National Institute for Health and Care Excellence

Draft

# Heart valve disease presenting in adults: investigation and management

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

*NICE guideline <number>*

*Economic analysis report*

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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 commonly 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 transcatheter aortic valve implantation (TAVI) to cost between £6,000-£9,000 (depending on co-morbidities and if a transfemoral approach is taken). It should be noted that these costs 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 as listed in the High Cost Device Exclusion List, cost of TAVI from the supply chain is around £20,000 and a biological valve is around £1,700.

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. Around 80% of patients are of a lower surgical risk.

# 2 Methods

## 2.1 Model overview

A cost-utility analysis was undertaken where lifetime 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[21]. 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 age and by operative risk:

- High and intermediate operative risk
- Age group in 10-year age bands.

### 2.1.3 Time horizon

A lifetime horizon was chosen to fully capture the long-term costs and benefits derived from using a TAVI compared with surgery. We used a shorter time horizon in the sensitivity analysis:13 years (reflecting the longest trial follow-up).

### 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** is 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. Further details on the decision tree model can be found in section 2.2.1.
- A **Markov model** is then used for the long-term extrapolation of outcomes and costs.

### 2.2.1 Model structure

#### 2.2.1.1 Post-procedural consequences decision tree

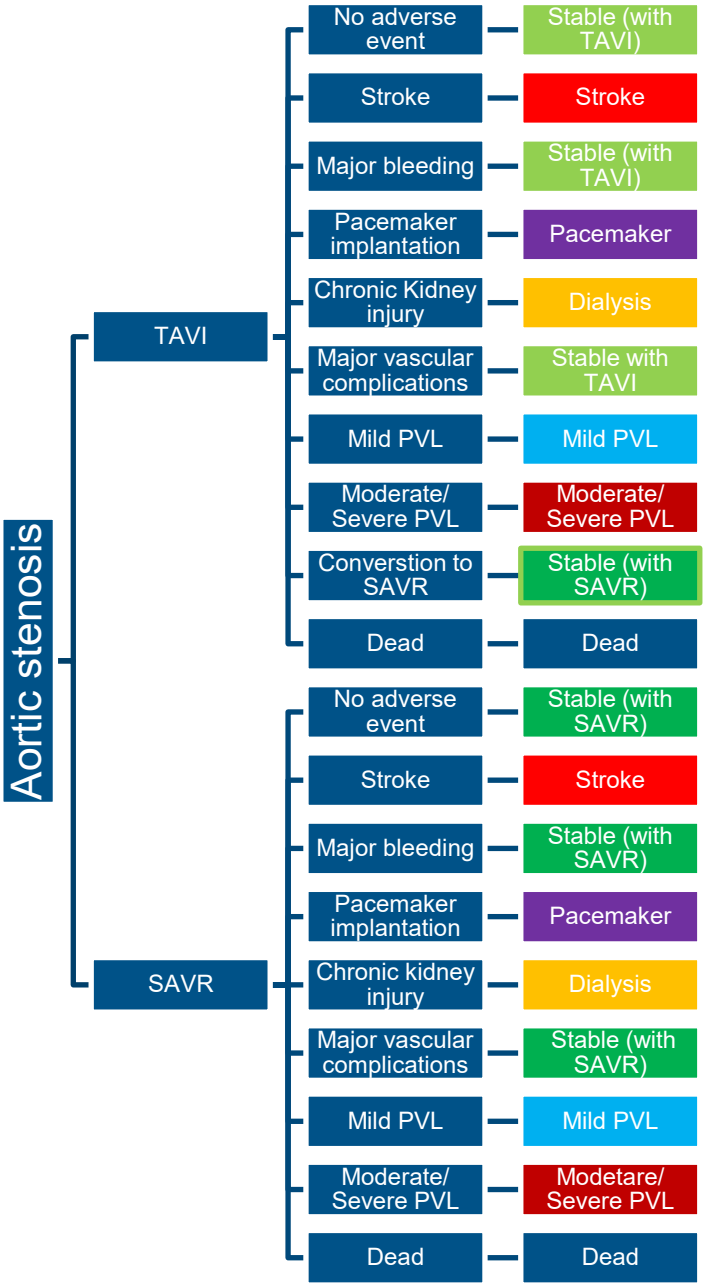
The decision tree reflects the initial month following the intervention when people in the intervention arm receive the transcatheter (TAVI). Hence, the model captures the costs and loss of utility associated with several intervention consequences or complication. Following the review of the literature 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. However, there was some uncertainty amongst the committee regarding the inclusion of these outcomes. Therefore, for modelling purposes a pragmatic decision was made to include only the most common outcomes reflecting clinical practice and in line with the literature.

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 and cost. Consequently, people experiencing major bleeding or vascular complication end in the stable state and have no long-term consequence. If a TAVI procedure is converted to SAVR, people move to the ‘stable with SAVR’ state even though they are in the TAVI arm, and costs and utility are calculated accordingly. Following the 30 days post-procedural period, people enter the Markov model in the same state they were at the end of the decision tree model.

**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 model long-term outcomes and extrapolate costs and consequence of the population over a lifetime time-horizon. Costs and outcomes were collected at each cycle for a period of 30 years after which most of the cohort was dead. Following the discussion with the committee and clinical advisor 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 30 repeated cycles representing 30 years of time.

Those who are alive and experienced no adverse events 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.

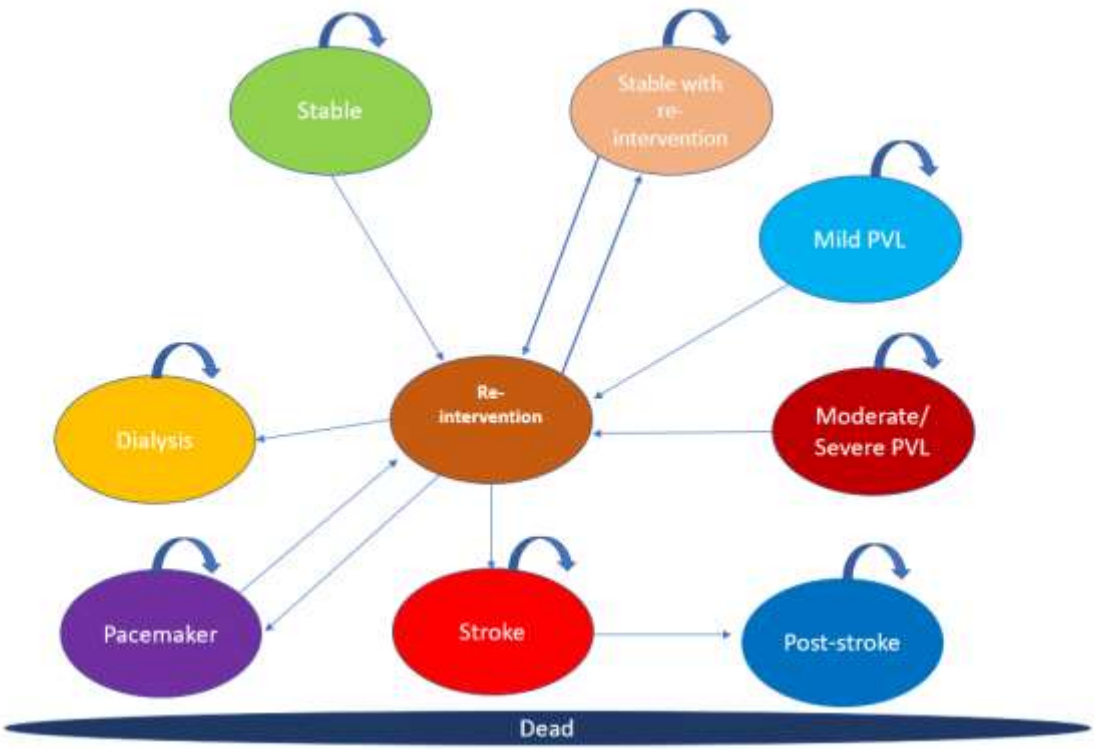
It was assumed that dialysis, stroke and post-stroke are long-term states and that, consequently, it is not possible to transit out of them (although it is always possible to move to the dead state). This is a clear simplification of reality and was done for modelling purpose. Stroke is a tunnel state 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 – 10,000 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:<br>• Alpha = (number of patients hospitalised)<br>Beta = (number of patients) − (number of patients hospitalised) |

| Parameter | Type of distribution | Properties of distribution |
|---|---|---|
| Hazard ratios<br>Odds ratios<br>Risk ratios | Lognormal | The natural log of the mean and standard error was calculated as follows:<br>• Mean = ln (mean cost) − $SE^2/2$<br>• SE = [ln (upper 95% CI) − ln (lower 95% CI)]/ (1.96×2)<br>$\sqrt{\ln \frac{SE^2 + mean^2}{mean^2}}$<br>This formula includes a correction to ensure the mean generated in the probabilistic analysis will be the same as the reported mean.[3] |
| Utilities | Beta | Bounded between 0 and 1. Derived from mean and its standard error, using the method of moments.<br>Alpha and Beta values were calculated as follows:<br>Alpha = $mean^2 \times [(1-mean)/SE^2] - mean$<br>Beta = alpha×[(1−mean)/mean] |
| Utility decrements | Gamma | Bounded at 0, positively skewed. Derived from mean and its standard error.<br>Alpha and beta values were calculated as follows:<br>• Alpha = $(mean/SE)^2$<br>• 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[31])
- Utility score in the general population (based on the paper from Ara 2010[2])

