Evidence Development Pilot Project:
Transcatheter Aortic Valve Implantation in Scotland

Report to Scottish Health Technologies Group

29th November 2010

1. Introduction

In September 2008, the Health Economics Appraisal Team at Glasgow University and NHS Quality Improvement Scotland organised a Workshop on 'Coverage with Evidence Development' with a particular focus on whether there were implications of this approach for Scotland (or similar countries). At the end of the workshop it was suggested that a number of pilot projects should be attempted to demonstrate the potential application of coverage with evidence development projects in Scotland. The Scottish Health Technologies Group (SHTG) was tasked with identifying a contemporary problem that represented a real issue for the health service in terms of a new technology seeking adoption for which the evidence base was immature. The SHTG chose transcatheter aortic valve implantation (TAVI).

TAVI is a promising new technology for patients presenting with Aortic Stenosis (AS) who, left untreated, have a poor prognosis. Current treatment options are conventional valve replacement (CVR) and medical management. CVR can restore life expectancy to something close to the usual age, sex adjusted life expectancy; however, due to its invasive nature it is only suitable for a small group of patients with AS. Many therefore are confined to medical management with associated poor life expectancy (mean survival 2-3 years). By contrast TAVI offers the opportunity to replace the aortic valve without opening the chest cavity – instead the device is delivered either transfemorally (through the leg) or transapically (through the chest) via a catheter inserted into an artery and fed into position in a minimally invasive operation that can even be conducted under local anaesthetic.

The promise of the TAVI procedure is that it could deliver the benefits of CVR without the need for an invasive CVR procedure. This has the potential to benefit two groups of patients. Firstly, those that currently receive CVR could benefit from the avoidance of a major surgical procedure. Secondly, those with life-threatening AS, who are currently not considered fit for surgery, but could be eligible for the minimally invasive procedure. However, the evidence that TAVI is equivalent (or even superior) to CVR in terms of outcomes is sparse. While many thousands of patients worldwide have successfully received the TAVI device, long term follow-up is not yet available.

The aims of this study are to consider the cost-effectiveness of TAVI on the basis of the evidence that is currently available and the requirement for further evidence gathering. The analysis employs a decision analytic model and considers 3 distinct patient groups (low, medium and high risk). Low risk patients are those who are assumed to be eligible for conventional valve replacement but for whom TAVI could be an alternative. For these patients there is a choice between TAVI and CVR. Medium risk patients are those for whom there is not currently a clear choice of treatment, as such the choice considered in the analysis is between CVR, TAVI and medical management (no AVR). Finally, high risk patients are those who are ineligible for conventional surgery so traditionally get medical management, as such the choice is between TAVI and medical management (no AVR).

This report presents the structure and parameters of the decision analytic model, the cost-effectiveness results and a measure of the uncertainty.

2. Modelling methods

In this section the modelling methods are described in full, including the assumptions underlying the modelling, the source of the parameter estimates and the associated uncertainty. The first sub-section below gives an overview of the model and this is followed by a detailed description of both the short-term and long term components of the model.

2.1 Model overview

The model is split into two time periods. The first considers the initial phase of treatment for a patient with AS, who depending on their risk level could potentially be managed medically, could receive a CVR or a TAVI procedure. This phase covers the surgery and the initial 30 day period. The second phase is the longer term projection of costs and life-expectancy which depends on the outcome of the initial phase.

The initial phase is modelled using a decision tree (Figure 1). Potentially three treatment options are available for those suffering from aortic stenosis – CVR, TAVI, and no valve replacement (medical management), although the specific options available to any particular patient will depend on the patients risk group. During a valve procedure (CVR or TAVI), patients are at risk of operative mortality. For those who survive, the procedure could result in complications. The model distinguishes minor complications, which are assumed to resolve with appropriate medical care, from major complications, which are assumed to result in failure of the valve implantation with the patient left in a state no better than their original manifestation of AS. Patients experiencing minor or no complications are assumed to have had a successful valve replacement. For those patients receiving TAVI (rather than CVR) there is an additional possibility that the TAVI procedure does not go to plan and that a decision is made to convert to CVR. Where this occurs the outcomes are assumed to be equivalent to, and occur in the same proportions as, CVR. Finally, patients receiving no valve replacement are assumed to receive appropriate medical management for their condition.

