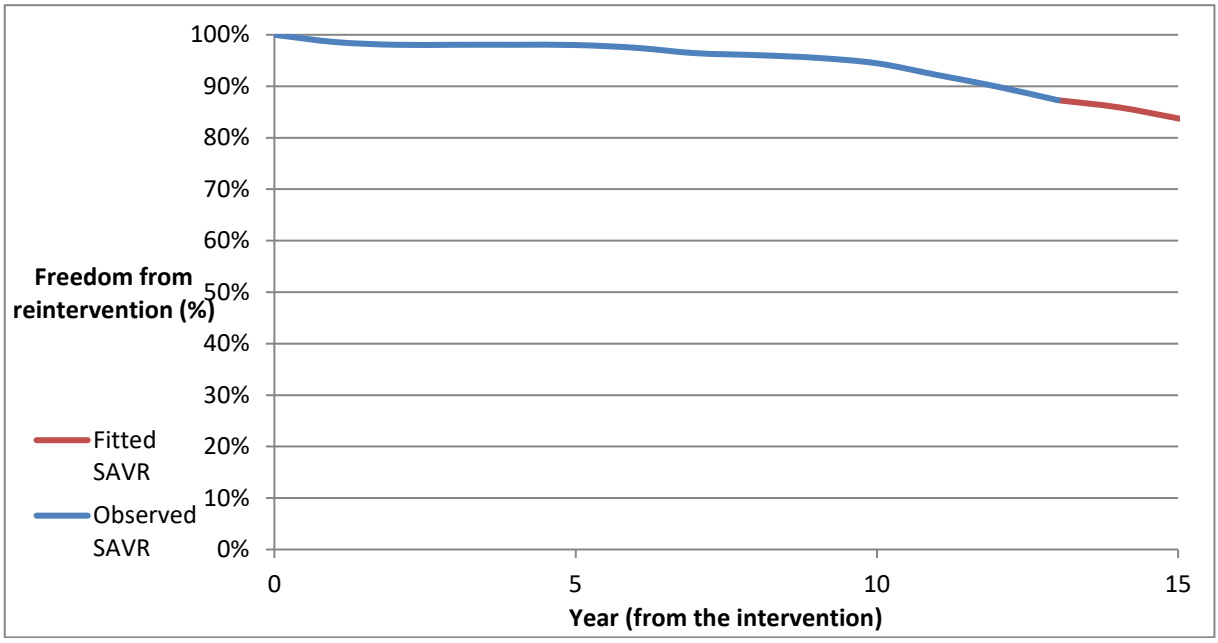
$$P_{Non-exposed} = \frac{P_{observed}}{(1-x) + x * RR}$$

where $P_{Non-exposed}$ is the probability of hospitalisation with no pacemaker, $P_{observed}$ is the probability of hospitalisation observed from the trials (table 4), x is the incidence of new pacemaker among TAVI patients and RR is the risk ratio of increased hospitalisation for those who carry a pacemaker. This probability of being hospitalised in people without a pacemaker was then applied in the model and then used to calculate hospitalisation rates in people with pacemakers, thus avoiding any double counting issues.

2.3.2.3 Reintervention after SAVR

Reintervention rates after surgery were obtained from the study from Rodriguez-Gabella[45] reporting the Kaplan-Meier curve of undertaking a reintervention during the 13 years following the first intervention. Reinterventions observed in the study were undertaken for multiple reasons: structural valve deterioration (SVD), endocarditis, valve thrombosis and aortic dissection. The paper was chosen as it offers the longest follow-up and thus had to rely less on statistical extrapolation which are known to increase the uncertainty of an economic analysis. Only for the last 2 year of the base case scenario, reintervention rates had to be extrapolated assuming that the curve follows a Weibull function. The resulting curve is shown in figure 3.

Figure 3: Freedom from reintervention after surgical aortic valve replacement



It was noted that there is no long-term data on reintervention rate in the UK to compare with the curve reported from Rodriguez-Gabella[45]. The latest evidence available from the UK, the UK TAVI trial[52], suggests a higher reintervention rate in the UK compared with the one used in the model in the first year (2.9% vs 1.4%) though long-term comparison is unknown.

The type of reintervention received was informed by the study of Pibarot 2020[41].

2.3.3 Relative treatment effects

Relative treatment effects in the base case scenario were calculated using recent trials of 2nd and 3rd generation valves (see table 5). A sensitivity analysis using treatment effects calculated from all trials available is presented in section 2.5, but was not used in the base case scenario as relative treatment effects estimated from historical data were not considerate appropriate for an economic analysis assessing the cost effectiveness of latest generations TAVI in the UK.

Table 5: Trials included in the meta-analysis used for the base case scenario

Trial	Surgical risk	TAVI valves assessed
PARTNER 2	Intermediate risk	Sapien XT
PARTNER 3	Low risk	Sapien 3
Evolut	Low risk	CoreValve, Evolut R, Evolut PRO

As table 5 shows, no trial assessing the effectiveness of TAVI on people at high surgical risk was included in the meta-analysis as there is no trial conducted recently on people at high

surgical risk using latest generations valves. CoreValve or PARTNER 1 (both high-risk RCT) could not be used to estimate relative treatment effects as those were assessing first generation valves not used anymore in the UK and, therefore, not reflecting outcomes of current valves. Nevertheless, data from CoreValve trial were still used to estimate utility scores in high-risk people (see section 2.3.6). This was mentioned as a limitation in section 4.2, although the committee believe that it was more important to capture the increased efficiency of new generation valves, hence a pragmatic decision was made to exclude the trials in high-risk patients.

The resulting relative treatment effects used in the base case scenario of the model are shown in table 6.

Table 6: Relative treatment effects in the base case scenario

Risk ratio	Value	Source
Stroke	0.83 (0.5 to 1.39)	PARTNER 2[20] PARTNER 3[19] Evolut[42]
Major Bleed	0.24 (0.2 to 0.29)	PARTNER 2[20] PARTNER 3[19] Evolut[42]
Pacemaker Implantation	1.81 (1.04 to 3.17)	PARTNER 2[20] PARTNER 3[19] Evolut[42]
Vascular complication	1.46 (1.11 to 1.92)	PARTNER 2[20] PARTNER 3[19] Evolut[42]
Kidney Injury	0.37 (0.22 to 0.59)	PARTNER 2[20] PARTNER 3[19] Evolut[42]
Mortality 30 days	0.81 (0.55 to 1.18)	PARTNER 2[20] PARTNER 3[19] Evolut[42]
Mild PVL	6.71 (5.37 to 8.39)	PARTNER 2[20] PARTNER 3[19] Evolut[42]
Moderate/severe PVL	10.82 (4.15 to 28.23)	PARTNER 2[20] PARTNER 3[19] Evolut[42]
All-cause mortality	1 year: 0.91 (0.75 to 1.15) 2 years: 0.97 (0.82 to 1.16)	PARTNER 2[20] PARTNER 3[19] Evolut[42]
Reintervention	1.87 (0.69 to 5.05)	PARTNER 2[20] PARTNER 3[19] Evolut[42]
Hospitalisation	1 year: 0.73 (0.46 to 1.17)	PARTNER 2[20] PARTNER 3[19]

Risk ratio	Value	Source
	Beyond 1 year: 1.91 (1.2 to 3.05)	Evolut[42]

In the sensitivity analysis, a different value for reintervention was tested and, as mentioned, a larger meta-analysis including old trials excluded in the base case scenario was used to derive alternative treatment effects that were utilized in another scenario analysis (see section 2.5).

2.3.4 Mortality

2.3.4.1 30-day mortality

Mortality rates at 30 days after surgery were collected from the latest audit on surgery (NACSA[14]). The audit provided mortality rates stratified by surgical risk and, therefore, risk-specific mortality rates could be assigned to each risk group separately (see table 7).

Table 7: 30 days mortality after SAVR in each risk group

Risk group	Mortality at 30 days	Source
Low surgical risk	0.7%	NACSA[14]
Intermediate surgical risk	2.3%	NACSA[14]
High surgical risk	5.6%	NACSA[14]

30 days mortality in the TAVI arm was calculated by applying the relative treatment effects shown in table 6 of section 2.3.3.

2.3.4.2 Relative survival with TAVI

A study on relative survival of TAVI patients in England by Martin 2017[27] was used to estimate survival rates in patients at low, intermediate and high surgical risk. The study was reviewed by several members of the committee who agreed that the population enrolled had most of the characteristics of people at intermediate risk. The mean STS of the enrolled patients was 5.06 suggesting that, indeed, the majority of patients are at intermediate surgical risk (STS between 4 and 8). Furthermore, if we compare the descriptive statistics of Martin 2017 with the latest PARTNER study on intermediate risk[20], we can see similarities (see table 8).

Table 8: Comparison between baseline characteristics of Martin 2017 patients and intermediate patients (PARTER 2)

Variable	Martin 2017[27]	PARTNER 2 (intermediate risk)[20]
Age	81.3	81.5
STS	5.06	5.8
NYHA class III or IV	80%	77%
COPD	26.2%	31.8%
Diabetes	33.6%	37.7%

Hence, survival in the population at an intermediate surgical risk was estimated by directly applying the relative survival from Martin to the mortality of the general population. General

population mortality was based on data from life tables for England 2018-2019[39]. Cycle-specific general population mortality was calculated taking into account the age and gender split for the population entering the model and how this changed over time.

Survival of patients at low or high surgical risk is obviously different to survival of intermediate risk patients as surgical risk is a proxy of several health-related characteristics and comorbidities. Patients at higher risks, for instance, have more severe comorbidities and are expected to die sooner.

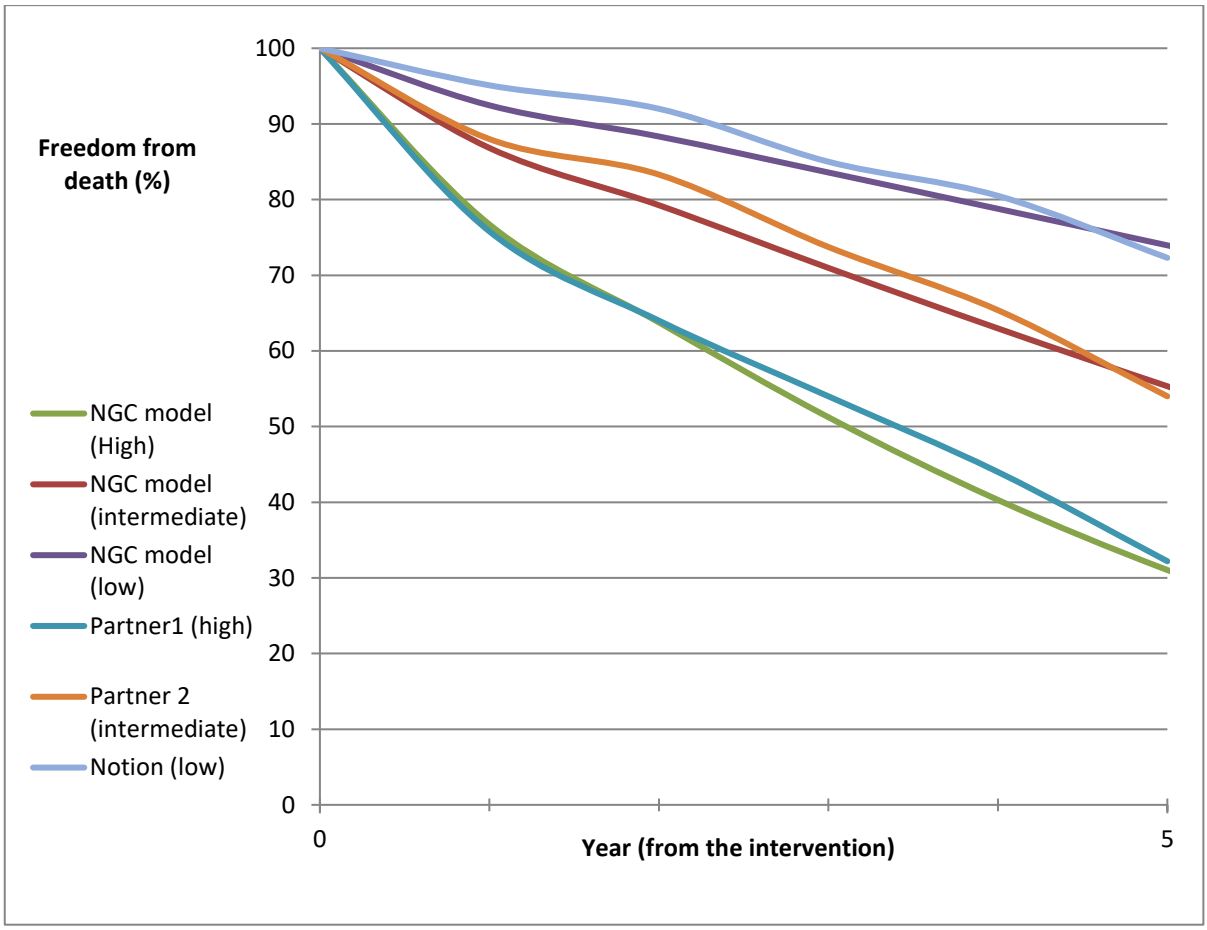
Barbash 2015[3] conducted a comparative analysis of mortality of TAVI patients at low, intermediate and high risk by using an adjusted Cox proportional hazards model to estimate hazard ratios for low vs intermediate risk and low vs high risk (see table 9). These hazard ratios were adjusted for age, gender, history of atrial fibrillation, left ventricular function, access route, kidney injury, bleeding and vascular complications.