### 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<br>• 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[21] | n/a |
| Time horizon | Lifetime | | n/a |
| Discount rate | Costs: 3.5%<br>Outcomes: 3.5% | NICE reference case[21] | n/a |
| **Cohort settings** | | | |
| Cohort size | 1000 | | n/a |
| Male start age | 60-70-80-90 | TAVI UK registry[14] | n/a |
| Female start age | 60-70-80-90 | TAVI UK registry[14] | n/a |
| Percentage of males entering the model | 54% | TAVI UK registry[14] | n/a |
| Percentage of females entering the model | 46% | TAVI UK registry[14] | n/a |
| **30 days decision tree baseline probabilities (TAVI)** | | | |
| Conversion to SAVR | 0.02 | Leon 201612<br>Reardon 201730<br>Smith 201132<br>Adams 20141<br>Thyregod 2015 35<br>Mack 2019 16 | n/a |
| **30 days decision tree baseline probabilities (SAVR)** | | | |
| **Intermediate risk** | | | |
| Stroke | 0.054 | Leon 2016[12]<br>Reardon 2017[30]<br>Smith 2011[32]<br>Adams 2014[1]<br>Thyregod 2015 [35]<br>Mack 2019 [16] | Beta |
| Major bleeding | 0.281 | | Beta |
| Pacemaker implantation | 0.063 | | |
| Vascular complications | 0.030 | | Beta |
| Chronic kidney injury | 0.028 | | Beta |
| Mortality | 0.028 | | Beta |
| **High risk** | | | |
| Stroke | 0.054 | | Beta |
| Major bleeding | 0.281 | | Beta |
| Pacemaker implantation | 0.063 | | |

| Input | Data | Source | Probability distribution |
|---|---|---|---|
| Vascular complications | 0.030 | | Beta |
| Chronic kidney injury | 0.028 | | Beta |
| Mortality | 0.054 | | Beta |
| **Markov model transition probabilities** | | | |
| Reintervention rate after SAVR | 1 year: 1.40%<br>2 years: 1.94%<br>3 years: 1.94%<br>4 years: 1.94%<br>5 years: 1.99%<br>6 years: 2.53%<br>7 years: 3.58%<br>8 years: 3.95%<br>9 years: 4.48%<br>10 years: 5.54%<br>11 years: 7.81%<br>12 years: 10.08%<br>13 years: 12.70% | Rodriguez-Gabella 2018[31] | n/a |
| Mild PVL | SAVR: 8.54%<br>TAVI: 33.65% | Leon 2016[12]<br>Reardon 2017[30]<br>Smith 2011[32]<br>Adams 2014[1]<br>Thyregod 2015 [35]<br>Mack 2019 [16] | Beta |
| Moderate/severe PVL | SAVR: 0.45%<br>TAVI: 4.63% | Leon 2016[12]<br>Reardon 2017[30]<br>Smith 2011[32]<br>Adams 2014[1]<br>Thyregod 2015 [35]<br>Mack 2019 [16] | Beta |
| Rehospitalisation | 0.12 | Leon 2016[12]<br>Reardon 2017[30]<br>Smith 2011[32]<br>Adams 2014[1]<br>Thyregod 2015 [35]<br>Mack 2019 [16] | Beta |
| Pacemaker hospitalisation risk ratio | 1.18 | Faroux 2020[6] | Log-normal |
| **Mortality** | | | |
| General population mortality | | ONS Life Tables 2016-2018[28] | n/a |
| TAVI relative survival (compared to the general population) | **Age <80**<br>1 year: 86.80%<br>2 years: 81.10%<br>3 years: 74.30% | Martin 2017[18] | Beta |

| Input | Data | Source | Probability distribution |
|---|---|---|---|
| | **Age 80-85**<br>1 year: 88.60%<br>2 years: 84.50%<br>3 years: 81.20%<br>**Age >80**<br>1 year: 94.30%<br>2 years: 96%<br>3 years: 95.4% | | |
| Dialysis mortality hazard ratio | 3.54 | Ferro 2017[7] | Log-normal |
| Pacemaker mortality risk ratio | 1.17 | Faroux 2020[6] | Log-normal |
| Mild PVL mortality hazard ratio | 1.23 | Makkar 2020[17] | Log-normal |
| Moderate/severe PVL mortality hazard ratio | 2.44 | Makkar 2020[17] | Log-normal |
| Stroke (OR) | 3.21 | Myat 2020[19] | Log-normal |
| Post-stroke (OR) | 1.58 | Myat 2020[19] calculated using the same ratio of Bronnum-Hansen 2001[5] | Log-normal |
| **Decision tree relative treatment effects (TAVI vs SAVR)** | | | |
| Stroke risk ratio | 0.89 | Leon 2016[12]<br>Reardon 2017[30]<br>Smith 2011[32]<br>Adams 2014[1]<br>Thyregod 2015 [35]<br>Mack 2019 [16] | Log-normal |
| Major Bleed risk ratio | 0.51 | | Log-normal |
| Pacemaker Implantation risk ratio | 2.43 | | Log-normal |
| Vascular complication risk ratio | 2.45 | | Log-normal |
| Kidney Injury risk ratio | 0.44 | | Log-normal |
| Mortality 30 days risk ratio | 0.88 | | Log-normal |
| **Markov model relative treatment effects (TAVI vs SAVR)** | | | |
| All-cause mortality risk ratio | 1 year: 0.91<br>Subsequent years: 1 | Leon 2016[12]<br>Reardon 2017[30]<br>Smith 2011[32]<br>Adams 2014[1]<br>Thyregod 2015 [35]<br>Mack 2019 [16] | Log-normal |
| Reintervention odds ratio | 1 year: 3.52<br>2-3 year: 3.55<br>5 year: 3.55 | Ler 2020[13] | Log-normal |
| **Health-related quality of life (utilities)** | | | |
| **Markov Model 1 Year Utilities** | | | |
| **High risk** | | | |
| TAVI first year | 0.70 | Gleason 2018[8] | Beta |

| Input | Data | Source | Probability distribution |
|---|---|---|---|
| TAVI >1 year | 0.72 | Gleason 2018[8] | Beta |
| SAVR first year | 0.65 | Gleason 2018[8] | Beta |
| SAVR >1 year | 0.72 | Gleason 2018[8] | Beta |
| **Intermediate risk** | | | |
| TAVI first year | 0.80 | Baron 2018[4] | Beta |
| TAVI >1 year | 0.80 | Baron 2018[4] | Beta |
| SAVR first year | 0.78 | Baron 2018[4] | Beta |
| SAVR >1 year | 0.80 | Baron 2018[4] | Beta |
| **Decision Tree Utility Decrements** | | | |
| Major bleeding | 0.45 | Kaier 2016[9] | Gamma |
| Vascular complications | 0.01 | Kaier 2016[9] | Gamma |
| Pacemaker | 0.00 | | |
| Major bleeding | 45 days | Kaier 2016[9] | n/a |
| Vascular complications | 30 days | Assumption | n/a |
| **Markov Model Utility Decrements** | | | |
| Stroke | 0.16 | Luengo Fernandez 2013[15] | Gamma |
| Post-stroke | 0.18 | Luengo Fernandez 2013[15] | Gamma |
| Dialysis | 0.18 | Kaier 2016[9] | Gamma |
| **Costs** | | | |
| **ICU** | | | |
| ICU cost (per day) | £1,415 | NHS Reference Costs 2018-2019[27] | n/a |
| **TAVI ICU** | | | |
| Intermediate risk | 2 days | Leon 2016[12] | Log-normal |
| High risk | 3 days | Smith 2011[32] | Log-normal |
| **SAVR ICU** | | | |
| Intermediate risk | 4 days | Leon 2016[12] | Log-normal |
| High risk | 5 days | Smith 2011[32] | Log-normal |
| **Total LOS** | | | |
| SAVR LOS cost (per day) | £325 | NHS Reference Costs 2017-2018[26] | n/a |
| TAVI LOS cost (per day) | £473 | NHS Reference Costs 2017-2018[26] | n/a |
| **TAVI total LOS** | | | |
| Intermediate risk | 6 days | Leon 2016[12] | Log-normal |
| High risk | 8 days | Smith 2011[32] | Log-normal |
| **SAVR total LOS** | | | |
| Intermediate risk | 9 days | Leon 2016[12] | Log-normal |
| High risk | 12 days | Smith 2011[32] | Log-normal |
| **Procedural cost** | | | |
| **TAVI** | | | |
| Intermediate risk | £9,658 | NHS Reference Costs 2017-2018[26] | n/a |