The second, long term, phase is modelled using a Markov state transition model (Figure 2). There are three states in the Markov model: functioning valve replacement; AS / failed valve replacement; or death. Outcomes from the initial phase (the decision tree) determine in which of these three states a patient enters the long term phase. Each cycle of the Markov model is 12 months in duration and the model is run until the majority of patients have died. Patients entering the Markov model in the successful valve replacement state are at risk for a valve related event that could either be fatal or result in loss of valve functioning moving them to the 'failed valve replacement' state.

The next two sub-sections detail the parameter estimates for the two elements of the model.

2.2 Short term modelling of the valve replacement procedures

Table 1 presents the transition probabilities that are employed in the decision tree. Both the operative mortality rate and the probability of having a major complication which results in valve failure are assumed to be the same for the CVR and TAVI procedures. This reflects the lack of data for the relative effectiveness of TAVI compared to CVR. Nevertheless, additional parameters are included in the model to allow the flexibility to model potential differences between TAVI and CVR in relation to operative mortality and major complications (further details below). The probability of a minor complication following a TAVI procedure is much greater than for CVR, since these minor complications are mainly associated with the catheter insertion. The probability of converting to CVR is only relevant to those receiving

TAVI. Finally, special mention is necessary for disabling stroke. In order to capture the potential for disabling stroke to be an important outcome in the model it is considered equivalent to death in terms of health outcomes. This avoids the need for a complex modelling of stroke outcomes while retaining the flexibility of the model to examine this potentially important end point. In the base case, the assumption of the model is that the risk of disabling stroke does not vary between CVR and TAVI although an additional parameter is used to allow for flexibility.

In Table 2, the detail of complications associated with valve replacement procedures is presented. This includes both the probabilities of these complications and the associated costs of those events. As described above, the base case assumption is that the risk of disabling stroke is the same across valve replacement procedures. However, a relative risk parameter for disabling stroke is included to account for potential differences between TAVI and CVR (see below for details). Major complications of the procedure that could lead to valve failure are also presented. The transition probability is estimated by averaging the absolute probabilities obtained from the literature across CVR and TAVI giving the same probability of major complication in the base case (see Appendix A for description). A small amount is added to the data for each event in order to adjust for those with an observed zero probability to allow for the small chance of such events occurring. The transition probabilities for each event are then estimated by averaging the adjusted probabilities across CVR and TAVI. The overall costs of major complications are then calculated by multiplying the cost of each complication by the proportion of total events that are represented by each event (weights). A similar approach is adopted for minor complications, although these are allowed to vary between CVR and TAVI.

In Table 3, the costs associated with each branch of the decision tree are specified. The costs of the CVR and TAVI devices are only presented as approximates, due to the commercial nature of these data. Sensitivity analysis is used to explore the impact of the cost to NHS Scotland of the devices. The costs of the procedures are assumed to have a slight advantage towards TAVI, but it is in the length of stay in hospital that the main advantage of the TAVI procedure is realised. Overall, it is assumed that TAVI patients will spend significantly less time in the more costly departments (intensive care and high dependency units), however, it is assumed that time on the general ward will be similar between the two devices. Following discharge from hospital, the assumption is that those needing cardiac rehabilitation and/or temporary nursing home care will be higher among patients receiving CVR.

Table 4 presents the impact on utility associated with each valve related complication. The assumption is made that disabling stroke is equivalent to death, as such it is assigned a utility of 0. The utilities associated with the major and minor valve related complications are estimated in a similar manner to the costs of major and minor valve related complications using weights to give the overall disutility of a major complication.