Table 9: Confounders-adjusted hazard ratio for high and intermediate risk

Adjusted hazard ratio	Value	Source
Intermediate vs low	1.6 (1 to 2.6)	Barbash 2015[3]
High vs low	2.7 (1.7 to 4.5)	Barbash 2015[3]

The hazard ratios illustrated in table 9 were applied to the mortality estimated using Martin 2017 to recover mortality in people at high and low surgical risks. Mortality for the years beyond the last follow-up was extrapolated assuming that the cumulative excess hazard between TAVI patients and the general population grows at a constant rate after the first year, as highlighted by Martin and colleagues. The resulting survival curves, together with a comparison of relevant trials with a 5-year follow-up, are shown in figure 4.

Figure 4: survival of TAVI patients predicted from the model vs observed data



Overall, it seems that the survival curves predicted by the model compare well with the survival observed in trials for people at each risk category, particularly in the long-term. In the short term, the model has a slightly lower survival for intermediate and low risk patients in the second year, although the difference is relatively small (around 3%).

It was noted that most recent valves may give better benefits in terms of survival than the ones observed in Martin 2017[27]. Martin and colleagues collected outcomes from a period going from 2011-2014, during which valves used in the NHS were mostly 1st or 2nd generation valves. Therefore, a sensitivity analysis was conducted where survival in the low-risk group after TAVI was assumed to be equal to survival in the general population. This is in line with was found in PARTNER 3 trial[19] (see section 2.5.7).

2.3.4.3 Survival with SAVR

The meta-analyses for mortality at 1 and 2 years of trials evaluating 2nd or 3rd generations TAVI valves suggest that there is a benefit in survival in the first year, albeit not statistically significant, which dissipates in the second year (see figure 5 and 6).

Figure 5: meta-analysis mortality at 1 year

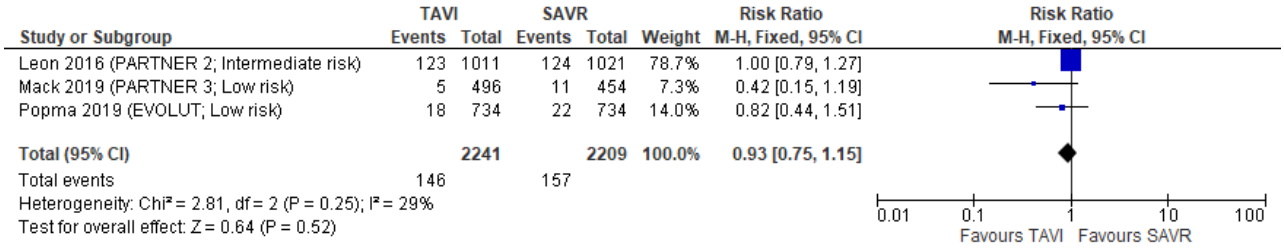
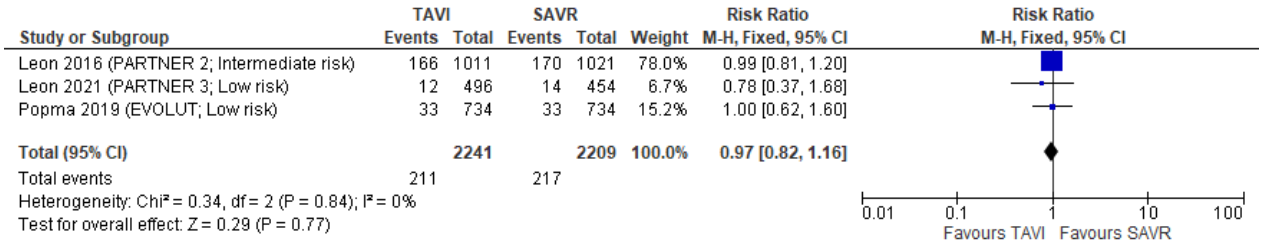
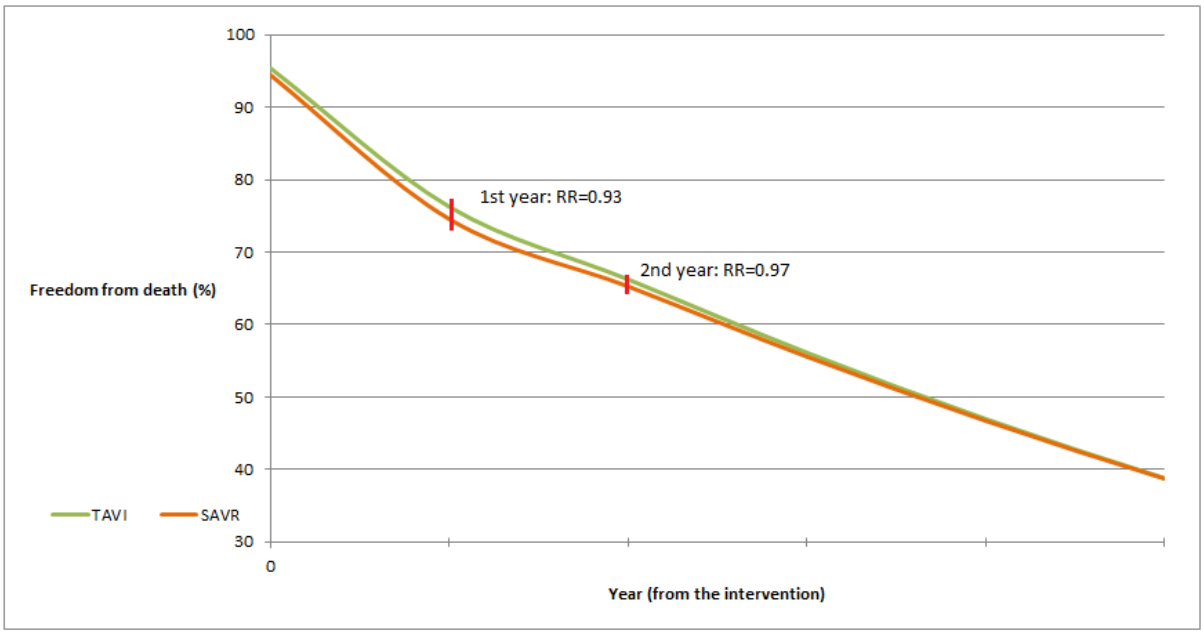


Figure 6: meta-analysis mortality at 2 years



The short-term improvement in mortality was considered important for the cost-effectiveness analysis and, therefore, two mortality calibration factors were added to the model to ensure that this effect was captured. These factors were obtained through iterative methods (the goal-seek function of Microsoft Excel) such that the relative risks between mortality in the surgical and TAVI arms match the relative risks observed in the meta-analyses at 1 and 2 years (figures 5 and 6). Beyond the second year, no calibration factor was used, so beyond 2 years survival is influenced by the distribution of patients across the different health states in each arm. The resulting survival curves for a cohort of people at high surgical risk are illustrated in figure 7.

Figure 7: 5-year survival curves for a TAVI and SAVR high risk cohort of patients



As the figure shows, the calibration factors ensures that the relative risks observed in the trials are reflected in the model, whereas in the longer-term the two curves appear to converge.

2.3.4.4 Mortality in the health states

Mortality rates in people who experiences a long-term event (pacemaker, paravalvular leak, stroke or dialysis) were sought from the published literature.

Mortality rates in people with stroke were calculated using the odds ratio reported in the study of Myat and colleagues[29]. The authors, using a UK cohort analysis, calculated the odds ratio of dying after 1 year after experiencing a stroke during a TAVI intervention. For the post-stroke state, it was assumed that the odds ratio of stroke was reduced using the same ratio found in a published study on mortality after stroke[7]. The resulting odds ratios are presented in table 4.

Mortality for people who underwent a pacemaker implantation was calculated using the risk ratio reported in the study from Faroux[10].

For mortality after dialysis, it was agreed to use a paper from Ferro 2017[11]on the outcomes after TAVI reported in the UK TAVI registry. The paper found the hazard ratio of dying 4 years later after receiving dialysis following a TAVI intervention. As the mortality in the first 30 days was captured already in the decision tree, the hazard ratio was recalculated using a methodology described in the literature[51] to exclude those who died in the first 30 days and applied in the first cycle of the model.

Finally, regarding paravalvular leak, the committee agreed to use a recent paper[26] reporting the hazard ratios of dying for people who showed clinical mild or moderate/severe paravalvular leak compared to those with no trace of paravalvular leak. In the base case scenario, it was assumed that only moderate/severe paravalvular leaks affect mortality whereas, in the sensitivity analysis, mild paravalvular leaks were allowed to increase mortality as well. Table 10 shows all the inputs used in the model to estimate mortality.

Table 10: Confounder-adjusted hazard ratio for high and intermediate risk

Event	Input	Value	Source
Stroke	Odds ratio	3.21 (2.15 to 4.78)	Myat 2020[29]
Post-stroke	Odds ratio	1.58 (1.07 to 2.3)	Myat 2020[29] calculated using the same ratio of Bronnum-Hansen 2001[7]
Pacemaker	Risk ratio	1.17 (1.11 to 1.25)	Faroux 2020[10]
Dialysis	Hazard ratio	2.81 (1.31 to 6.01)	Calibrated from Ferro 2017[11]
Mild PVL (none vs mild)	Hazard ratio	Base case: 1 Sensitivity analysis: 0.81 (0.62 to 1.07)	Makkar 2020[26]
Moderate PVL (none vs moderate)	Hazard ratio	0.41 (0.24 to 0.7)	Makkar 2020[26]
Conversion to SAVR	Hazard ratio	4.38 (3 to 6.39)	Ferro 2017[11]

These parameters could not be applied to the mortality predicted by the model, as this latter represents the mortality of all TAVI or SAVR patients, a cohort including stable and patients with adverse events. A hazard ratio/risk ratio is defined as the ratio of the rate/probability of an event occurring in the exposed group versus the rate/probability of the event occurring in the non-exposed group. The mortality calculated with the methodology described in 2.3.4.2 and 2.3.4.3 refers to a population with exposed and non-exposed individuals alike. Failing to recognize this would inevitably lead to an over-estimation of the overall mortality observed in Martin 2017[27] and potentially invalidate the results of the model.

Hence, mortality of people in the stable state, i.e. with no adverse event, needed to be estimated first, and then used as a function to estimate the mortality in the other events. This was achieved by applying a calibration factor, a multiplier, to the mortality rates of the general TAVI population to get an estimation of the mortality rates of those in the stable with TAVI state. The calibration factor was obtained through iterative methods (the goal-seek function of Microsoft Excel) such that the overall mortality predicted by the model matches the one observed at the third year (the last follow-up of the study from Martin[27]).

In table 11, survival predicted by the model during the first 10 cycles was compared against the survival derived from application of the relative survival estimates from Martin 2017[27] to general population survival (intermediate risk). The percentages in bold are derived from the relative survival estimates directly reported in Martin 2017 whereas the numbers, for the cycles beyond the third one, we used the extrapolation discussed in sectionsection 2.3.4.2.

Table 11: Survival expected vs survival predicted by the model – TAVI arm 80-year-old patients

Years from the intervention	Survival derived from Martin 2017[27]	Survival in model
0	**100%**	100%
1	**87%**	86%
2	**80%**	80%
3	**73%**	73%
4	65%	66%
5	58%	60%
6	52%	53%
7	45%	47%
8	39%	41%
9	33%	36%
10	27%	30%

Overall, the inclusion of the calibration factor ensured that the mortality in the model matches the mortality observed for the first 3 cycles of the Markov model, although for the remaining cycles the mortality predicted by the model remains slightly lower than the one extrapolated from Martin 2017[27]. This implies that the model might be slightly over-estimating survival in the long-term, although survival in the longer term is more uncertain anyway.