| Input | Data | Source | Probability distribution |
|---|---|---|---|
| | | NHS Reference Costs 2018-2019[27] | |
| High risk | £11,979 | NHS Reference Costs 2017-2018[26] NHS Reference Costs 2018-2019[27] | n/a |
| **SAVR** | | | |
| Intermediate risk | £17,640 | NHS Reference Costs 2017-2018[26] NHS Reference Costs 2018-2019[27] | n/a |
| High risk | £21,940 | NHS Reference Costs 2017-2018[26] NHS Reference Costs 2018-2019[27] | n/a |
| **Valve cost** | | | |
| TAVI valve | £20,280 | NHS Supply Chain Catalogue[25] | n/a |
| Home-rehabilitation costs | £982 | National Audit of Intermediate Care 2017[20] | n/a |
| Intermediate care costs | £5,965 | National Audit of Intermediate Care 2017[20] | n/a |
| **Decision Tree Costs** | | | |
| Major bleeding | £1,972 | NHS Reference Costs 2018-2019[27] | n/a |
| Vascular complications | £1,826 | NHS Reference Costs 2018-2019[27] | n/a |
| Pacemaker | £2,623 | NHS Reference Costs 2018-2019[27] | n/a |
| **1 Year Markov Model Costs** | | | |
| Rehospitalisation | £2,275 | NHS Reference Costs 2018-2019[27] | n/a |
| Stroke | £18,948 | Xu 2018 SSNAPP project inflated to 2018-2019[36] | n/a |
| Post-stroke | £6,727 | Xu 2018 SSNAPP project inflated to 2018-2019[36] | n/a |
| Dialysis | £37,893 | NICE guideline NG107[24] and NHS Reference Costs 2018-2019[27] | n/a |
| PVL (echo + visit) | £250 | NHS Reference Costs 2018-2019[27] | 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

The decision tree model was populated with the baseline probabilities after SAVR from the literature review. Baseline risks for intermediate- and high-risk patients were pooled together using data from the control arm of the papers included in the clinical review, with the

exception of mortality at 30 days which uses different values for high and intermediate risk people.

In the Markov model (used to predict long-term outcomes and mortality), people have the same transition probabilities regardless of their risk category.

The related probabilities in the TAVI arm were obtained by applying the corresponding relative treatment effect (see section 2.3.4 for more details).

**Mortality**

Mortality after TAVI was calculated using the relative survival rates reported in the study from Martin and colleagues[18] who looked at the mortality rate of patients in the UK TAVI registry at different age. The relative survival was then applied to the survival of the general population to obtain the mortality in the TAVI arm. The authors reported different relative survival rates according to three different age groups. These are illustrated in Table 3.

**Table 3: Relative survival compared to the general population after TAVI**

| Age | People younger than 80 | People between 80 and 85 | People older than 85 |
|---|---|---|---|
| 1 year | 86.80% | 88.60% | 94.30% |
| 2 years | 81.10% | 84.50% | 96.00% |
| 3 years | 74.30% | 81.20% | 95.40% |

Figures 3, 4 and 5 illustrate the survival curves of three cohorts of patients at 80, 85 and 90 years of age. As the figures show, the highest difference in mortality between TAVI patients and the general population occur for younger patients whereas, in people older than 85, the difference in mortality is minimal.

**Figure 3: TAVI vs general population survival in a cohort at 80 years old**

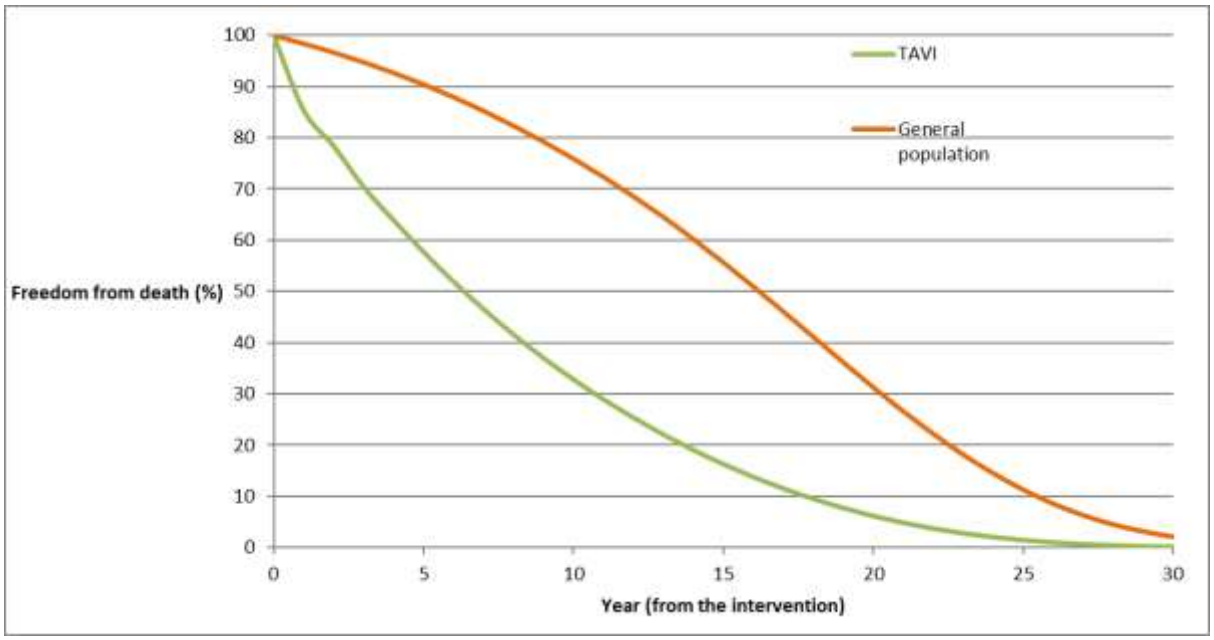


**Figure 4: TAVI vs general population survival in a cohort at 85 years old**

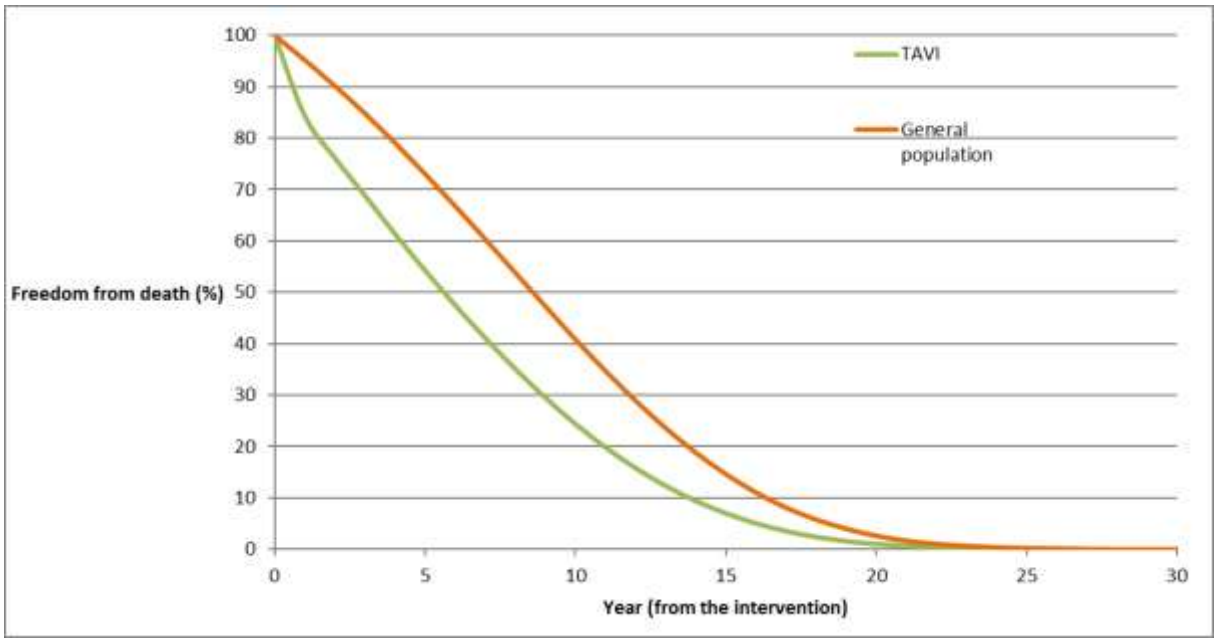
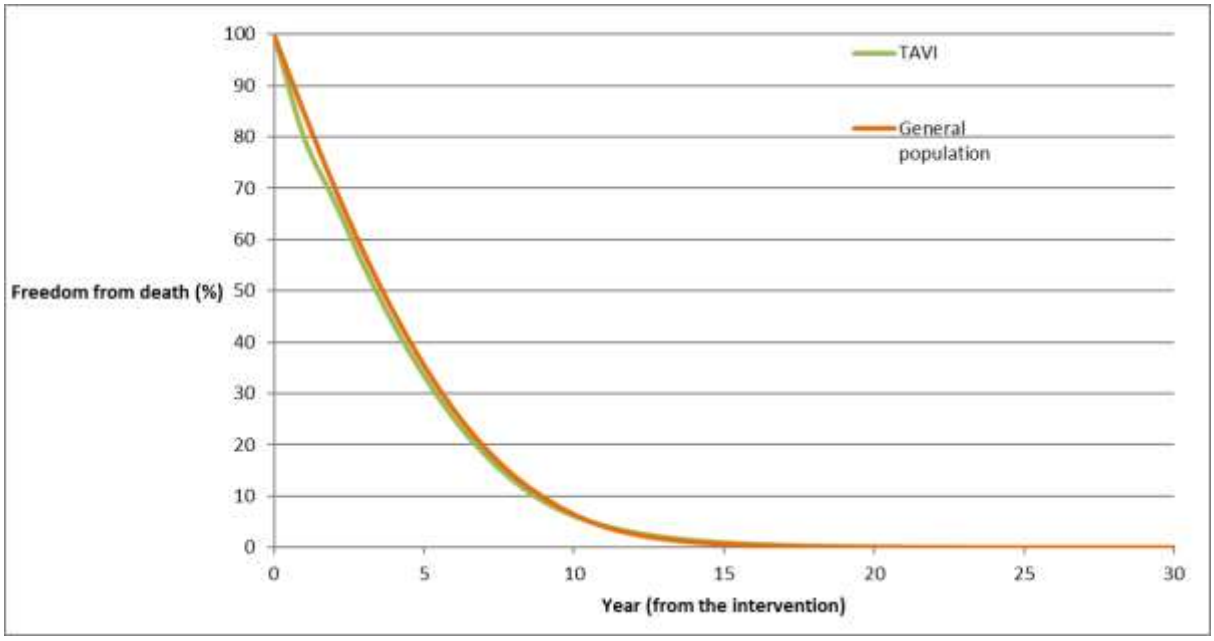