Table 5 presents the utilities associated with persistent aortic stenosis (i.e. failed valve replacement) and functioning valve replacement. These utilities are calculated based on the estimated utility by NYHA class as per Maliwa et al (2003). From the Revive Trials, the proportion in each NYHA class is estimated for those with aortic stenosis and those with functioning valve replacement. The utilities are then applied to calculate the utility of being in each of the aforementioned states. With respect to the disabling aspects of the valve procedures, these are assigned disutility of 0.012 for 13 weeks and 0.0035 for 6 weeks for CVR and TAVI respectively.

2.3 Long term modelling of prognosis

The Markov model (Figure 2) requires probabilities to govern the transitions between the states in each annual cycle. Table 6 lists the transition probability parameters that are employed in the long-term Markov model. The probability of a Valve Related Event (VRE) is assumed to be 0.17 per annual cycle. It is further assumed that 22% of VRE events are fatal, while the remaining non-fatal VREs (78%) result in failure of the valve, returning the patient to a state equivalent to the original AS state. These transition probabilities were estimated by averaging the absolute probabilities obtained from the literature on valve replacement (see Appendix A for details). In addition to experiencing a fatal VRE, patients in the functioning valve state of the model are also assumed to be at risk from death from natural causes. The natural mortality rate is assumed to follow the background age/sex adjusted mortality rates, but with a standardised mortality ratio of 1.5 to adjust for the fact that patients undergoing valve replacement are likely to be at higher risk of death than the average patient of the same age/sex in the population. For patients in the AS / Failed VR state of the model, the life expectancy is assumed to be approximately 3 years, which equates to a transition probability of 0.33.

Table 7 presents the probabilities and costs of valve related events (VREs) that result in loss of valve functioning. The cost of a VRE is determined from the event costs and the weightings as previously.

To calculate the costs associated with the states in the Markov model the annual number of hospitalisations was estimated using hospitalisation rates per NYHA class[1] and the proportion of patients in each NYHA class per state from the Revive Trials. In addition medication costs were added to calculate the cost of functioning and failed valve replacement. It is also recognised that even with functioning valve replacement some patients will require permanent nursing home care. The resulting estimated annual costs for each health state are presented in Table 8.

Utility scores associated with VREs are presented in Table 9, again using weights to estimate the overall disutility associated with a (non fatal) VRE. The utility scores for the functioning valve and AS health states are identical to those calculated in Table 5.

2.4 Accounting for flexibility in TAVI parameters

One of the principles of the modelling reported here is to explore the potential uncertainty related to the relative effectiveness of TAVI compared to conventional valve replacement. Therefore, while the base case assumption of the model is that TAVI is comparable to CVR in a number of key respects, flexibility is built into the model to represent the potential for differential outcomes for TAVI in a number of key areas (Table 10). The relative impact of TAVI is represented by a ratio parameter which if set to unity represents equality of outcomes, while values below unity represent superiority for TAVI. For example, the relative cost of TAVI compared to CVR with respect to the procedure, hospital stay and post discharge care are all set to a value below unity reflecting the assumption that TAVI is cheaper than CVR with respect to each of these outcomes.

[1] Ahmed et al (2006)

2.5 Parameter uncertainty

The uncertainty surrounding the parameters is incorporated into the model through the assignment of probability distributions. Probabilistic sensitivity analysis is then used to propagate this uncertainty and generate distributions of expected outcomes (costs and QALYs). The mean values of these distributions provide estimates of the expected cost-effectiveness of TAVI compared to CVR and medical management, given the uncertainty, while analysis of the distribution provides estimates of the potential worth of further evidence gathering.

In this model normal distributions were applied to the costs and utilities of the procedures, complications, valve related events and follow up drug therapy. Log normal distributions were applied to the TAVI specific (relative risk) parameters: relative operative mortality; risk of failure; risk of stroke; risk of valve related events; and relative cost of procedure, length of stay and post discharge care of TAVI. Beta distributions were applied to the probabilities in the short term decision tree as well as to the probability of valve related events and the probability of death from a valve related event in the longer term Markov Model. In addition Beta distributions were applied to the probability of hospitalisations and permanent nursing home care with a functioning and failed valve replacement. A Dirichlet distribution (multinomial version of the Beta distribution) was applied to estimate the uncertainty surround the proportion of patients in each NYHA class used to estimate the utility associated with having aortic stenosis, a failed valve replacement resulting in persistent aortic stenosis and functioning valve replacement.