2.3.5 Utilities

2.3.5.1 Utility after TAVI or surgery

Quality of life scores for people who received TAVI or SAVR were sought from the trials included in the clinical review. Different sets of utility scores were applied to people with high, intermediate and low surgical risk to account for the differences between these risk groups.

Quality of life scores in the high-risk population were taken from the study of Gleason 2018[12] based on the CoreValve US pivotal high-risk trial. The values were measured in terms of SF-12 composite scores divided in SF-12 mental scores and SF-12 physical score and were collected at baseline, 1 month, 6 months and 12 months after the intervention. To convert these scores into EQ-5D scores, which is the preferred measure of NICE, mapping studies were sought using the database for mapping studies. It was ultimately decided to use the algorithm provided by the study of Lawrence et al[18]. referring to how to map SF-12 composite scores into EQ-5D. The algorithm used is the following:

$$EQ-5D = -1.6984 + 0.07927 * PCS + 0.02859 * MCS - 0.000126 * PCS * MCS - 0.00141 * PCS^2 - 0.00014 * MCS^2 + 0.0000107 * PCS^3$$

where MCS is SF-12 mental composite score whereas PCS is SF-12 physical score. It is worth mentioning that the study used is based on a US population sample and therefore it may not reflect the UK population. To calculate the associated standard deviation a second algorithm included in the paper was used.

For the intermediate risk population, Baron 2018[6] reported EQ-5D scores at baseline, 1 month and 12 months after the intervention collected from PARTNER 2 intermediate risk trial.

Finally, for low surgical risk people, the study on quality of life from Baron 2019[5] based on PARTNER low risk trial was used reporting EQ-5D at baseline, 1, 6, 12 months after interventions.

The resulting EQ-5D scores for each risk group are presented in table 12

Table 12: Utility scores in people at high, intermediate and low surgical risk

Follow-up	High risk		Intermediate risk		Low risk	
	TAVI	SAVR	TAVI	SAVR	TAVI	SAVR
Baseline	0.57	0.59	0.75	0.74	0.83	0.83
1 month	0.69	0.56	0.82	0.74	0.89	0.82
6 months	0.72	0.71	-	-	0.88	0.88
12 months	0.72	0.72	0.80	0.80	0.87	0.87

Table 12 shows a common pattern in all risk groups where TAVI patients experience a higher utility gain compared to SAVR patients in the short term (1 month after the intervention) whereas in the long term (12 months after the intervention) the difference in the utility scores becomes zero. This is particularly evident in the high-risk group, where people receiving surgery incurred a clinically important loss of quality of life (0.03) whereas TAVI patients experience a large improvement (0.11).

To capture this effect in the model, two different utility scores where applied: one in the first year after the intervention based on the average utility scores collected during the first year,

and one for the following years based on the utility score collected at 12 months. The average utility score in the first year was calculated assuming that the utility values vary each month at a constant rate.

It was assumed that people requiring a reintervention would show symptoms comparable to patients who have not received an intervention yet. The committee agreed that those symptoms would not last for the duration of an entire cycle (1 year) as people would likely receive a reintervention before. It was agreed though, to limit this loss of utility to the average waiting time before a reintervention, which was assessed to be around 6 months according to the committee.

The resulting utility values used in the model are illustrated in table 13.

Table 13: QALY used in the model

Follow-up	High risk		Intermediate risk		Low risk	
	TAVI	SAVR	TAVI	SAVR	TAVI	SAVR
First year	0.70	0.65	0.80	0.78	0.87	0.86
>1 year	0.72	0.72	0.80	0.80	0.87	0.87
People needing a reintervention	0.57	0.59	0.75	0.74	0.83	0.83

The utility scores obtained were compared to the utility score of the general UK population reported by Ara and Brazier[2] and a utility multiplier was calculated by dividing the utility score observed in the trials with the corresponding utility score in the general population with the same mean age. This factor was then multiplied with the utility scores of the general population at each year of age to calculate the utility score by age for people in the TAVI and surgical arms. This method ensured that utility decreases with age as expected. Surprisingly, the utility multipliers calculated were often positive suggesting that this population has somehow better health-related quality of life than the general population. This may be because these people are all suitable for surgery, therefore with less comorbidities and, possibly, in some respects healthier than the general population.

2.3.5.2 Utility decrements

Several short and long-term states result in a loss of utility for people experiencing such events. Utility decrements associated with these states were sought by looking at studies reporting patients` utility score after a heart valve intervention.

A study from Kaier and colleagues[16] reports the EQ-5D decrements following a range of post-procedural outcomes after a TAVI. Following a discussion with the clinical advisor, it was decided to use this source to inform the utility decrements of all health events except stroke. The reason to use another source for stroke is that in Kaier only a small group of individuals (around 6) experienced stroke; therefore, it did not seem appropriate to apply this value to the whole population of the model. As TAVI is performed through an artery, major bleeding tends to be severe if compared with other transcatheter interventions. Hence, it was decided to apply the loss of utility caused by life-threatening major bleeding and it was assumed that the loss of utility lasts for one month and a half as Kaier found major bleeding to have a moderate effect during the second monthly follow-up after the event. Other events,

such as vascular complications, were assumed to affect quality of life for 30 days only. The loss of utility caused by a severe kidney injury requiring dialysis (AKIN 3) was assumed to be permanent.

Regarding stroke, it was agreed to use the study from Luengo-Fernandez[24] reporting the quality of life after a stroke using the ten-year results of the Oxford vascular study. To calculate the average utility during the first year, it was assumed that the utility score increased at a constant rate each month. The loss of utility caused by stroke during the first year was calculated by subtracting the annual average utility score in the stroke group from the corresponding annual average utility score in the control group. Likewise, to calculate the loss of utility caused by post-stroke (>1 year), an average across 5 years was calculated assuming, again, that the utility score increased or decreased at a constant rate each year.

The resulting utility decrements used in the model are presented in table 14.

Table 14: Utility decrements

Condition	Utility detriments	Duration	Source
Major bleeding	0.45	45 days	Kaier 2016[16]
Vascular complication	0.00695	30 days	Kaier 2016[16]
Dialysis	0.161	Permanently	Kaier 2016[16]
Pacemaker	0	Permanently	Assumed
Stroke	0.16	1 year	Luengo-Fernandez 2013[24]
Post-stroke	0.179	Permanently	Luengo-Fernandez 2013[24]

2.3.6 Resource use and costs

2.3.6.1 Intervention costs

The cost of a TAVI or SAVR intervention was sought from the NHS Reference Costs 2018-2019[37]. A limitation of using NHS Reference Costs is represented by the fact that currently in the UK only high-risk patients receive TAVI and therefore the cost reported is not representative of the cost incurred by other risk groups. The currency code EY21A, referring to TAVI to those with severe comorbidities, was excluded from the analysis as considered to reflect the cost on inoperable patients or with very high surgical risk, which was not the focus of this analysis. Additionally, the cost reported in the NHS Reference Costs does not include the cost of staying in an intensive care unit (ICU) after the intervention which, as the trials in the clinical review show, tend to be an important component of the total cost of the intervention.

Therefore, we recalculated the cost of the intervention using the following methodology.

The cost of the intervention per se was recalculated by subtracting from the NHS reference cost the cost of the hospital stay. This latter was obtained by multiplying the excess bed day cost for the average hospital length of stay for each specific HRG. The cost of the intervention without the hospital stay component therefore was calculated using the following equation and is illustrated in 5:

$$Cost\ of\ the\ intervention\ without\ hospital\ stay = NHS\ reference\ cost - excess\ bed\ day\ cost \times average\ length\ of\ stay\ (\text{for that HRG})$$

It is worth mentioning that the most recent version of the NHS Reference Costs (2018-2019)[37] does not include excess bed day cost and therefore, the previous version (2017-2018)[36] had to be used.

Table 15: The cost of the intervention

State	NHS Reference Cost	Cost of the intervention without the hospital stay component
Transcatheter Aortic Valve Implantation (TAVI) using Transfemoral Approach, with CC Score 0-7	£6,006	£4,503
Complex, Single Heart Valve Replacement or Repair, with CC Score 11+	£16,403	£14,640
Complex, Single Heart Valve Replacement or Repair, with CC Score 6-10	£13,472	£10,619
Complex, Single Heart Valve Replacement or Repair, with CC Score 0-5	£11,994	£10,206
Standard, Single Heart Valve Replacement or Repair, with CC Score 11+	£13,471	£10,539
Standard, Single Heart Valve Replacement or Repair, with CC Score 6-10	£11,893	£10,091
Standard, Single Heart Valve Replacement or Repair, with CC Score 0-5	£10,735	£9,196

Regarding TAVI, it was decided to assign to all risk groups the cost associated with an intervention with a CC between 0 and 7. For SAVR, complex and standard interventions were pooled together, and the costs were assigned according to the CC score: 11+ to high risk, 6-10 to intermediate risk. When TAVI was converted intraoperatively to SAVR, the cost of a complex intervention was applied according to CC score: 11+ to high risk, 6-10 to intermediate risk. This is because SAVR conversion was considered a major complication of the intervention and, therefore, assumed to be associated with higher costs than a standard SAVR.

Hospital length of stay and days spent in ICU were taken from the latest available trial evidence from the UK, the UK TAVI trial[52], reporting median days spent in the hospital and in an ICU in a low risk population undergoing TAVI or SAVR. These figures were considered

representative of the UK current practice, showing that, for instance, the trend for TAVI has shifted towards less days spent in the hospital and almost no day spent in ICU if compared with the data from the US trials. Whereas data from the UK TAVI trial could be directly applied to the low-risk population, hospital LOS and ICU had to scaled up for the other risk groups as evidence shows that surgical risk is a very important predictor of hospital resource use. An analysis from Reinöhl 2015[44] studied the effect of risk on hospital LOS and ICU finding that risk is an important predictor of resource use after SAVR, but less relevant after TAVI. The incremental effect per one-unit change of STS score found in the analysis was used to calculate hospital LOS and ICU in intermediate and high risks (see table 16). ICU after TAVI was set to 0 for all risk groups as evidence from the UK suggest that ICU is rarely needed after a transcatheter intervention.

Table 16: Mean Length of stay (LOS) in model by risk category

Surgical risk	Hospital LOS (days)		ICU LOS (days)		Source
	TAVI	SAVR	TAVI	SAVR	
Low risk	3	8	0	1	UK TAVI trial[52] - median
Intermediate risk	3.2	10.5	0	1.5	UK TAVI trial[52] – median - scaled up using Reinöhl 2015[44]
High risk	3.3	12.1	0	1.8	UK TAVI trial[52] – median - scaled up using Reinöhl 2015[44]

It should be noted that the days reported in the UK TAVI trial are medians and not means. Mean days are usually preferred in economic analyses although sample mean length of stay can be strongly influenced by a small number of patients with rare complications. Using mean instead than median days would have probably led to an increase of the estimations of costs for both TAVI and SAVR and this was discussed in the limitations section (4.2).

The length of stay in table 16 were used to calculate the cost of ICU and hospital ward stay after the intervention. The cost of one day of ICU was obtained by calculating the average cost of adult critical care from the NHS Reference Cost 2018-2019 weighted for the number of episodes (see table 17).

Table 17: ICU costs

Currency Code	Currency Description	Number of Episodes	National Average Unit Cost
XC01Z	Adult Critical Care, 6 or more Organs Supported	1297	£3,382
XC02Z	Adult Critical Care, 5 Organs Supported	5810	£2,696
XC03Z	Adult Critical Care, 4 Organs Supported	17292	£2,051
XC04Z	Adult Critical Care, 3 Organs Supported	52290	£1,526
XC05Z	Adult Critical Care, 2 Organs Supported	53490	£1,338
XC06Z	Adult Critical Care, 1 Organ Supported	47699	£963

Currency Code	Currency Description	Number of Episodes	National Average Unit Cost
XC07Z	Adult Critical Care, 0 Organs Supported	2070	£824
Weighted average			£1,415

The unit cost of a day spent in the hospital ward was calculated using the excess bed days data from the NHS Reference Costs 2017-2018[36]. An average of the unit cost was calculated weighted by the number of excess bed days reported for each HRG as shown in table 18.

The resulting averages were used to cost a day spent in the hospital; the same cost was used for for both groups

Table 18: Hospital ward stay cost

Currency Code	Currency Description	Excess Bed days	National Average Unit Cost
ED24A	Complex, Single Heart Valve Replacement or Repair, with CC Score 11+	134	£183
ED24B	Complex, Single Heart Valve Replacement or Repair, with CC Score 6-10	69	£437
ED24C	Complex, Single Heart Valve Replacement or Repair, with CC Score 0-5	156	£372
ED25A	Standard, Single Heart Valve Replacement or Repair, with CC Score 11+	238	£368
ED25B	Standard, Single Heart Valve Replacement or Repair, with CC Score 6-10	320	£289
ED25C	Standard, Single Heart Valve Replacement or Repair, with CC Score 0-5	372	£340
Weighted average			£325

Finally, the cost of ICU and hospital stays were added to the cost of the procedure to determine the overall cost of the intervention (including LOS and ICU but excluding the cost of the TAVI valve). These are reported in 19.