**Figure 5: TAVI vs general population survival in a cohort at 90 years old**




Mortality for the years following the last follow-up was extrapolated assuming that the cumulative excess hazard between the TAVI and the general population follows a linear relationship after the first year. This was found and highlighted in the original study[18].

General population mortality was based on data from lifetables for England 2016-2018. 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: not only mortality increases by age, but the gender split varies as well as males have a higher

probability of dying than females and therefore die at a higher rate. As population mortality is not available beyond 100 years, the model applied the mortality rate for age 100 to those who are 100 years or older.

Mortality rates for people who experienced 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[19]. 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[5]. 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[6].

For mortality after dialysis, it was agreed to use a paper from Ferro 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.

Finally, regarding paravalvular leak, the committee agreed to use a recent paper[17] 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 leak was assumed to influence mortality as well. Table 4 shows all the inputs used in the model to estimate mortality.

**Table 4: Inputs used to estimate mortality**

| Event | Input | Value | Source |
|---|---|---|---|
| Stroke | Odds ratio | 3.21 (2.15 to 4.78) | Myat 2020[19] |
| Post-stroke | Odds ratio | 1.58 (1.07 to 2.3) | Myat 2020[19] calculated using the same ratio of Bronnum-Hansen 2001[5] |
| Pacemaker | Risk ratio | 1.17 (1.11 to 1.25) | Faroux 2020[6] |
| Dialysis | Hazard ratio | 3.54 (2.99 to 4.19) | Ferro 2017[7] |
| Mild PVL (only in the sensitivity analysis) (none vs mild) | Hazard ratio | 0.81 (0.62 to 1.07) | Makkar 2020[17] |
| Moderate PVL (none vs moderate) | Hazard ratio | 0.41 (0.24 to 0.7) | Makkar 2020[17] |

### Calibration of survival

Although we had estimates of relative survival that would predict overall mortality in the TAVI group, for the stable TAVI state we needed mortality rates specifically for patients who had no event (no PVL, no stroke and no dialysis). And the mortality in the other health states (stroke, post-stroke, dialysis, PVL) are a function of the mortality in the stable TAVI state.

We applied 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[18]).

In Table 5, 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[18] to general population survival. 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 the previous chapter.

**Table 5: Survival expected vs survival predicted by the model – TAVI arm 80-year-old patients**

| Time | Survival derived from Martin 2017[18] | Survival in model |
|---|---|---|
| 0 | **100%** | 100% |
| 1 | **84%** | 82% |
| 2 | **76%** | 75% |
| 3 | **69%** | 69% |
| 4 | 62% | 63% |
| 5 | 55% | 57% |
| 6 | 48% | 51% |
| 7 | 42% | 46% |
| 8 | 36% | 40% |
| 9 | 30% | 35% |
| 10 | 25% | 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[18]. This implies that the model might be under-estimating survival in the long-term, although survival in the longer term is more uncertain anyway.

**Reintervention**

Reintervention rates in the SAVR arm were obtained from the study from Rodriguez-Gabella[31] reporting the Kaplan-Meier curve of undertaking a reintervention during the 13 years following the first intervention. Reintervention rates for the years following the last follow-up were extrapolated assuming that the curve followed a Weibull function as often done in the literature. Reintervention in the TAVI arm was calculated by applying the odds ratio recovered from the literature[13]. These are shown in table 6.

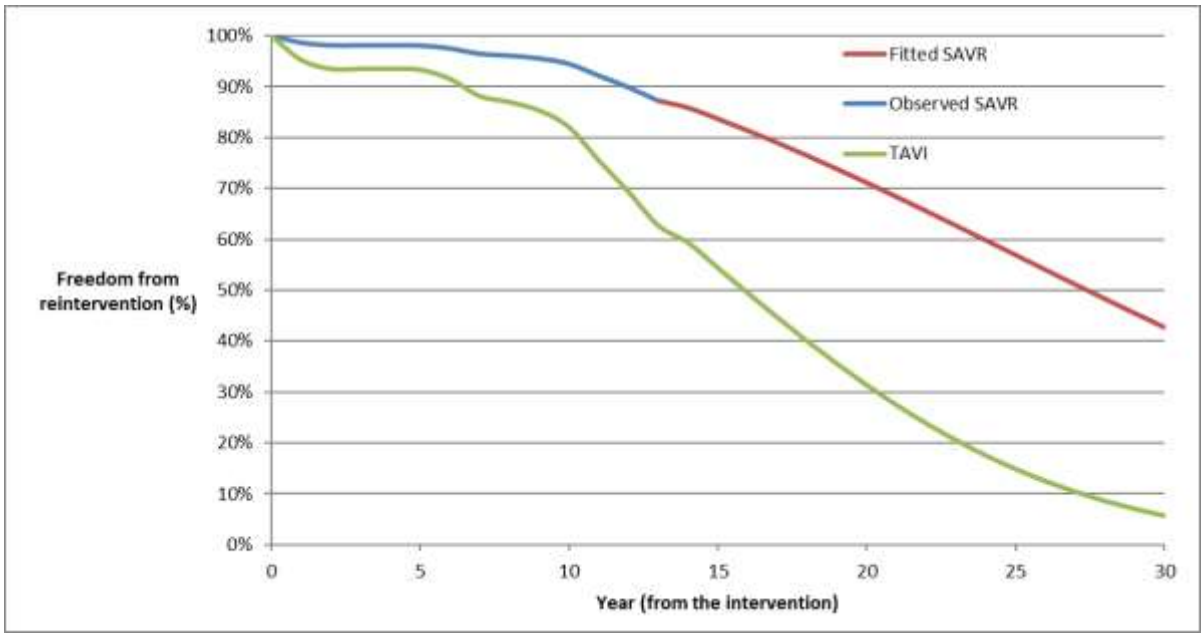
**Table 6: Reintervention odds ratio (TAVI vs SAVR)**

| Years | Odds ratios | Source |
|---|---|---|
| 1 | 3.52 (1.78-6.96) | Ler 2020[13] |
| 2-3 | 3.55 (1.86-6.77) | |
| 5 | 3.55 (1.22-10.38) | |

It was agreed to use this study[13] instead of the clinical meta-analysis as the first reported odds ratio at different years and, therefore, would have captured differences occurring in the short or medium term. Nevertheless, these odds ratios barely change during the 5 years of the study suggesting that reintervention rates after TAVI and SAVR follow a similar pattern.

Figure 6 illustrates the freedom from reintervention curve in the TAVI and SAVR arms obtained using the methodology described.