Table B1, in Appendix B, presents an overview of the probabilistic sensitivity analysis, illustrating the distributions and the values used to specify the distributions for the probabilistic sensitivity analysis. The resulting ranges considered through the probabilistic sensitivity analysis are also shown on Table B2 in Appendix B.

A number of validation exercises were performed on the model to confirm stability. The exercises included increasing the simulation size from 1,000 to 10,000; widening the range around the relative risk parameters and examining the co-variances in the model. The exercises confirmed that the model was stable.

3. Results

In presenting the results, consideration is given to 3 sub-groups of risk – low, medium and high. Low risk patients are assumed to be eligible for conventional value replacement -- for these patients the choice is between TAVI and CVR. The base case for low risk is assumed to be 60 year old males with an operative mortality of 5%. Medium risk patients may or may not receive CVR -- for these patients the choice is between TAVI, CVR and medical management. The base case for medium risk is assumed to be 70 year old males with an operative mortality of 15%. High risk patients are assumed ineligible for surgery and therefore receive only medical management of their AS -- for these patients the choice is between TAVI and medical management. The base case for high risk is assumed to be 80 year old males with an operative mortality of 20%. Table 11 presents estimates of the size of the potential population in each of these 3 risk sub-groups for the UK as a whole and for Scotland specifically, assuming the rates are proportional to the overall populations of each jurisdiction.

The cost-effectiveness results are presented below for each risk sub-group separately. A final section then considers the potential value of further research.

3.1 Low risk patients – TAVI vs CVR

The results in Table 12 illustrate that for patients at low risk TAVI is both more costly and more effective than CVR across all age/sex sub-groups. For the base case, the incremental benefit of TAVI over CVR is slight, being driven by a reduction in the operative mortality rate, while the additional cost is considerable, being driven by the cost of the device. As such, the ICER for the base case is estimated as £87,293 per QALY gained. This is considerably higher than the level usually considered cost-effective in the UK (£20k-£30k per QALY).

The ICE plane (figure 3) illustrates the existence and extent of the uncertainty surrounding both the incremental cost and incremental effect. In this case there is considerable uncertainty surrounding the existence of a benefit advantage for TAVI (over CVR) and uncertainty surrounding the extent of the benefit advantage. There is also some uncertainty surrounding the fact that TAVI is more expensive than CVR and the extent of the additional cost. The CEAC (figure 4) represents the uncertainty surrounding the cost-effectiveness of each procedure. In this case the uncertainties in incremental costs and effect do not translate into uncertainty regarding the cost-effectiveness of TAVI over the range usually considered cost-effective (£20k-£30k per QALY) - at a ceiling ratio of £30k per QALY the probability that CVR is cost-effective is 85% while the probability that TAVI is cost-effective is 15%.

It is important to note that small changes in the base case assumptions of the modelling could drastically change the interpretation. For example, reducing the cost of the device by £3,647 would result in TAVI being cost neutral, but with a slight health advantage due to the lower operative mortality, resulting in an ICER of £22,715 which is within the usually accepted range. Similarly, greater reductions in operative mortality than the 10% conservatively assumed here, would give a much greater potential health gain, for example assuming a 50% reduction in operative mortality would reduce the ICER to £39,461.

3.2 Medium risk patients: TAVI vs CVR vs medical management

The results (Table 13) illustrate that for patients at medium risk TAVI is both more costly and more effective than CVR which is in turn more costly and more effective than medical management across all age/sex sub-groups.