Table 19: Cost of the intervention including ICU and hospital stay

Surgical risk	TAVI (excluding the cost of the valve)	SAVR (including the cost of the valve)	SAVR conversion (including the cost of the valve)
Low risk	£5,479	£13,393	£13,898
Intermediate risk	£5,540	£15,489	£15,753
High risk	£5,575	£18,572	£20,623

Valve cost

The cost of a TAVI valve is not included in the NHS Reference Costs as it is listed in the High Cost Device Exclusion List. NHS Supply Chain confirmed that 80% of the valves are purchased under the NHSE High-Cost Tariff Excluded Devices Programme at an average price of £17,500. This is an average across different NHS trusts and different valve brands but was considered to represent the average price NHS is spending on a TAVI valve in 2020 and therefore used in the base case scenario of the analysis (table 20). In the sensitivity analysis a different price of £15,000 was tested and, in addition, a threshold analysis on the price of the valve was conducted (see section 3.3)

Table 20: The price of a TAVI valve

State	Price	Source
TAVI valve	£17,500	NHS Supply Chain

Intermediate care and rehabilitation

Data from a clinical trial[25] show that more patients in the SAVR arm were discharged to an intermediate care centre for rehabilitation post-surgery or to receive home-based rehabilitation. To capture the increased cost of rehabilitation after SAVR, the costs of home-rehabilitation and intermediate care were added to the overall cost of the procedure. Those were sought from the National Audit on Intermediate Care (NAIC 2017) whereas the proportion of people receiving rehabilitation in each arm was informed by Mack 2019[25] as reported in table 21.

Table 21: The cost of rehabilitation

Currency Code	TAVI	SAVR	Source
Discharge at intermediate care centre	0.8%	14.8%	Mack 2019[25]
Cost of intermediate care centre	£5965		NAIC 2017[30]
Home-based rehabilitation	2.8%	11.3%	Mack 2019[25]
Cost of home-based rehabilitation	£982.00		NAIC 2017[30]

It should be noted that the study[25] used to inform the proportion of patients needing home-based or intermediate care centre rehabilitation was conducted in US, therefore it may not reflect the current practice in the UK.

2.3.6.2 Health states

Several health states are associated with a cost sustained by the NHS. The sources of costs data were sought by reviewing existing models and by conducting a non-systematic review online. Costs were divided in short-term decision tree costs and long-term Markov states costs according to whether they are sustained immediately after the surgery or continuously over the years following the intervention. In the base case scenario, all the short-term event costs were assumed to be included in the TAVI or SAVR HRG.

Where possible, the NHS Reference costs were used. These are the average unit costs to the NHS and are based on data submitted by all Trusts in England. Providers cost reference costs on a full absorption basis, which means that all the running costs of providing these services are included within the submission including overheads. This includes the full range of staffing inputs, equipment and building costs.

2.3.6.2.1 Decision tree outcomes (major bleeding, vascular complications and Pacemaker)

Three post-procedural outcomes, namely major bleeding, vascular complication and pacemaker, are associated with a cost sustained by the NHS. These costs are sustained only once, at the offsetting of the state, and are not repeated over time. In the base case scenario, all the costs of these events were assumed to be captured by the associated HRG, and therefore not counted separately by the model (see table 22).

Table 22: Decision tree costs

State	Cost	Source
Major bleeding	Base case: £0 Sensitivity analysis: £1,971	NHS Reference Costs 2018-2019[34]
Vascular complication	Base case: £0 Sensitivity analysis: £1,826	NHS Reference Costs 2018-2019[34]
Pacemaker	Base case: £0 Sensitivity analysis: £2,451	NHS Reference Costs 2018-2019[34]

Cost of major bleeding

The cost of major bleeding was sought from the NHS Reference Cost database under the item gastrointestinal bleed. An average weighted by the number of attendances of NHS reference costs for all categories of non-elective long stay and short stay gastrointestinal bleed admission was used in the model. The cost of gastrointestinal bleed without intervention with CC score between 0 and 4 was omitted as this category represent minor events. This is shown in table 23.

Table 23: Cost of major bleeding

Currency Code	Currency Description	Number of FCE's	National Average Unit Cost
Non-elective long stay			
FD03A	Gastrointestinal Bleed with Multiple Interventions, with CC Score 5+	1,110	£5,377
FD03B	Gastrointestinal Bleed with Multiple Interventions, with CC Score 0-4	885	£3,510
FD03C	Gastrointestinal Bleed with Single Intervention, with CC Score 8+	1,642	£3,866
FD03D	Gastrointestinal Bleed with Single Intervention, with CC Score 5-7	2,329	£2,796
FD03E	Gastrointestinal Bleed with Single Intervention, with CC Score 0-4	5,481	£2,247
FD03F	Gastrointestinal Bleed without Interventions, with CC Score 9+	2,891	£2,818
FD03G	Gastrointestinal Bleed without Interventions, with CC Score 5-8	7,278	£2,198
Non-elective short stay			
FD03A	Gastrointestinal Bleed with Multiple Interventions, with CC Score 5+	30	£2,360
FD03B	Gastrointestinal Bleed with Multiple Interventions, with CC Score 0-4	16	£2,088
FD03C	Gastrointestinal Bleed with Single Intervention, with CC Score 8+	41	£1,345
FD03D	Gastrointestinal Bleed with Single Intervention, with CC Score 5-7	46	£2,360
FD03E	Gastrointestinal Bleed with Single Intervention, with CC Score 0-4	108	£1,089

Currency Code	Currency Description	Number of FCE's	National Average Unit Cost
Non-elective long stay			
FD03F	Gastrointestinal Bleed without Interventions, with CC Score 9+	2,213	£591
FD03G	Gastrointestinal Bleed without Interventions, with CC Score 5-8	8,830	£541
Weighted average			£1,971.51

Vascular complications

The cost of vascular complication was sought by looking at International Classification of Diseases (ICD) codes related to various injuries to blood vessels around the body. The ICD code was then converted into an HRG code to find the associated cost for the public sector in the NHS References Costs. The associated HRG description was “peripheral vascular disorder” and the cost for the model was obtained by calculating the average non-elective long and short stay cost weighted by the number of attendances. This is shown in table 24.

Table 24: Cost of Vascular complications

Currency Code	Currency Description	Number of FCE's	National Average Unit Cost
Non-elective long stay			
YQ50A	Peripheral Vascular Disorders with CC Score 15+	2,529	£5,402
YQ50B	Peripheral Vascular Disorders with CC Score 11-14	3,543	£3,995
YQ50C	Peripheral Vascular Disorders with CC Score 8-10	3,539	£3,289
YQ50D	Peripheral Vascular Disorders with CC Score 5-7	3,869	£2,882
YQ50E	Peripheral Vascular Disorders with CC Score 2-4	2,906	£2,451
YQ50F	Peripheral Vascular Disorders with CC Score 0-1	910	£2,399
Non-elective short stay			
YQ50A	Peripheral Vascular Disorders with CC Score 15+	673	£852

Currency Code	Currency Description	Number of FCE's	National Average Unit Cost
Non-elective long stay			
YQ50B	Peripheral Vascular Disorders with CC Score 11-14	1,519	£710
YQ50C	Peripheral Vascular Disorders with CC Score 8-10	2,685	£597
YQ50D	Peripheral Vascular Disorders with CC Score 5-7	4,438	£541
YQ50E	Peripheral Vascular Disorders with CC Score 2-4	6,924	£452
YQ50F	Peripheral Vascular Disorders with CC Score 0-1	5,050	£350
Weighted average			£1,826

Cost of Pacemaker

The cost of pacemaker was collected from the NHS reference costs 2018/19[34] as shown in table 25. Biventricular pacemaker costs were omitted as these particularpacemakers relate to the treatment of heart failure and are not used for issues related to TAVI.

Table 25: Cost of Pacemaker

Currency Code	Currency Description	Activity	Total
Non-elective long stay			
EY05A	Implantation of Dual-Chamber Pacemaker with Other Percutaneous Intervention, with CC Score 6+	281	£7,407
EY05B	Implantation of Dual-Chamber Pacemaker with Other Percutaneous Intervention, with CC Score 0-5	265	£4,703
EY06A	Implantation of Dual-Chamber Pacemaker with CC Score 12+	1158	£6,247

Currency Code	Currency Description	Activity	Total
Non-elective long stay			
EY06B	Implantation of Dual-Chamber Pacemaker with CC Score 9-11	1386	£4,035
EY06C	Implantation of Dual-Chamber Pacemaker with CC Score 6-8	3293	£3,324
EY06D	Implantation of Dual-Chamber Pacemaker with CC Score 3-5	7710	£2,697
EY06E	Implantation of Dual-Chamber Pacemaker with CC Score 0-2	10704	£2,286
EY07A	Implantation of Single-Chamber Pacemaker with Other Percutaneous Intervention, with CC Score 6+	165	£7,565
EY07B	Implantation of Single-Chamber Pacemaker with Other Percutaneous Intervention, with CC Score 0-5	120	£4,539
EY08A	Implantation of Single-Chamber Pacemaker with CC Score 12+	1090	£5,555
EY08B	Implantation of Single-Chamber Pacemaker with CC Score 9-11	1093	£3,809
EY08C	Implantation of Single-Chamber Pacemaker with CC Score 6-8	2306	£3,075
EY08D	Implantation of Single-Chamber Pacemaker with CC Score 3-5	4746	£2,290
EY08E	Implantation of Single-Chamber	13331	£1,085

Currency Code	Currency Description	Activity	Total
Non-elective long stay			
	Pacemaker with CC Score 0-2		
Weighted average			£2,451

Cost of paravalvular leak (PVL)

It was agreed by the committee that PVL required a simple echocardiogram and a consultant led appointment. The calculation used to estimate the cost for the model is shown in table 26.

Table 26: PVL costs

State	Cost	Source
Simple echocardiogram	£115	NHS Reference Costs 2018-2019[34]
Consultant led		
Non-admitted Face-to Face Attendance, follow-up	£135	NHS Reference Costs 2018-2019[34]
Total	£250	

2.3.6.2.2 Long-term outcome costs (Stroke and post-stroke)

Stroke is associated with a substantial cost borne by the NHS and social care and it is known to affect in the long-term the quality of life, the survival and the demand for NHS resources of the patients. To capture both the acute and chronic phase of the disease, stroke was modelled in two different states: stroke and post-stroke. The first state represents the acute phase of the event, and it is associated with the highest use of NHS resource. The second state captures the long-term demand of NHS and social care service occurring up to several years after the event. As mentioned before, it was assumed that patients did not transit out from the post-stroke state and that they required NHS and social care services until the die.

To cost stroke and post-stroke the same approach used in the Acute Coronary Syndrome model was adopted. The cost was based on the work of Xu 2018[54] which estimated the total burden of stroke in the UK to the NHS and social services. This was done using a patient simulation based on UK Sentinel Stroke National Audit Programme (SSNAP) data. The cost of stroke was reported in the study for 1 and 5 years table 27.

Table 27: Burden of stroke

Health state	Cost	Source
Stroke 1 year	£23,052	Xu 2018 – SSNAP project inflated to 2017/18[54]
Stroke 5 year	£47,023	Xu 2018 – SSNAP project inflated to 2017/18[54]

Cost associated with NHS and social service were reported separately. The latter includes both publicly financed social service and privately funded social service. As NICE reference case provides that the cost-effectiveness analysis is conducted from a public sector point of view only, non-publicly funded cost cannot be included in this analysis. A recent paper Patel 2019[40] used the assumption that approximately 50% of the social cost is born by the NHS and, therefore, the same assumption was used in the model.

Costs associated with stroke and post-stroke are assumed to be borne during the year following the events and therefore were modelled as Markov state costs. When applying the half-cycle correction, it was used the assumption that the cost of an acute stroke is sustained during the first 6 months following the event, whereas the cost of post-stroke is spread over the year.

The costs used in the model related to stroke or post-stroke are summarized in table 28.

Table 28: Cost of stroke and post-stroke

Health state	Cost	Source
Stroke	£18,948	Xu 2018[54] 1-year costs with 50% of social care costs removed and inflated to 2018/2019
Post-stroke	£6,727	Xu 2018[54] 5-year costs adjusted to remove 1-year cost and annualised; 50% of social care costs removed and inflated to 2018/2019

Rehospitalisation

The cost of a cardiac hospitalisation episode was sought from the NHS Reference Costs 2018/2019 under the item “Cardiac valve disorder”. An average weighted for the level of activity was calculated and used in the model table 29.