**Figure 6: freedom from reintervention**



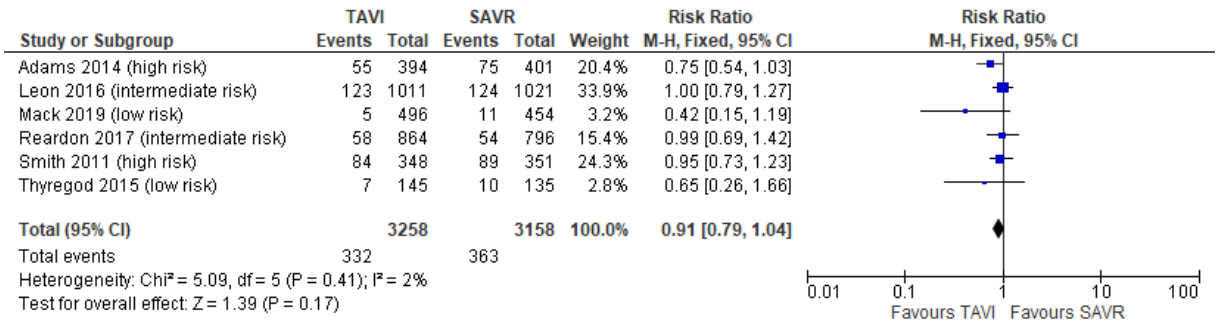

### 2.3.3 Relative treatment effects

Relative treatment effects were informed from the clinical review.

Due to the limited availability of studies, it was agreed to meta-analyse all studies pooling together all the papers referring to low-, intermediate- and high-risk patients. Table 7 illustrates all the relative treatment effects used in the decision tree and Markov model together with their sources.

The clinical review (Evidence review H) found no long-term improvement in mortality with TAVI compared to SAVR. However, a meta-analysis of the studies reporting 1-year outcomes found TAVI to show a moderate improvement in survival at least in the year immediately following the intervention (see forest plot in figure 7).

**Figure 7: TAVI vs SAVR all-cause mortality (12 months)**




Therefore, the mortality rate of the stable state in the first cycle of the surgery arm was adjusted through the inclusion of a second calibration factor (obtained through the goal-seek function of Microsoft Excel) to ensure that the risk ratio in the first year of the Markov model

matches exactly the one found in the meta-analysis. For the following cycles, we assumed that people in the TAVI and SAVR stable states have the same set of mortality rates.

**Table 7: Relative treatment effect**

| Input | Data | Source | Probability distribution |
|---|---|---|---|
| **Decision tree relative treatment effects (TAVI vs SAVR)** | | | |
| Stroke risk ratio | 0.89 | Leon 2016[12]<br>Reardon 2017[30]<br>Smith 2011[32]<br>Adams 2014[1]<br>Thyregod 2015 [35]<br>Mack 2019 [16] | Log-normal |
| Major Bleed risk ratio | 0.51 | | Log-normal |
| Pacemaker Implantation risk ratio | 2.43 | | Log-normal |
| Vascular complication risk ratio | 2.45 | | Log-normal |
| Kidney Injury risk ratio | 0.44 | | Log-normal |
| Mortality 30 days risk ratio | 0.88 | | Log-normal |
| **Markov model relative treatment effects (TAVI vs SAVR)** | | | |
| All-cause mortality risk ratio | 1 year: 0.91<br>Subsequent years: 1 | Leon 2016[12]<br>Reardon 2017[30]<br>Smith 2011[32]<br>Adams 2014[1]<br>Thyregod 2015 [35]<br>Mack 2019 [16] | Log-normal |
| Reintervention odds ratio | 1 year: 3.52<br>2-3 year: 3.55<br>5 year: 3.55 | Ler 2020[13] | Log-normal |

### 2.3.4 Utilities

**Utility**

Utilities of people who received TAVI or SAVR were sought from the papers included in the clinical review. Two different utility scores were applied to people with high risk and intermediate to account for the differences between these two populations.

Utility scores in the high-risk population were recovered from the study of Gleason 2018[8]. 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 are the preferable measures by 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[11]. 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 population, it was agreed to use the paper from Baron 2018[4] reporting EQ-5D scores at baseline, 1 month and 12 months after the intervention. No algorithm was needed to convert these scores. The resulting EQ-5D scores for both populations are presented in Table 8

**Table 8: Utility scores in high and intermediate**

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

The table shows a common pattern in both 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. 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. 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 with SVD requiring a reintervention would show symptoms comparable to patients who have not received an intervention yet. Therefore, their utility score during the year prior the reintervention is expected to be equal to the utility score at baseline.

The resulting utility values used in the model are illustrated in table 9.

**Table 9: Utility scores used in the model**

| Follow-up | High-risk | | Intermediate | |
|---|---|---|---|---|
| | TAVI | SAVR | TAVI | SAVR |
| First year | 0.70 | 0.65 | 0.80 | 0.78 |
| >1 year | 0.72 | 0.72 | 0.80 | 0.80 |
| SVD requiring a reintervention | 0.57 | 0.59 | 0.75 | 0.74 |

The utility scores obtained were compared to the utility score of the general UK population reported by Ara and Brazier[2] and an utility multiplier was calculated by dividing the utility score observed in the trials with the corresponding utility score in the general population. The multiplier was then multiplied for 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 methodology ensured that utility decreases with ageing as expected in the real world. 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.

**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[9] reports the EQ-5D decrements following a range of post-procedural outcomes after a transcatheter aortic valve replacement (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 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 required dialysis (AKIN 3) was assumed to be permanent.

Regarding stroke, it was agreed to use the study from Luengo-Fernandez[15] 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 10.

**Table 10: Utility decrements**

| Condition | Utility detriments | Duration | Source |
|---|---|---|---|
| Major bleeding | 0.45 | 45 days | Kaier 2016[9] |
| Vascular complication | 0.00695 | 30 days | Kaier 2016[9] |
| Dialysis | 0.161 | Permanently | Kaier 2016[9] |
| Pacemaker | 0 | Permanently | Assumed |
| Stroke | 0.16 | 1 year | Luengo-Fernandez 2013[15] |
| Post-stroke | 0.179 | Permanently | Luengo-Fernandez 2013[15] |

## 2.3.5 Resource use and costs

### 2.3.5.1 Intervention costs

The cost of a TAVI or SAVR intervention was sought from the NHS Reference Costs 2018-2019[27]. 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. 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 decided to recalculate 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

It is worth mentioning that the most recent version of the NHS Reference Costs (2018-2019)[27] does not include excess bed day cost and therefore, the previous version (2017-2018)[26] had to be used.

Table 11:

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

It is worth mentioning that the most recent version of the NHS Reference Costs (2018-2019)[27] does not include excess bed day cost and therefore, the previous version (2017-2018)[26] had to be used.

**Table 11: 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 8+ | £7,681 | £5,369 |
| 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 | £11,893 | £10,091 |

| State | NHS Reference Cost | Cost of the intervention without the hospital stay component |
|---|---|---|
| Repair, with CC Score 6-10 | | |
| Standard, Single Heart Valve Replacement or Repair, with CC Score 0-5 | £10,735 | £9,196 |

Regarding TAVI, it was decided to assign to the high-risk population the cost associated with an intervention with a CC higher than 8 and to the intermediate population an unweighted average of the costs associated with a CC higher and lower than 8. 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.

The trials included in the clinical review report information on hospital length of stay and ICU length of stay for the different risk categories. These are reported in Table 12.

**Table 12: ICU and length of stay by risk categories**

| Operative risk | LOS (days) | | ICU (days) | | Source |
|---|---|---|---|---|---|
| | TAVI | SAVR | TAVI | SAVR | |
| Intermediate risk | 6 | 9 | 2 | 4 | Leon 2016[12] |
| High risk | 8 | 12 | 3 | 5 | Smith 2011[32] |

It should be noted that these numbers come from studies conducted in a setting different than the UK and therefore may be not representative of the UK NHS case. Moreover, it was assumed that median and mean values are equivalent, which is often not the case when the data is skewed as hospital length of stay.

The numbers illustrated in Table 12 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 FCE (see Table 13).

**Table 13: ICU costs**

| Currency Code | Currency Description | Number of FCE's | 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 FCE's | 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[26]. An average of the unit cost was calculated weighted by the number of excess bed days reported for each HRG as shown in Table 14. The resulting averages were used to cost a day spent in the hospital not in ICU for TAVI and SAVR patients.

**Table 14: Hospital ward stay cost**

| Currency Code | Currency Description | Excess Bed days | National Average Unit Cost |
|---|---|---|---|
| EY21A | Transcatheter Aortic Valve Implantation (TAVI) using Transfemoral Approach, with CC Score 8+ | 172 | £448 |
| EY21B | Transcatheter Aortic Valve Implantation (TAVI) using Transfemoral Approach, with CC Score 0-7 | 166 | £500 |
| **Weighted average** | | | £473 |
| 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 | 372 | £340 |

| Currency Code | Currency Description | Excess Bed days | National Average Unit Cost |
|---|---|---|---|
| | Repair, with CC Score 0-5 | | |
| **Weighted average** | | | £325 |

Finally, the cost of ICU and hospital stays were added to the cost of the intervention per se to determine the overall cost of the intervention (including LOS and ICU). These are reported in Table 15.