Table 29: Cardiac valve disorder hospitalisation

Currency Code	Currency Description	Activity	Unit Cost
EB03A	Cardiac Valve Disorders with CC Score 13+	3344	£3,672
EB03B	Cardiac Valve Disorders with CC Score 9-12	53801	£2,518
EB03C	Cardiac Valve Disorders with CC Score 5-8	60844	£1,865
EB03D	Cardiac Valve Disorders with CC Score 0-4	38935	£1,382
Weighted average			£2,275.43

Dialysis

The cost of a session of dialysis was based on a weighted average of all haemodialysis categories from the NHS Reference Cost 2018-2019 (see table 30).

Table 30: Cardiac valve disorder hospitalisation

Currency Code	Currency Description	Activity	Unit Cost
LD01A	Hospital Haemodialysis or Filtration, with Access via Haemodialysis Catheter, 19 years and over	429546	£147.26
LD02A	Hospital Haemodialysis or Filtration, with Access via Arteriovenous Fistula or Graft, 19 years and over	708759	£156.52
LD03A	Hospital Haemodialysis or Filtration, with Access via Haemodialysis Catheter, with Blood-Borne Virus, 19 years and over	19196	£154.14
LD04A	Hospital Haemodialysis or Filtration, with Access via Arteriovenous Fistula or Graft, with Blood-Borne Virus, 19 years and over	23938	£166.27
LD05A	Satellite Haemodialysis or Filtration, with Access via Haemodialysis Catheter, 19 years and over	577621	£145.31
LD06A	Satellite Haemodialysis or Filtration, with Access via Arteriovenous Fistula or Graft, 19 years and over	1211636	£157.07
LD07A	Satellite Haemodialysis or Filtration, with Access via Haemodialysis Catheter, with Blood-Borne Virus, 19 years and over	24903	£139.07
LD08A	Satellite Haemodialysis or	49499	£160.08

Currency Code	Currency Description	Activity	Unit Cost
	Filtration, with Access via Arteriovenous Fistula or Graft, with Blood-Borne Virus, 19 years and over		
LD09A	Home Haemodialysis or Filtration, with Access via Haemodialysis Catheter, 19 years and over	41633	£200.01
LD10A	Home Haemodialysis or Filtration, with Access via Arteriovenous Fistula or Graft, 19 years and over	81223	£218.36
LD01A	Hospital Haemodialysis or Filtration, with Access via Haemodialysis Catheter, 19 years and over	885	£680.37
LD02A	Hospital Haemodialysis or Filtration, with Access via Arteriovenous Fistula or Graft, 19 years and over	386	£386.61
LD03A	Hospital Haemodialysis or Filtration, with Access via Haemodialysis Catheter, with Blood-borne Virus, 19 years and over	4	£158.05
LD05A	Satellite Haemodialysis or Filtration, with Access via Haemodialysis Catheter, 19 years and over	32	£204.45
LD06A	Satellite Haemodialysis or Filtration, with Access via Arteriovenous Fistula or Graft, 19 years and over	119	£233.55
LD09A	Home Haemodialysis or Filtration, with Access via	3	£253.88

Currency Code	Currency Description	Activity	Unit Cost
	Haemodialysis Catheter, 19 years and over		
Weighted average			£153.92

Overall, the average cost of a dialysis session was found to be £153.92. Assuming that a person would have 3 sessions a week for 52 weeks a year, the annual cost of a dialysis amounts to £24,010.95. Transport costs for dialysis are largely sustained by the NHS and therefore need to be added to the annual cost of dialysis. This cost was estimated to be £4058 in the renal replacement therapy and conservative management guideline[34] and therefore, the same estimation was used in this model. Finally, the cost of dialysis was inflated by 15% to capture the other costs associated with the treatment (access procedures, out-patient appointments and management of complications) as previously done in the HDF guideline[34]. This gives a final cost of dialysis of £37,893.

2.4 Computations

The model was constructed in Microsoft Excel 2010 and was evaluated by cohort simulation. Time dependency was built in by cross referencing the cohort's age as a risk factor for mortality. Baseline utility was lower in the first-year post procedure, but higher and assumed to be constant afterwards.

People started in the decision tree in the TAVI or SAVR arm. People then moved to the other health states (major bleeding, vascular complication, pacemaker implantation, chronic kidney injury, PVL, stroke, conversion to SAVR and dead) based on probabilities of events occurring which was calculated from baseline risks and treatment effects. Those alive at the end of the decision tree at 30 days, entered the model and started in cycle 0. The health state they entered was determined by which health state they were in at the end of the 30 days decision tree. Those who did not experience any events or experienced only temporary events such as bleeding or vascular complication entered the "stable" health state in the Markov model. Those who had a stroke entered the "stroke" health state in the Markov model. Mortality transition probabilities in the Markov model depend on the health states people are in.

Mortality rates were converted into transition probabilities for the respective cycle length (1 year in the base case) before inputting into the Markov model.

$Transition\ Probability\ (P) = 1 - e^{-rt}$	Where r=selected rate t=cycle length (1 year)

To calculate QALYs for each cycle, life years were weighted by a utility value which was treatment dependent. A half-cycle correction was applied, assuming that people transitioned between states on average halfway through a cycle. QALYs were then discounted at 3.5% to reflect time preference. QALYs during the first cycle were not discounted. The total discounted QALYs were the sum of the discounted QALYs per cycle.

Costs per cycle were calculated on the same basis as QALYs and were discounted at 3.5% to reflect time preference. Each of the health states had specific costs applied.

Discounting formula:

$$\text{Discounted total} = \frac{\text{Total}}{(1+r)^n}$$	Where: *r*=discount rate per annum *n*=time (years)

In the deterministic and probabilistic analyses, the total cost and QALYs accrued by each cohort was divided by the number of patients in the population to calculate a cost per patient and cost per QALY.

2.5 Sensitivity analyses

In addition to the probabilistic sensitivity analysis, a range of one-way sensitivity analyses were undertaken. These are shown in table 31, where the scenarios used in the base case scenario are highlighted in green:

Table 31: Scenario analyses

Feature	Scenarios	Description
Time horizon	5 years	Model run for 5 years
	10 years	Model run for 10 years
	15 years	Model run for 15 years
	30 years	Model run for the lifetime of patients
Treatment effects	Treatment effects calculated using all trials	1st/2nd/3rd generation valves trials
	Treatment effects calculated using only 2nd and 3rd generation trials	2nd/3rd generation valves: PARTNER 2 PARTNER 3 Evolut
	Treatment effects calculated using 2nd and 3rd generation trials except reintervention which is calculated using only 3rd generation trial	Only 3rd generation valves PARTNER 3 Evolut
Paravalvular leak and mortality	Only moderate and severe PVL affects mortality	Based on the effect found in Makkar 2020
	All types of PVL affect mortality	Based on the effect found in Makkar 2020
	No PVL affects mortality	

Cost of the valve	With NHSE actual discounted price	The valves are purchased at £17,500
	With NHSE target discounted price	The valves are purchased at £15,000
Hospital and ICU length of stay	UK TAVI trial data used for all risk groups	ICU and LOS from UK TAVI trial are applied to all risk groups
	UK TAVI trial data scaled up based on risk	ICU and hospital LOS from UK TAVI trial are applied to low risk, and then scaled up using predictors of in-hospital resource use calculated by Reinöhl 2015[44]
Cost of short-term complications	Costs assumed not to be included in the HRG (healthcare resource group) cost	Cost of pacemaker implantation, bleeding and vascular complication are costed separately in the model
	Costs assumed to be included in HRG cost	Cost of pacemaker implantation, bleeding and vascular complication are set at 0 as they are assumed to be already included in the intervention HRG
Mortality with TAVI	Mortality based on the study of Martin 2017	Mortality for intermediate risk extracted from Martin. Mortality in high and low risk calculated using HRs from Barbash 2015[3].
	Mortality in the low-risk group equal to mortality general population	Mortality in the low risk group assumed to be equal to mortality in the general population. Mortality in high and intermediate risk calculated through HRs from Barbash 2015[3].

In the next sections, all the scenario analyses and their rationale are explained

2.5.1 Time horizon

One of the main challenges of the model was the extrapolation of data coming from trials with follow-up no longer than 5 years, for a period much longer. Hence, although in the base

case scenario a period of 15 years was chosen as the time horizon, other periods of time were tested in the scenario analysis:

- 5 years
- 10 years
- 30 years

2.5.2 Treatment effects

In the base case scenario, treatment effects are calculated through a meta-analysis of the most recent trials on second and third generations valves (see section 2.3.3). In the scenario analysis, treatment effects were estimated instead using a meta-analysis including all TAVI trials available on recent and old generation valve. The treatment effects of this scenario analysis are illustrated in table 32.

Table 32: treatment effects in the scenario analysis

Risk ratio	Value	Source
Stroke	0.89	[42]CoreValve[1] SURTAVI[43] PARTNER 1A[46] NOTION[50] PARTNER 2[20] PARTNER 3[19] Evolut[42]
Major Bleed	0.45	CoreValve[1] SURTAVI[43] PARTNER 1A[46] NOTION[50] PARTNER 2[20] PARTNER 3[19] Evolut[42]
Pacemaker Implantation	2.47	CoreValve[1] SURTAVI[43] PARTNER 1A[46] NOTION[50] PARTNER 2[20] PARTNER 3[19] Evolut[42]
Vascular complication	2.15	CoreValve[1] SURTAVI[43] PARTNER 1A[46] NOTION[50] PARTNER 2[20] PARTNER 3[19] Evolut[42]
Kidney Injury	0.41	CoreValve[1] SURTAVI[43] PARTNER 1A[46]

Risk ratio	Value	Source
		NOTION[50] PARTNER 2[20] PARTNER 3[19] Evolut[42]
Mortality 30 days	0.79	CoreValve[1] SURTAVI[43] PARTNER 1A[46] NOTION[50] PARTNER 2[20] PARTNER 3[19] Evolut[42]
Mild PVL	4.21	CoreValve[1] SURTAVI[43] PARTNER 1A[46] NOTION[50] PARTNER 2[20] PARTNER 3[19] Evolut[42]
Moderate/severe PVL	11.84	CoreValve[1] SURTAVI[43] PARTNER 1A[46] NOTION[50] PARTNER 2[20] PARTNER 3[19] Evolut[42]
All-cause mortality	1 year: 0.90 2 years: 0.98	CoreValve[1] SURTAVI[43] PARTNER 1A[46] NOTION[50] PARTNER 2[20] PARTNER 3[19] Evolut[42]
Reintervention	2.78	CoreValve[1] SURTAVI[43] PARTNER 1A[46] NOTION[50] PARTNER 2[20] PARTNER 3[19] Evolut[42]
Hospitalisation	1 year: 1.07 Beyond 1 year: 2.04	CoreValve[1] SURTAVI[43] PARTNER 1A[46] NOTION[50] PARTNER 2[20] PARTNER 3[19] Evolut[42]

In a second scenario analysis, the risk ratio of reintervention was estimated from PARTNER 3[19] and Evolut[42] only. These 2 trials, although with a shorter time horizon, found a lower risk ratio than PARTNER 2[20]: 1.08. This may be explained both by the shorter time horizon (PARTNER 2 found most of the reinterventions in the TAVI arms occurring between year 2 and 5) and by the generation of the valves assessed although it is worth mentioning that, whereas PARTNER 3 studied third generation Sapien 3 only, Evolut had a mixture of different generations valves.

2.5.3 PVL and mortality

Although the study from Makkar 2020[26] found that both mild and moderate/severe paravalvular leaks affect mortality, several members of the committee pointed out that mild paravalvular leak is often considered as an issue of minor concern and, consequently, asked to include in the model only the effects on mortality of moderate/severe PVL. Therefore, although in the base case scenario it was assumed that only moderate/severe PVL affects mortality, the hypothesis that mild PVL affects mortality as well was tested in a separate sensitivity analysis.

Furthermore, an additional scenario analysis was tested where PVL does not affect mortality at all.

2.5.4 Cost of the valve

In the base case scenario, the cost of a TAVI valve was assumed to be £17,500, which is the average price across the volume 80% of TAVI valves are purchased in England and Wales under the NHSE High-Cost Tariff Excluded Devices Programme. A second price of £15,000 was tested in the scenario analysis representing a realistic price reduction that may be achieved in the following years. In addition, a threshold analysis on the price of the valve is presented in section 3.3

2.5.5 Hospital and ICU length of stay

In the base case scenario hospital and ICU length of stay (LOS) from the UK TAVI trial[52] were scaled up for the intermediate and high risk cohorts using the analysis on hospital resource by Reinöhl 2015[44]. In the scenario analysis, the same ICU and hospital LOS were assigned to all risk groups. This scenario arguably underestimates the cost-effectiveness of TAVI in intermediate and high risk patients as hospital and ICU LOS are expected to increase with the risk, particularly with surgery, but was conducted to see the impact of the adjustment based on Reinöhl[44].

2.5.6 Cost of the short-term complications

As discussed in section 2.3.6.2.1, short term complication cost were assumed to be included in the NHS Reference Costs HRG as often they occur during the same hospitalisation, and therefore, they were not costed separately. It was noted that some of these events, e.g., a new pacemaker implantation, happen after the first hospitalisation and therefore should be costed separately. A scenario analysis was conducted adding a specific cost for each short-term complication in the decision tree to assess the impact of this assumption.

2.5.7 Mortality with TAVI

Mortality after TAVI in the base case scenario was modelled using the study on relative survival from Martin and colleagues[27]. Outcomes used for this analysis were calculated from the period going from 2011 and 2014. It was noted that during this period of time, valves used in the NHS were most likely 1st and 2nd generation valves, so it is possible that survival benefits have increased in recent years following the introduction of new generation valves. Therefore, a sensitivity analysis was conducted where the survival of people at low surgical risk was assumed to be equal to the survival of the general population in the UK estimated though the life tables for England 2018-2019[39]. Survival in people at high or intermediate surgical risk was estimated by applying the corresponding hazard ratio from Barbash 2015[3] to the new survival rates in the low risk group.

2.6 Model validation

The model was developed in consultation with the committee; model structure, inputs and results were presented to and discussed with the committee for clinical validation and interpretation.

The model was systematically checked by the health economist undertaking the analysis; this included inputting null and extreme values and checking that results were plausible given inputs.

The model was systematically checked by an external peer-reviewer from the NICE Economic Methods Unit.

2.7 Estimation of cost effectiveness

The widely used cost-effectiveness metric is the incremental cost-effectiveness ratio (ICER). This is calculated by dividing the difference in costs associated with 2 alternatives by the difference in QALYs. The decision rule then applied is that if the ICER falls below a given cost per QALY threshold the result is considered to be cost effective. If both costs are lower and QALYs are higher the option is said to dominate and an ICER is not calculated.

$$ICER = \frac{Costs(B) - Costs(A)}{QALYs(B) - QALYs(A)}$$

Where: Costs(A) = total costs for option A; QALYs(A) = total QALYs for option A

Cost effective if:
- ICER < Threshold

It is also possible, for a cost-effectiveness threshold, to re-express cost-effectiveness results in term of net monetary benefit (NMB). This is calculated by multiplying the total QALYs for a comparator by the threshold cost per QALY value (for example, £20,000) and then subtracting the total costs (formula below). The decision rule then applied is that the comparator with the highest NMB is the cost-effective option at the specified threshold. That is the option that provides the highest number of QALYs at an acceptable cost.

$$Net\ Monetary Benefit(X) = \left(QALYs(X) \times \lambda\right) - Costs(X)$$

Where: λ = threshold (£20,000 per QALY gained)

Cost effective if:
- Highest net benefit

Both methods of determining cost effectiveness identified the same optimal strategy. For ease of computation NMB is used in this analysis to identify the optimal strategy.

Results are also presented graphically where total costs and total QALYs for each diagnostic strategy are shown. Comparisons not ruled out by dominance or extended dominance are joined by a line on the graph where the slope represents the incremental cost-effectiveness ratio.

2.8 Interpreting results

NICE sets out the principles that committees should consider when judging whether an intervention offers good value for money.[31-33] In general, an intervention was considered to be cost effective if either of the following criteria applied (given that the estimate was considered plausible):

- The intervention dominated other relevant strategies (that is, it was both less costly in terms of resource use and more clinically effective compared with all the other relevant alternative strategies), or
- The intervention costs less than £20,000 per quality-adjusted life-year (QALY) gained compared with the next best strategy.

3 Results

3.1 Base case

The analysis was repeated three times to simulate cohorts at low, intermediate and high surgical risk. In the following sections the mean probabilistic results of each cohort are presented.

3.1.1 High risk

Table 32 shows the probabilistic results for a high-risk cohort starting at age 81 and simulated for a period of 15 years.

Table 32: probabilistic results of a high-risk population (mean per patient)

	TAVI	SAVR	TAVI - SAVR
Intervention	£23,064	£18,569	£4,494
Rehabilitation	£77	£898	-£821
Stroke	£794	£987	-£193
Dialysis	£2,236	£5,874	-£3,639
Reintervention	£1,284	£612	£672
Hospitalisation + echo	£705	£424	£281
Total cost	**£28,052**	**£27,237**	**£815**
QALYs	**3.02**	**2.91**	**0.12**

As the table shows, although TAVI intervention is more expensive than SAVR, downstream savings for the NHS meant that TAVI cost only £815 more than SAVR. TAVI is also associated with a QALYs improvement of 0.12. The cost-effectiveness results are presented in table 33

Table 33: Probabilistic cost-effectiveness results by surgical risk level

TAVI vs SAVR	High	Inter-mediate	Low
Cost per QALY	£7,014	£47,324	£132,078
Probability TAVI is cost effective at £20,000 threshold	66%	33%	31%
Probability TAVI is cost effective at £30,000 threshold	74%	40%	34%

The probabilistic cost per QALY is significantly below the NICE threshold of £20,000 per QALY suggesting that TAVI is highly cost effective compared to surgery in patients at high surgical risk. The probabilistic analysis indicates that there is a 74% probability TAVI is cost effective at a threshold of £30,000 per QALY and 66% at a threshold of £20,000 per QALY.

3.1.2 Intermediate risk

Table 34 shows the probabilistic results for an intermediate-risk cohort starting at age 80 and simulated for a period of 15 years.

Table 34: probabilistic results of an intermediate-risk population (mean vale per patient)

	TAVI	SAVR	TAVI - SAVR
Intervention	£23,002	£15,499	£7,502
Rehabilitation	£79	£930	-£851
Stroke	£1,046	£1,286	-£193
Dialysis	£3,536	£9,245	-£241
Reintervention	£1,944	£873	-£5,709
Hospitalisation + echo	£981	£546	£436
Total cost	**£30,234**	**£27,973**	**£2,261**
QALYs	**4.66**	**4.61**	**0.048**

As the table shows, for a cohort at intermediate risk, the differential cost is higher than high risk, mostly because a surgical aortic valve replacement intervention is less expensive when conducted on people at lower risk. TAVI is also associated with a lower utility gain due to the increased number of reinterventions and the lower utility benefit of TAVI in the first year after the intervention (see section 2.3.5.1),

The cost-effectiveness results are presented in Table 33.

The probabilistic cost per QALY is around £47,324 significantly above the NICE threshold of £30,000 per QALY suggesting that TAVI is not cost effective compared to surgery in patients at intermediate surgical risk. The probabilistic analysis indicates that there is a 40% probability TAVI is cost effective at a threshold of £30,000 per QALY and 33% at a threshold of £20,000 per QALY.

3.1.3 Low risk

Table 36 shows the probabilistic results for a low-risk cohort starting at age 75 and simulated for a period of 15 years.

Table 36: probabilistic results of a low-risk population (mean value per patient)

	TAVI	SAVR	TAVI - SAVR
Intervention	£22,930	£13,387	£9,544
Rehabilitation	£80	£946	-£866
Stroke	£1,567	£1,877	-£310
Dialysis	£6,053	£15,167	-£9,115
Reintervention	£3,652	£1,613	£2,039

	TAVI	SAVR	TAVI - SAVR
Hospitalisation + echo	£1,343	£715	£629
Total cost	**£33,333**	**£30,915**	**£2,418**
QALYs	**6.77**	**6.76**	**0.018**

The differential cost is slightly higher if compared with the intermediate-risk cohort although QALYs benefits are lower than the benefits estimated in a population at high or intermediate surgical risk. The cost-effectiveness results are presented in table 33

The probabilistic cost per QALY is around £132,078, significantly above the NICE threshold of £30,000 per QALY, suggesting that TAVI is not cost effective compared to surgery in patients at low surgical risk. The probabilistic analysis indicates that there is a 34% probability TAVI is cost effective at a threshold of £30,000 per QALY and 31% at a threshold of £20,000 per QALY.

3.2 Sensitivity analysis

Several one-way sensitivity analyses were conducted as mentioned in section 2.5. The incremental cost-effectiveness ratio was found to be sensitive to the price of the valve, to the assumption impact of paravalvular leak, the reintervention treatment effect, inclusion of older randomised trials and length of stay. The deterministic results of the scenario analysis for each risk group are illustrated in the following sections.

3.2.1 High risk

Table 38 illustrates the deterministic results of the scenario analyses in people at high surgical risk.

Table 38: Deterministic results of the scenario analyses for the high-risk cohort

Scenario	Incremental costs	Incremental QALYs	Incremental cost per QALY gain
Base case (deterministic)	£1,487	0.098	£15,209
Time horizon 5 years	£1,774	0.093	£19,087
Time horizon 10 years	£1,476	0.098	£14,997
Time horizon 30 years	£1,488	0.098	£15,227
Treatment effects estimated using all trials	£2,767	0.078	£35,643
Reintervention treatment effect estimated from Evolut and PARTNER 3 only	£942	0.101	£9,292
All PVLs affect mortality	£1,433	0.049	£29,068
PVLs do not affect mortality	£1,491	0.108	£13,781
Cost of the valve reduced to £15,000	-£1,085	0.098	TAVI dominates SAVR

Scenario	Incremental costs	Incremental QALYs	Incremental cost per QALY gain
ICU and LOS from TAVI trial not scaled up for higher risks	£3,689	0.098	£37,730
Cost of short-term complications costed separately	£1,476	0.098	£15,093
Mortality in low risk equal to general population	£971	0.093	10,455

In most scenarios, TAVI is highly cost effective and it becomes dominant when the price of a TAVI valve is reduced to £15,000. TAVI becomes not cost-effective when:

- Historical and old trials are included in the meta-analysis estimating relative treatment effects
- Mild PVLs are assumed to affect mortality
- ICU and LOS are not scaled up for higher risk

3.2.2 Intermediate risk

Table 39 illustrates the deterministic results of the scenario analyses in people at intermediate surgical risk.

Table 39: Deterministic results of the scenario analyses for the intermediate-risk cohort

Scenario	Incremental costs	Incremental QALYs	Incremental cost per QALY gain
Base case (deterministic)	£3,124	0.056	£55,686
Time horizon 5 years	£3,965	0.063	£62,934
Time horizon 10 years	£3,186	0.063	£50,692
Time horizon 30 years	£3,108	0.052	£59,388
Treatment effects estimated using all trials	£5,021	0.029	£175,923
Reintervention treatment effect estimated from Evolut and PARTNER 3 only	£2,286	0.064	£35,891
All PVLs affect mortality	£3,014	-0.014	SAVR dominates
PVLs do not affect mortality	£3,149	0.079	£40,007
Cost of the valve reduced to £15,000	£502	0.056	£8,953
ICU and LOS from TAVI trial not scaled up for higher risks	£4,518	0.056	£80,544
Cost of short-term complications costed separately	£3,116	0.056	£55,560

Scenario	Incremental costs	Incremental QALYs	Incremental cost per QALY gain
Mortality in low risk equal to general population	£2,582	0.051	£50,294

In most of the scenarios tested, TAVI is not cost effective compared to surgery. Although, if the price of the valve reaches £15,000, TAVI becomes highly cost effective for people at intermediate risk as well, confirming that the results of the model are extremely sensitivity to the price of the valve.

3.2.3 Low risk

Table 40 illustrates the deterministic results of the scenario analyses in people at low surgical risk.