**Table 15: Cost of the intervention including ICU and hospital stay**

| State | TAVI | SAVR | SAVR conversion |
|---|---|---|---|
| Intermediate risk | £9,658 | £17,640 | £17,904 |
| High risk | £11,979 | £21,940 | £23,990 |

### Valve costs

The costs of a TAVI valve is not included in the NHS Reference Costs as it is listed in the High Cost Device Exclusion List and had to obtained from the NHS Supply Chain catalogue instead. Its cost is presented in Table 16.

**Table 16: The price of the valve**

| State | Price | Source |
|---|---|---|
| TAVI valve | £20,280 | NHS Supply Chain Catalogue 2020[25] |

### Intermediate care and rehabilitation

Data from a clinical trial[16] show that more patients in the SAVR arm tend to be 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[16] as reported in Table 17.

**Table 17: The cost of rehabilitation**

| Currency Code | TAVI | SAVR | Source |
|---|---|---|---|
| Discharge at intermediate care centre | 0.8% | 14.8% | Mack 2019[16] |
| Cost of intermediate care centre | £5965 | | NAIC 2017[20] |
| Home-based rehabilitation | 2.8% | 11.3% | Mack 2019[16] |
| Cost of home-based rehabilitation | £982.00 | | NAIC 2017[20] |

It should be noted that the study[16] 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.

#### 2.3.5.2 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.

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.

##### *2.3.5.221 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. See Table 18 for the decision tree costs and their sources.

**Table 18: Decision tree costs**

| State | Cost | Source |
|---|---|---|
| Major bleeding | £1,971 | NHS Reference Costs 2018-2019[24] |
| Vascular complication | £1,826 | NHS Reference Costs 2018-2019[24] |
| Pacemaker | £2,623 | NHS Reference Costs 2018-2019[24] |

**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 19.

**Table 19: 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 | 1,642 | £3,866 |

| Currency Code | Currency Description | Number of FCE's | National Average Unit Cost |
|---|---|---|---|
| **Non-elective long stay** | | | |
| | Intervention, with CC Score 8+ | | |
| 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 |
| 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 |

1

2 **Vascular complications**

3 The cost of vascular complication was sought by looking at International Classification of
4 Diseases (ICD) codes related to various injuries to blood vessels around the body. The ICD
5 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 20.

**Table 20: 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 |
| 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[24] as shown in Table 21.

**Table 21: Cost of Pacemaker**

| Currency Code | Currency Description | Activity | Total |
|---|---|---|---|
| **Non-elective long stay** | | | |
| EY03Z | Implantation of Biventricular Pacemaker with Other Percutaneous Intervention | 127 | £10,977 |
| EY04A | Implantation of Biventricular Pacemaker with CC Score 6+ | 1641 | £4,950 |
| EY04B | Implantation of Biventricular Pacemaker with CC Score 0-5 | 2452 | £3,972 |
| 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 |
| 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 | 165 | £7,565 |

| Currency Code | Currency Description | Activity | Total |
|---|---|---|---|
| **Non-elective long stay** | | | |
| | Intervention, with CC Score 6+ | | |
| 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 Pacemaker with CC Score 0-2 | 13331 | £1,085 |
| **Weighted average** | | | £2,623 |

## Cost of 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 22.

**Table 22: PVL costs**

| State | Cost | Source |
|---|---|---|
| Simple echocardiogram | £115 | NHS Reference Costs 2018-2019[24] |
| Consultant led | | |
| Non-admitted Face-to Face Attendance, follow-up | £135 | NHS Reference Costs 2018-2019[24] |
| Total | £250 | |

#### *2.3.5.212 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[36] 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 23.

**Table 23: Burden of stroke**

| Health state | Cost | Source |
|---|---|---|
| Stroke 1 year | £23,052 | Xu 2018 – SSNAP project inflated to 2017/18[36] |
| Stroke 5 year | £47,023 | Xu 2018 – SSNAP project inflated to 2017/18[36] |

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[29] 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 24.

**Table 24: Cost of stroke and post-stroke**

| Health state | Cost | Source |
|---|---|---|
| Stroke | £18,948 | Xu 2018[36] 1-year costs with 50% of social care costs removed and inflated to 2018/2019 |
| Post-stroke | £6,727 | Xu 2018[36] 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 25.

**Table 25: 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 26).

**Table 26: 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 | 577621 | £145.31 |

| Currency Code | Currency Description | Activity | Unit Cost |
|---|---|---|---|
| | Catheter, 19 years and over | | |
| 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 Filtration, with Access via Arteriovenous Fistula or Graft, with Blood-Borne Virus, 19 years and over | 49499 | £160.08 |
| 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 | 32 | £204.45 |

| Currency Code | Currency Description | Activity | Unit Cost |
|---|---|---|---|
| | Filtration, with Access via Haemodialysis Catheter, 19 years and over | | |
| 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 Haemodialysis Catheter, 19 years and over | 3 | £253.88 |
| 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[24] 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[24]. 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<br>*r*=selected rate<br>*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 the following:

1. Vary the cost of a TAVI Valve (full price, discounted cost)
2. Shorter time horizon (13 years being the longest follow-up without extrapolation)
3. No effect of PVL on mortality
4. Mild and moderate PVL affect mortality
5. Pacemaker cost removed and assumed to be included in the HRG

In this chapter, the one-way sensitivity analyses are presented.

### 2.5.1 Cost of TAVI valve

The cost of the TAVI valve was discussed by the committee as it was highlighted that the price of the valve quoted in the NHS supply chain catalogue differed from that paid in many hospitals. It was noted that around 80% of hospitals purchased the TAVI valve at a discounted cost of £17,500 under the National Procurement Scheme. This is a price-by-volume arrangement, which means that even if the scheme is nationally available, the price varies by Trust. For NICE evaluations, analyses based on price reductions for the NHS will be considered only when the reduced prices are transparent and can be consistently available across the NHS, and when the period for which the specified price is available is guaranteed. Therefore, in the base case analysis, the full NHS Supply Chain price was used. Both the discounted price and a hypothetical lower price of £15,000 were tested in sensitivity analyses for 80% of the valves.

**Table 27: Cost of TAVI valve**

| Scenario | Cost | Source |
|---|---|---|
| Base case | £20,280 | NHS Supply chain price[25] |
| Discounted price 1 | £17,500 | National Procurement Scheme |
| Discounted price 2 | £15,000 | Hypothetical lower price |

A one-way sensitivity analysis was undertaken to explore the impact of using the three different estimations in the model.

### 2.5.2 Time horizon

There was limited long-term data availably reporting reintervention rates. The longest observed data available had a 13-year follow-up. Hence a shorter time horizon of 13 years was tested to see the impact on the ICER without any extrapolation.

### 2.5.3 No Effect of PVL on mortality

The committee discussed the inclusion of effect of PVL on mortality. Previous economic models assume that PVL does not affect mortality. Therefore, a scenario where PVL only cause costs but do not affect mortality was tested.

### 2.5.4 Mild and moderate PVL affect mortality

Although the study from Makkar 2020[17] 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.

### 2.5.5 Pacemaker cost included in the HRG

The committee discussed the cost of the pacemaker and noted that in some cases pacemakers are implanted during the same procedure of TAVI and hence, its cost is included in the NHS reference cost for TAVI procedure. In other cases, pacemaker is implanted in a second procedure, and therefore should be costed using its own reference cost figure. Both these scenarios were tested to see the impact it has on the ICER.

## 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.

## 2.8.4 Interpreting results

NICE sets out the principles that committees should consider when judging whether an intervention offers good value for money.[21-23] 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 cost effectiveness results are presented in table 28 and 29 concerning, respectively, intermediate- and high-risk patients.

**Table 28: Cost-effectiveness deterministic results for TAVI versus SAVR (Intermediate risk, deterministic)**

| Age | Incremental costs | Incremental QALYs | Incremental cost per QALY gained |
|---|---|---|---|
| 60 | £14,670 | 0.10 | £142,162 |
| 70 | £13,967 | 0.10 | £134,874 |
| 80 | £13,387 | 0.10 | £129,343 |
| 90 | £12,444 | 0.09 | £136,796 |

**Table 29: Cost-effectiveness deterministic results for TAVI versus SAVR (High risk, deterministic)**

| Age | Incremental costs | Incremental QALYs | Incremental cost per QALY gained |
|---|---|---|---|
| 60 | £13,147 | 0.12 | £111,487 |
| 70 | £12,392 | 0.12 | £102,634 |
| 80 | £11,767 | 0.12 | £97,023 |
| 90 | £10,716 | 0.11 | £100,335 |

As expected, TAVI is more cost-effective for older cohorts reflecting the fact that older patients have a lower life-expectancy and, therefore, a lower probability of needing a second intervention. For none of the risk and age categories considered TAVI was found to be cost effective at a threshold of £20,000 and £30,000 suggesting that TAVI is not cost effective in England at the current price.

Table 30 illustrates the number of events occurring in the two arms for a cohort of 1,000 people at 80 years and high operative risk. This age category was chosen as the base case as it reflects the mean age reported in the UK TAVI registry.