Table 40: Deterministic results of the scenario analyses for the low-risk cohort

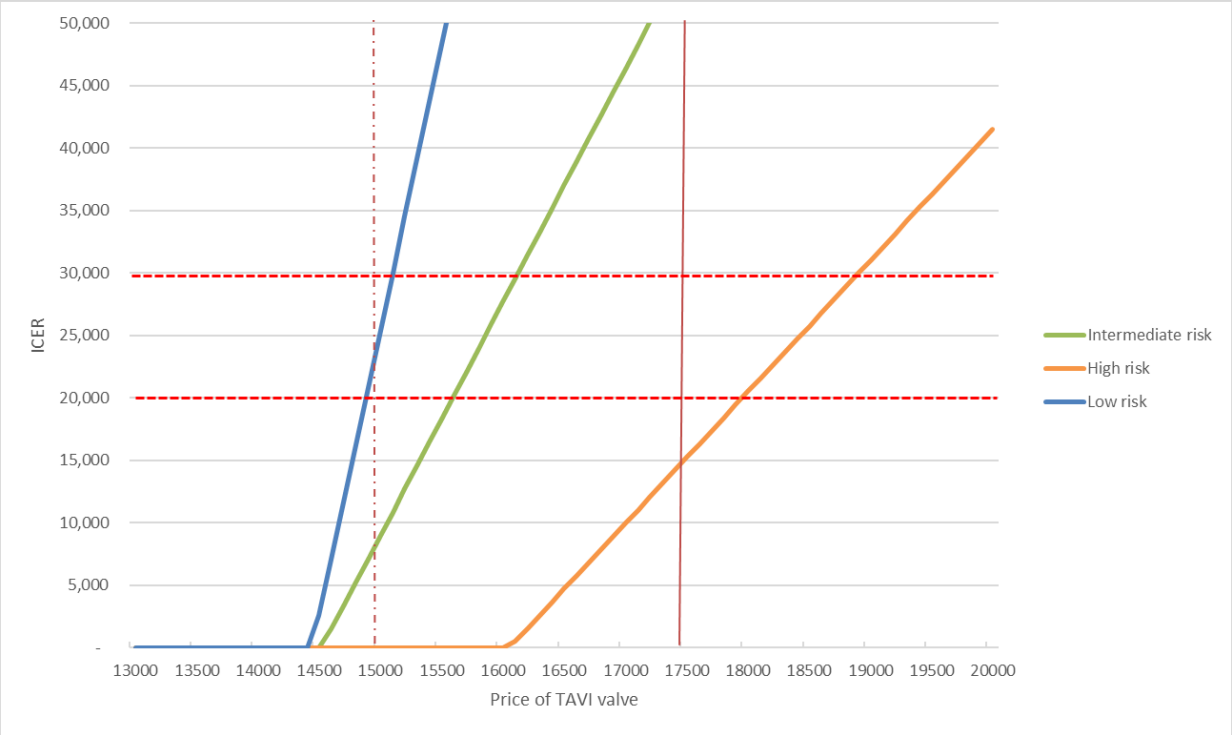
Scenario	Incremental costs	Incremental QALYs	Incremental cost per QALY gain
Base case (deterministic)	£3,300	0.024	£139,799
Time horizon 5 years	£5,199	0.044	£119,493
Time horizon 10 years	£3,687	0.041	£89,661
Time horizon 30 years	£3,035	-0.010	SAVR dominates
Treatment effects estimated using all trials	£6,123	-0.011	SAVR dominates
Reintervention treatment effect estimated from Evolut and PARTNER 3 only	£1,985	0.036	£54,750
All PVLs affect mortality	£3,210	-0.034	SAVR dominates
PVLs do not affect mortality	£3,335	0.052	£64,259
Cost of the valve reduced to £15,000	£600	0.024	£25,413
ICU and LOS from TAVI trial not scaled up for higher risks	£3,300	0.024	£139,799
Cost of short-term complications costed separately	£3,300	0.024	£139,789
Mortality in low risk equal to general population	£2,391	0.023	£103,242

As with intermediate risk people, TAVI is not cost effective in most scenarios tested. If the price of a TAVI valve is reduced to £15,000, TAVI is cost effective at a threshold of £30,000 per QALY gained, though not at a threshold of £20,000.

3.3 Threshold analysis

A threshold analysis on the price of a TAVI valve was conducted to determine the threshold value of the price at which a TAVI procedure becomes cost effective in each risk category. This was achieved by letting the price of the valve vary from £10,000 to £20,000 and looking at the corresponding incremental cost effectiveness ratios. The results are presented in figure 8.

Figure 8: TAVI valve threshold analysis



The results showed that for intermediate-risk patients, TAVI becomes cost effective at a threshold of £20,000 per QALY gained when the price drops below £15,500. For low-risk patients TAVI becomes cost effective at the same threshold when the price of the valve is reduced to £14,800.

Discussion

3.4 Summary of results

One original cost-utility analysis found that for treating aortic stenosis:

- In people at high surgical risk (STS or EuroSCORE 2 > 8) TAVI is cost effective compared to surgical aortic valve implantation (ICER: £7,014 per QALY gained)
- In people at intermediate surgical risk (STS or EuroSCORE 2 between 4 and 8) TAVI is not cost effective compared to surgical aortic valve implantation (ICER: £47,324 per QALY gained)
- In people at low surgical risk (STS or EuroSCORE 2 < 4) TAVI is not cost effective compared to surgical aortic valve implantation (ICER: £132,078 per QALY gained)

The analysis was assessed as directly applicable with minor limitations.

3.5 Limitations and interpretation

The analysis demonstrated that TAVI is cost effective in patient at high surgical risk but not cost effective in patients at intermediate or low surgical risk compared to surgical aortic valve replacement.

The sensitivity analysis shows that the results are extremely sensitive to the price of the TAVI valve. In a scenario where price is reduced to £15,000, TAVI would become cost effective in people at intermediate surgical risk and the same for the low-risk group at a price of £14,800. These prices are not too distant from the prices TAVI valves are purchased in other countries. For instance, the price of a Sapien 3 in Canada appears to be £14,400[49], which would make TAVI cost effective in both low and intermediate risk patient groups. In other European countries, like France, a Sapien 3 is purchased at an even lower price [28]. If similar prices can be negotiated in the UK, TAVI would be highly cost effective for people at lower surgical risks.

The greater cost-effectiveness of TAVI in people at higher surgical risk can be explained. Firstly, patients at lower risks are on average younger and have a more favourable survival than patients at higher risks. Hence, during their lifetime, they will likely experience more reinterventions as their life expectancy might exceed the duration of the valve. As in the base case scenario TAVI was associated with a higher reintervention rate, the increased number of reinterventions in the TAVI arm in low and intermediate risk patients directly translates into higher costs and lower QALYs in the risk groups.

Secondly, although the cost of a TAVI procedure was found to be almost the same in each risk group (around £5,500), the cost of surgery varies by risk ranging from £13,400 in low risk patients to £18,570 in high risk patients.

Finally, one of the most important benefits associated with TAVI, the quicker recovery after a less invasive procedure compared with the heavier burden caused by surgery during the first months following the intervention, was found to be more significant in people at higher surgical risks (see tables 12 and 13 in 2.3.5.1). This translates into a higher quality of life benefit for people in higher risk groups, making TAVI more cost effective for them.

This analysis is subject to some limitations. Firstly, data coming from trials with relatively short follow-up, were used to model outcomes for a period of 15 years. This adds some uncertainty in the model as some of its assumption may not hold over time. For instance, dialysis and stroke were both considered permanent states, but it is possible that, in some cases, people may recover and go back to the stable state. Unfortunately, no sufficiently robust data were found to model transition from the dialysis and stroke states to the stable state. If this occurs often in the real world, it is possible that the analysis is overestimating the cost associated with these two states, and therefore overestimating the cost effectiveness of TAVI. Likewise, reinterventions in the long term may behave differently as TAVI and biological valves generally require reintervention for different causes: PVL for TAVI and SVD for biological valves. For all these reasons, different time horizons were explored and, in particular, a very short time horizon of 5 years was included to assess the cost-effectiveness of TAVI in a scenario not heavily relying on long-term extrapolation and assumptions. The results illustrated in section 3.2 shows that the incremental cost effectiveness ratio in a scenario with a time horizon of 5 years is comparable with the base case scenario of 15 years, suggesting that extrapolating data over a longer time horizon does not distort the conclusions about TAVI cost effectiveness.

Secondly, the treatment effects were pooled together across all trials and applied to the patients regardless of their surgical risk. This was done mainly for pragmatic reasons as the meta-analysis in the base case scenario does not include any trials on high-risk population, as no trial has been conducted on people at high surgical risk using new generations valves. The committee agreed that it was more important to capture differences in relative treatment effects due to technological improvements of new valves rather than differences caused by surgical risk. Likewise, data on people needing rehabilitation after the intervention was not stratified by risk and informed by a low-risk trial[25], as this was the only evidence available reporting discharge destination. It is plausible that people with higher surgical risk need more rehabilitation after the intervention and therefore generate a higher rehabilitation cost.

Thirdly, although double counting of hospitalisation events due to pacemaker was dealt with as explained in section 2.3.2.2, it is plausible that some of the hospitalisation episodes predicted by the model are due to the increased need of health care services by people in a long-term health states (stroke, post-stroke and dialysis). It is hard to tell which proportion of the hospitalisation are due to the complications and remove them from the overall calculation although we expect this to be only a minimal part given the low prevalence of long-term health complications in the model. Hence, we do not expect this to affect the estimate of cost per QALY gained.

It is worth mentioning that for hospital and ICU length of stay, median days from a trial were used as proxies for the mean values. In economic evaluation we are interested only in mean costs but in a sample the mean cost can be affected by a very small number of patients with extremely severe comorbidities that could distort the real difference.

Finally, the reintervention rate in the surgical arm was estimated using the study from Rodriguez-Gabella[45]. This study, although recent, included patients who had surgery for an aortic valve replacement in 2002-2004. If the durability of biological valve has improved over the recent years, this source may overestimate the number of reinterventions occurring after a surgical aortic valve replacement. As reintervention in the TAVI arm is calculated based on the rates used in the surgical arm, reinterventions occurring after a TAVI would be likewise overestimated and the incremental effect should still be captured by the model.

3.6 Generalisability to other populations or settings

This analysis is based on operable patients at low, intermediate and high surgical risk.

This analysis does not apply to inoperable people. Economic evidence for this category of patients was reviewed separately finding TAVI to be cost effective compared to medical management (Evidence review H).

The conclusion of this analysis is based upon the current cost of treatments and clinical outcomes. It is likely that over time the cost of a TAVI procedure would fall as procedural efficiency grows and new products are placed on the market. Furthermore, lower prices may be negotiated if more valves are ordered by the NHS. It is possible therefore that, over time, TAVI will become cost effective for people at intermediate and low surgical risk.

As the valve cost varies between countries, the results of this study may not be transferable to other jurisdictions.

3.7 Comparisons with published studies

The results of this analysis are generally in line with the results of other published health economics evaluation on TAVI for high, intermediate and low surgical risk people although the heterogeneity in price of TAVI valves across different countries needs to be taken into account.

A previous health economics UK analysis was based on the findings of PARTNER A for people at high surgical risk[9]. The analysis found TAVI to dominate SAVR although it was noted that the cost of a TAVI procedure (including the valve) used in the model was extremely low, amounting to £16,500, whereas NHS Supply Chain reports an average cost of a TAVI device alone of £17,500 (See Evidence Review H). However, a threshold analysis conducted on the price of the valve revealed that TAVI is no longer cost effective when the price of the device rises above £19,000. This is in line with our own threshold analysis which found TAVI no longer cost effective at a £20,000 threshold in a high-risk population when the price is above £18,000, and no longer cost effective at a £30,000 threshold when the price lies above £19,000. In addition, estimated incremental QALYs in Fairbairn[9] are similar to the incremental QALYs estimated by our model

Previous models on people at intermediate surgical risk and based on PARTNER 2 generally reached the same conclusions as our analysis. A Japanese cost-utility analysis[17] found TAVI to be cost effective in inoperable patients but not cost effective in operable patients at intermediate risk. The incremental cost effectiveness ratio found in the analysis, £51,210, is fairly aligned with the results of the NGC model for people at intermediate risk. A second Canadian study[48] with a lifetime horizon found TAVI not cost effective in intermediate-risk people with an ICER of £43,055. A Norwegian health technology assessment[38] evaluating TAVI for people at intermediate risk and based on PARTNER 2 found an ICER of £54,160 in the scenario with a life-long time horizon. Finally, a French analysis on Sapien 3[13] found third generation TAVI valves to dominate SAVR having a higher QALYs gain and lower costs. It is unclear which price for TAVI was used in the analysis but it is worth mentioning that Sapien 3 appears to be considerably cheaper in France than in the UK[28]. Assuming the same price in our own analysis would result in TAVI being dominant in people at intermediate risk.

Two recent studies assessed the cost effectiveness of third generation valves using Evolut and PARTNER 3 trials in people at low surgical risk finding TAVI cost effective against

SAVR[47, 55]. However, both studies were conducted in settings where the price of TAVI is considerably lower than the UK NHS price: Canada and Australia. When the price of the device was adjusted to reflect current UK price, none of these analyses found TAVI cost-effective at a £20,000 threshold (see Evidence Review H). This confirms our hypothesis that the locally available price of the device plays a major role in determining the cost effectiveness of TAVI.

3.8 Conclusions

This economic evaluation demonstrated that TAVI compared to SAVR for treating aortic stenosis is cost effective in people at high surgical risk, but not cost effective in people at intermediate and low surgical risk at the current price of a TAVI valve. The analysis showed that the results are sensitive to the price of the valve, implying that TAVI may become cost effective for intermediate and low risk alike if a price reduction is achieved in the future. In particular, published evidence found TAVI cost effective in countries like Canada, Australia and France where the valves appear to be purchased at a considerably lower price. If we assume similar prices in our model, TAVI appears to be cost effective in the UK as well.

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Appendix I: Relative treatment effects forest plots

Figure 9: mortality 30 days

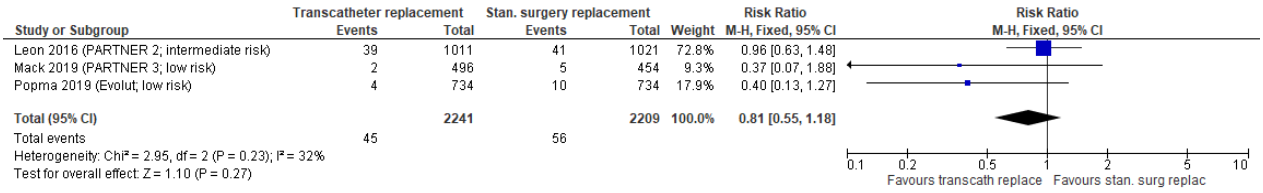

Figure 10: mortality 1 year

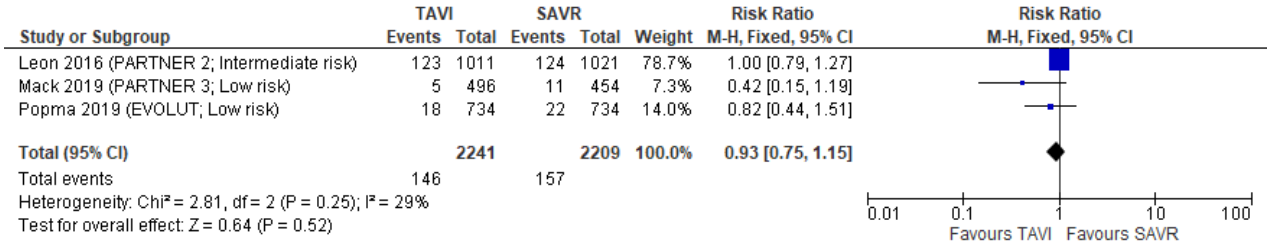

Figure 11: mortality 2 years

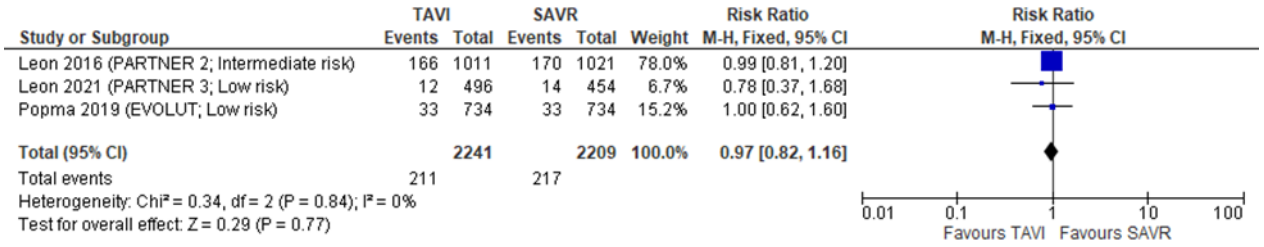

Figure 12: stroke or TIA 30 days

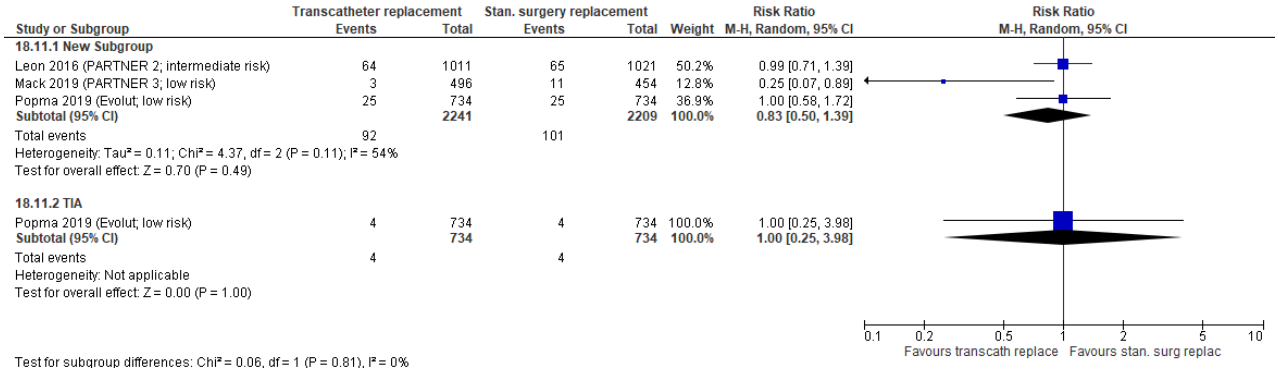

Figure 13: major bleeding 30 days

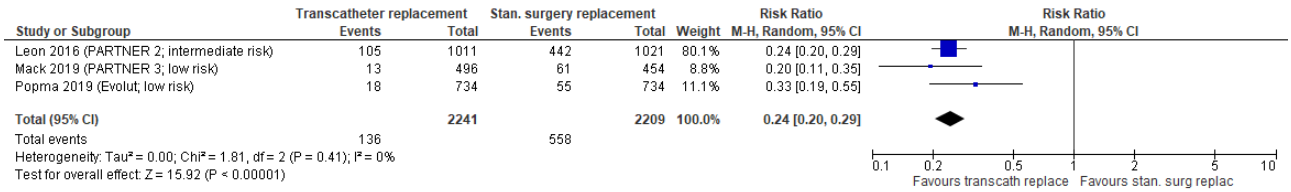

Figure 14: new pacemaker 30 days

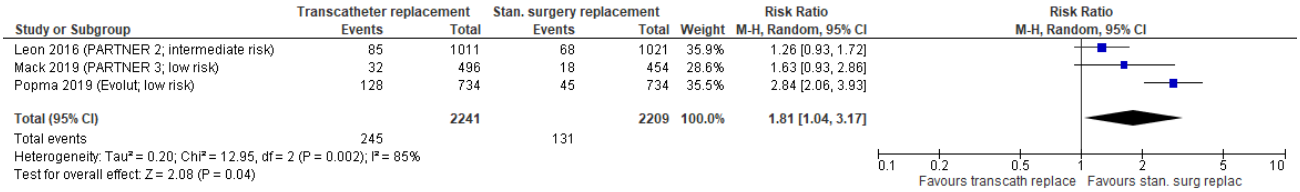

Figure 15: vascular complication 30 days

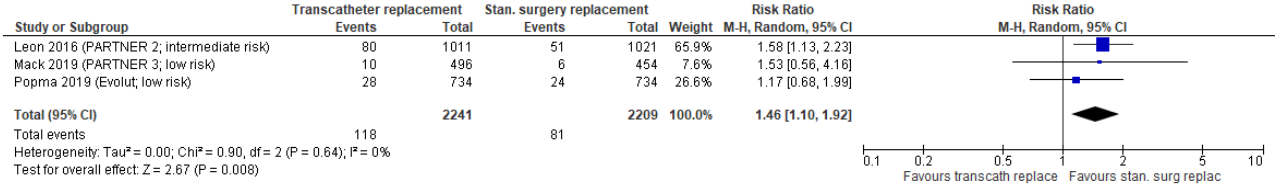

Figure 16: hospitalisation 1 year

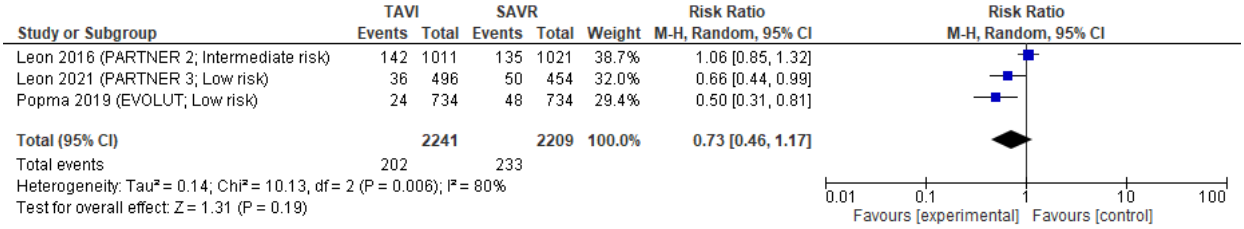

Figure 17: hospitalisation 2nd year

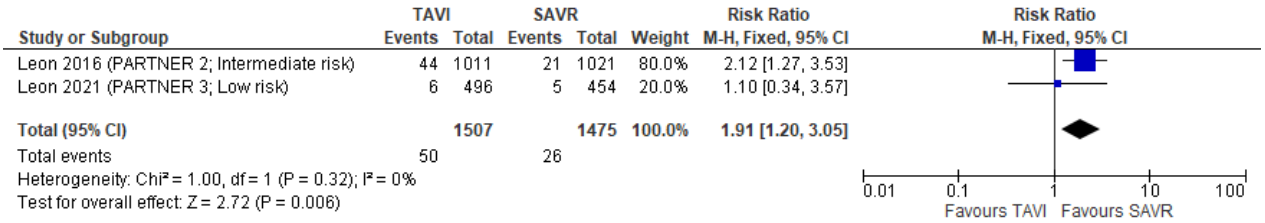

Figure 18: moderate or severe PVLs

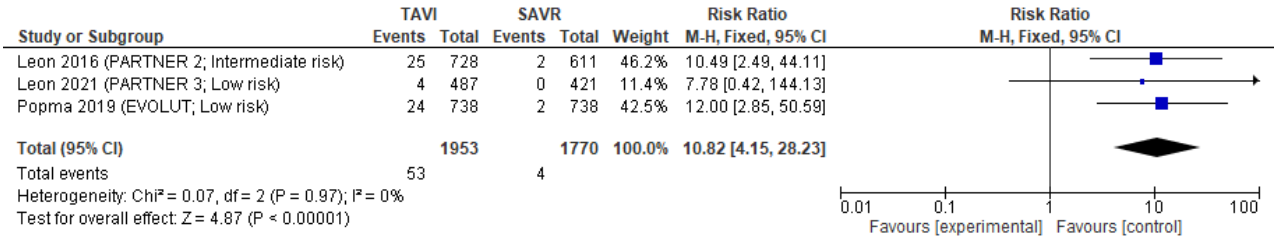

Figure 19: mild PVLs

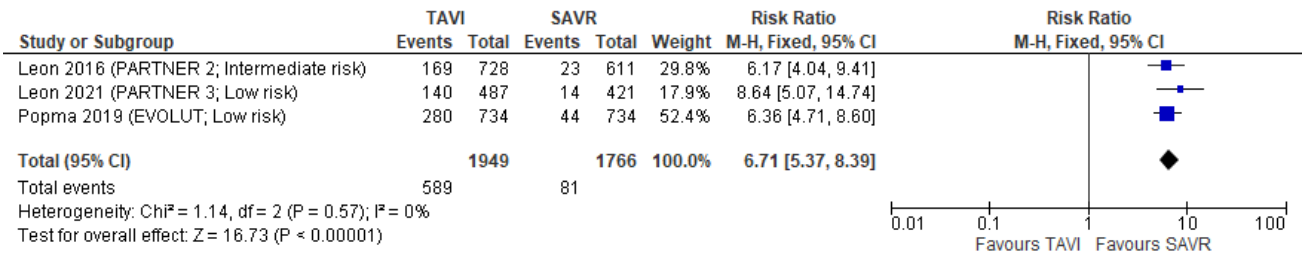

Figure 20: renal failure 30 days

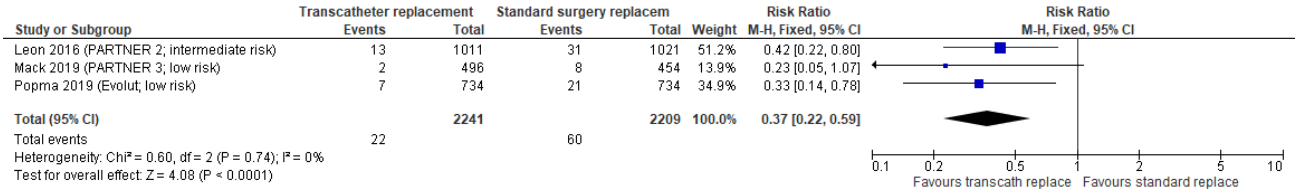

Figure 21: reintervention