**Table 30: Events for 1000 patients (Deterministic, 80 years old, high risk)**

| Cost category | TAVI | SAVR | Difference (TAVI minus SAVR) |
|---|---|---|---|
| Vascular complications | 87 | 30 | 56 |
| Major bleeding | 143 | 281 | -137 |
| Stroke | 61 | 58 | 3 |
| Dialysis | 18 | 30 | -12 |
| Pacemaker implantation | 173 | 69 | 104 |
| Hospitalisation | 1,069 | 840 | 229 |
| Reintervention | 203 | 68 | 135 |

People in the TAVI arm experience more vascular complication, stroke, pacemaker implantation, hospitalisation episodes and reinterventions. On the other hand, TAVI reduces cases of dialysis and major bleeding.

Table 31 offers a breakdown of the costs per patients of the two strategies.

**Table 31: Breakdown of costs (per patient at 80 years old, high risk, probabilistic)**

| Cost category | TAVI | SAVR | Difference (TAVI minus SAVR) |
|---|---|---|---|
| Intervention | £32,067 | £21,957 | £10,110 |
| Cost rehab | £89 | £941 | -£852 |
| Vascular complications | £158 | £56 | £102 |
| Bleeding | £296 | £553 | -£257 |
| Pacemaker implantation | £402 | £164 | £238 |
| Stroke | £2,575 | £2,494 | £82 |
| Dialysis | £1,621 | £2,810 | -£1,189 |
| Reintervention | £4,017 | £1,335 | £2,682 |
| Hospitalisation | £2,010 | £1,575 | £434 |
| Echo | £377 | £109 | £268 |
| Total | £43,613 | £31,994 | £11,619 |

The total cost is driven mostly by the difference in the intervention and reintervention costs, which are higher in TAVI arm. TAVI seems to reduce the cost related to rehabilitation, bleeding and dialysis. Overall, a patient in TAVI arm has a cost £11,619 higher than a patient in SAVR arm.

## 3.2 Sensitivity analysis

Several one-way sensitivity analyses were conducted and are illustrated in table 32. The incremental cost-effectiveness ratio was found to be sensitive to the price of the valve, to the assumption on PVL and reintervention rate. When a most favourable scenario to TAVI was tested with the highest discount, no effect of PVL on mortality, same reintervention rate and no additional cost for pacemaker, the incremental cost-effectiveness ratio was found to lie below the threshold of £30,000 at a value similar to the ICERs found in other studies with similar favourable assumptions.

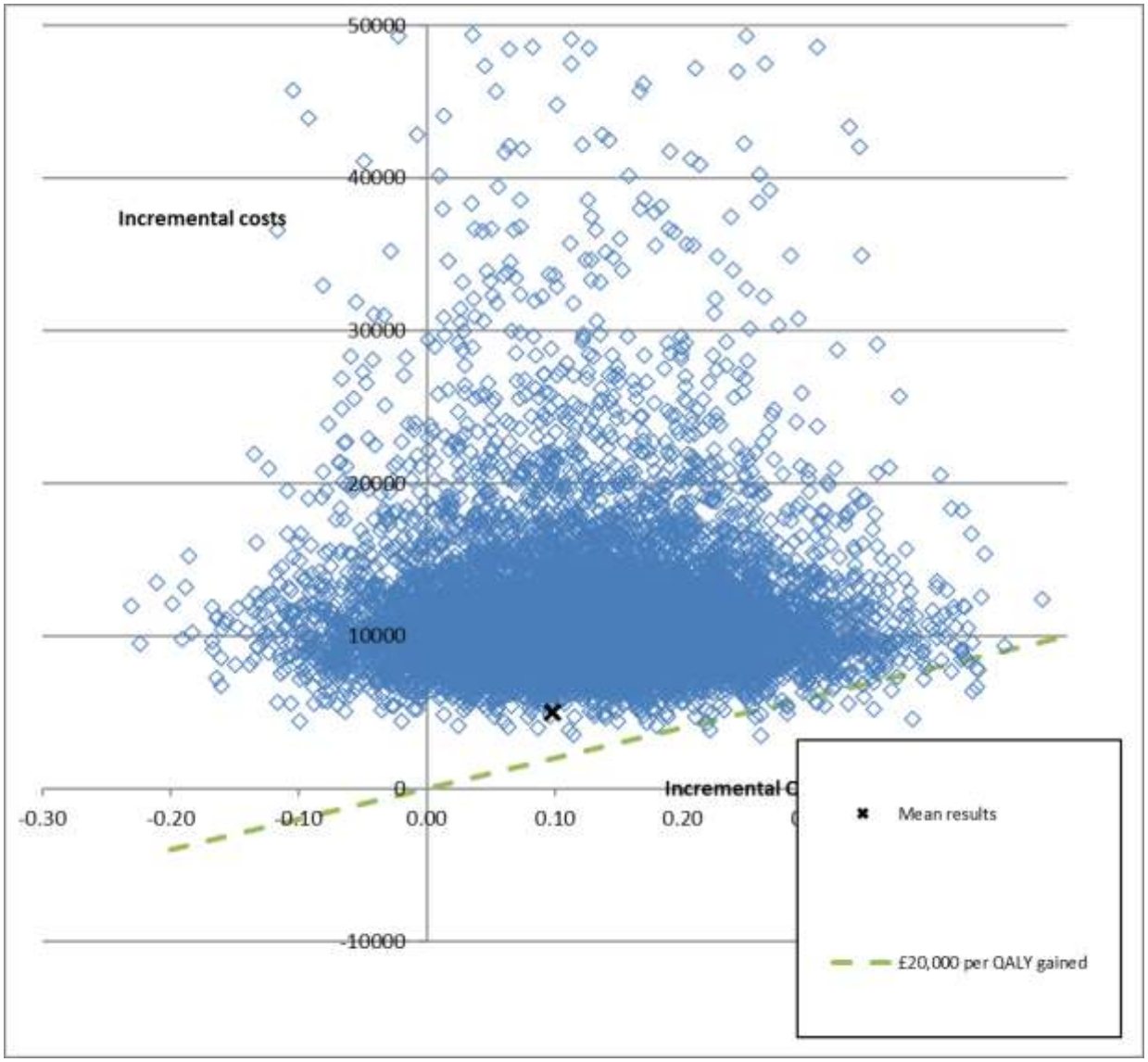
**Table 32: One-way sensitivity analyses for TAVI vs SAVR – 80 years-old high risk (deterministic)**

| Scenario | Incremental costs | Incremental QALYs | Incremental cost per QALY gain |
|---|---|---|---|
| Deterministic results | £11,767 | 0.121 | £97,023 |
| Probabilistic results | £11,619 | 0.125 | £92,945 |
| 13-years time horizon | £11,141 | 0.12 | £93,752 |
| No effect of PVL on mortality | £11,767 | 0.16 | £74,004 |
| Mild and moderate PVL affect mortality | £11,675 | 0.06 | £200,778 |
| Valve discounted | £9,650 | 0.14 | £67,788 |
| Valve hypothetical lower price | £7,609 | 0.14 | £53,451 |

| Scenario | Incremental costs | Incremental QALYs | Incremental cost per QALY gain |
|---|---|---|---|
| Pacemaker cost included in the HRG | £11,654 | 0.14 | £81,868 |
| Same reintervention rate | £8,620 | 0.12 | £69,220 |
| Most favourable scenario | £4,286 | 0.16 | £25,993 |

The scatterplot in figure 8 shows the results of the probabilistic analysis. All the points lie in the north-east and north-west quadrant and almost none is below the threshold line of £20,000 per QALY gained confirming that TAVI is unlikely to be cost effective in England. The probabilistic analysis suggest that there is a 0% probability that TAVI is cost effective at a threshold of £20,000 and a 3% probability that it is cost effective at threshold of £30,000.

**Figure 8: Probabilistic analysis scatterplot (80 years old high-risk patients)**

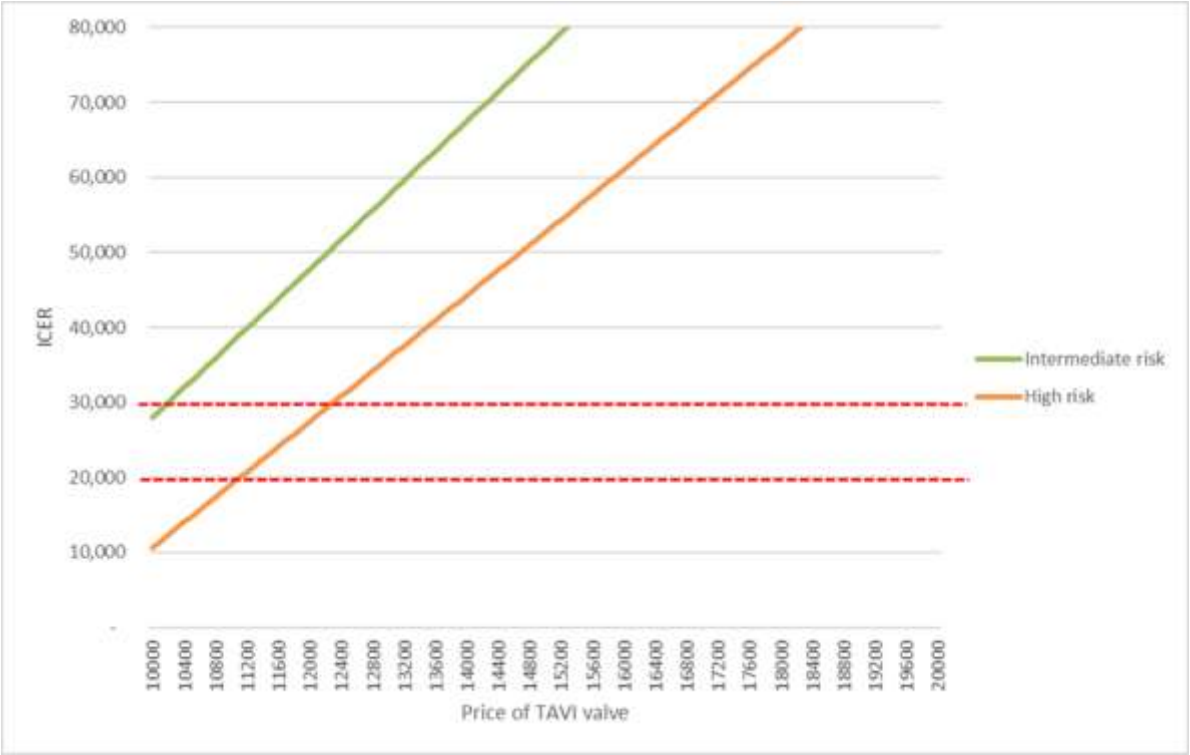



## 3.3 Threshold analysis

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 intermediate- and high-risk patients. This was achieved by varying the price of the valve from £10,000 to

£20,000 and looking at the corresponding incremental cost effectiveness ratios. The results are presented in figure 9.

**Figure 9: TAVI valve threshold analysis**




The results showed that for intermediate-risk patients, TAVI becomes cost effective at a threshold of £30,000 per QALY gained when the price drops below £10,200. For high-risk patients TAVI becomes cost effective when the price of the valve ranges between £11,000 and £12,400. This is equal to a discount of around 39%-45%. This price is not too distant from the price TAVI is currently purchased in other developed countries as France or Germany, hence, if the price in the UK drops to similar levels, TAVI may become cost effective in England at least for high-risk patients.

# 4 Discussion

## 4.1 Summary of results

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

- In intermediate operative risk patients TAVI is not cost effective compared to surgical aortic valve implantation (ICER: £129,343 per QALY gained)
- In high operative risk patients TAVI is not cost effective compared to surgical aortic valve implantation (ICER: £92,945 per QALY gained)

The analysis was assessed as directly applicable with minor limitations.

## 4.2 Limitations and interpretation

The analysis demonstrated that TAVI is not cost effective in patients at intermediate or high operative risk at any age compared to surgical aortic valve replacement. The results are robust to the assumptions used in the model as the sensitivity analysis showed that TAVI remains not cost effective at a threshold of £20,000 even in the most favourable scenario, although the incremental cost effectiveness ratio dropped below $30,000.

The model has some limitations. Firstly, as the source used for extrapolating long-term mortality is based on the UK TAVI registry[18], mortality data refer to the population currently treated with TAVI in the UK, who are mostly patients at high and intermediate operative risk (average Society of Thoracic Surgeons Score 5.06). As a result, we excluded low operative risk patients from the model as their long-term mortality could not be modelled on the basis of the available literature. Nevertheless, it is likely that low risk patients would show costs and outcomes similar to intermediate risk patients and that the intervention would be even less cost effective in this category of people. For high and intermediate risk groups mortality was extrapolated beyond 3 years based on the assumption that cumulative excess hazard function between TAVI and the general population follows a linear function as suggested in the source paper[18]. If this assumption does not hold over time, then the estimated QALYs might be inaccurate.

Secondly, the costs of the procedure were calculated taking into account days spent into the hospital ward and intensive care unit for each risk category of patients. These data come from two randomised trials included in the clinical review and conducted in the US[12 32]. No UK studies reporting days spent in ICU or hospital ward were identified. Although the total length of hospital stay for TAVI reported in these 2 studies seems reasonably consistent with the UK data for 2017 from BCIS[14], which reported a mean of 5.5 days, the committee noted that these studies may not be generalizable to the NHS setting when it comes to ICU stay as people tend to spend fewer days in ICU after a TAVI or surgical intervention in the UK. Therefore, it is possible that this analysis is overestimating the actual cost of a TAVI or SAVR intervention in the UK. Nevertheless, the committee expect that the differential cost between these two procedures is still captured by the analysis even if the absolute cost is overestimated.

Thirdly, the cost of a day spent on hospital ward was estimated using the excess bed day reported in the NHS Reference Costs 2017/2018. Paragraph 180 of National cost collection guidance, NHS Improvement 2019, says: “We would expect that care of patients is less intensive during the excess bed days than at the beginning of the FCE and that costs are less per day than for the inlier bed days, although we recognise that active treatment does sometimes continue beyond the trim point – especially for specialised services”. It is likely therefore that using excess bed day cost underestimates the actual cost of spending a day in in the hospital ward.

Finally, reintervention rate in the surgical arm was extrapolated using the study from Rodriguez-Gabella[31]. 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.

## 4.3 Generalisability to other populations or settings

This analysis is based on operable patients at intermediate and high operative risk. Although people at low risk were not studied in this analysis, we expect TAVI to be even less cost effective in this category of patients.

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 at least for high risk patients.

The results were found to be very sensitive to the price of the valve in the UK. As the valve cost highly varies between countries, the results of this study may not be transferable to other jurisdictions.

## 4.4 Comparisons with published studies

Several cost-utility analyses were identified comparing TAVI to surgery in intermediate or high-risk population. Some of these studies reached the same conclusion of this analysis whereas others disagreed.

A Japanese cost-utility analysis[10] found TAVI to be cost effective in inoperable patients but not cost effective in operable patients at intermediate risk. The incremental cost is fairly aligned to this analysis as Kodera estimated that TAVI costs £11,731 more per person whereas the NGC model found TAVI to cost between £13,000 to £14,000 more than surgery for intermediate risk patients. On the other hand, Kodera study found TAVI to give 0.22 QALYs more than surgery whereas the NGC model estimated a QALY gain around 0.1. This is likely due to the fact that the authors assumed TAVI to be 10% more superior than SAVR in terms of mortality whereas, based on the findings of the clinical review (Evidence Review H), we assume a smaller improvement in mortality with TAVI.

A Canadian study[33] with a lifetime horizon found TAVI not cost effective in intermediate-risk people. Their estimation in terms of QALY gained is in line with our analysis as they found TAVI to give 0.15 QALY more per person compared to the 0.1 estimated with our own model. However, costs are rather different as, according to Tam 2018, TAVI costs only £6,343 more than surgery against the £13,000 to £14,000 estimated with our own model. A major limitation of Tam model was that procedural costs for SAVR and TAVI were estimated through expert opinion whereas we used standard UK source. Furthermore, Tam model does not seem to address reintervention which was found to be an important source of cost in the NGC model, accounting for around £3,000 of the whole cost associated with TAVI.

A second Canadian study[34] with a 15-year time horizon found TAVI to be cost effective in intermediate and high risk patients alike. The study found TAVI to improve considerably

QALYs (0.43 in high risk patients and 0.48 in intermediate risk patient) at a relatively low incremental cost (£4,000 in high risk patients and £7,500 in intermediate risk patients). The model based its extrapolation of mortality on a source finding a persistent improvement in mortality with TAVI after 1 year. In addition, they assumed more hospitalization episodes with SAVR than with TAVI. This was not in line with our own clinical review, which found a little or no long-term improvement in mortality and a significantly lower hospitalization rate with SAVR than TAVI.

Finally, it should also be noted that this is the first analysis to our knowledge taking into account the effects on mortality caused by moderate and severe paravalvular leaks. This significantly increased the incremental cost per QALY gained of TAVI as the trials evidence showed that TAVI patients are more likely to experience paravalvular leak than surgical patients. We suspect this to be one of the reasons the analysis found an incremental cost per QALY gained significantly above the estimates in published studies.

## 4.5 Conclusions

This economic evaluation demonstrated that TAVI compared to SAVR for treating aortic stenosis in patients at intermediate and high operative risk is not cost effective in England at the current price of the valve. The results of the analysis are robust to the assumptions of the model as, even in the most favourable scenario, TAVI failed to show an incremental cost effectiveness ratio below the threshold of £30,000 per QALY gained. This analysis is in line with some economic evaluations which found TAVI to be not cost effective in different countries. On the other hand, other published analyses found instead TAVI to be cost effective arguably due to the different assumptions and sources used as well as to differences in the price of the valve across countries.

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