In comparing CVR to medical management for medium risk patients the ICER is £9,880 per QALY gained which is well within the level usually considered cost effective (£20k-£30k per QALY). However, the incremental benefit of TAVI over CVR is slight, being driven by a reduction in the operative mortality rate, while the additional cost is considerable, being driven by the cost of the device. As such the ICER for TAVI vs CVR for the base case is estimated as £72,412 per QALY gained. This is considerably higher than the level usually considered cost-effective in the UK (£20k-£30k per QALY).

The ICE plane (figure 5) illustrates the existence and extent of the uncertainty surrounding the incremental costs and incremental effects. Here there is considerable uncertainty with respect to the extent of differences in effectiveness and costs, although there is no uncertainty with respect to the existence of these differences – both valve procedures are considerably more expensive and effective than medical management for this patient group. For ease of comparison, Figure 6 focuses on the comparison of TAVI and CVR. This shows uncertainty in both the existence and extent of the differences in costs and effects for TAVI compared to CVR for medium risk patients. The CEAC (figure 7) represents the uncertainty surrounding the cost-effectiveness of each of the possible treatments.

For this group of medium risk patients, the uncertainties surrounding the incremental costs and benefits do not translate into uncertainty regarding the cost effectiveness of the treatments over the range usually considered cost effective (£20k-£30k per QALY). At a ceiling ratio of £30k per QALY the probability that medical management is cost-effective is 0%, while the probability that CVR is cost-effective is 88% and the probability that TAVI is cost-effective is only 12%.

Again, in this patient group, it is clear that small changes to the base case assumptions of the model could alter the conclusions. A reduction of £3,647 of the device would make TAVI cost neutral compared to CVR, but with a greater health advantage in this group due to the higher operative mortality rate, resulting in a ICER of £24,377 which is just inside the usually accepted range.

3.3 High risk patients: TAVI vs medical management

The results (Table 14) illustrate that for patients at high risk TAVI is both more costly and more effective than medical management across all age/sex sub-groups. For the base case, the incremental benefit of TAVI is high as is the additional cost of TAVI, being driven by the cost of the device. As such, the ICER for the base case is estimated as £22,603 per QALY gained, well within the level usually considered cost-effective (£20k-£30k per QALY).

The ICE plane (figure 8) illustrates the existence and extent of the uncertainty surrounding the incremental effect and the extent of the uncertainty surrounding the incremental cost. In this case, there is some uncertainty surrounding the existence of benefit for TAVI (over medical management) and considerable uncertainty with respect to the extent of these differences in effects. There is no uncertainty with respect to the existence of differences in costs, with TAVI being more expensive than medical management. This is driven by the cost of the TAVI device. However, there is considerable uncertainty surrounding the extent of the

differences in cost. The CEAC (figure 9) represents the uncertainty surrounding the cost-effectiveness of each treatment. In this scenario the uncertainties in cost and effect do not translate into uncertainty regarding the cost-effectiveness of TAVI over the range usually considered cost-effective (£20k-£30k per QALY) - at a ceiling ratio of £30k per QALY the probability that TAVI is cost-effective is 82% while the probability that medical management is cost-effective is only 18%.

Compared to the other risk group scenarios above, the potential for cost-effectiveness is clearer in this group due to the poor prognosis of patients ineligible for surgical valve replacement.

3.4 Value of further research

The potential value of undertaking further research is estimated by determining the value of eliminating all the uncertainties within the model (i.e. the expected value of perfect information). In order to generate a Scottish specific value for further information over the lifetime of the technologies we have summed the annual Scottish population data for each risk subgroup for a period of 10 years discounted at 3.5%. 10 years has been used as this is the period over which a choice between TAVI, CVR and medical management is considered a viable decision (i.e. advances in technology do not make the decision obsolete/invalid). Figure 10 illustrates the expected value of perfect information (summing across the various risk sub-groups) for the Scottish population. This provides a maximum value for the return on further research based on the assumption of information independence across the sub-groups. The results show that for the Scottish population the overall value of the EVPI is in the order of £1,565,836 for the ceiling ratio usually considered to be cost-effective (£30,000 per QALY). This provides an upper bound on the potential value for additional research in the Scottish context and it is clear that there should be considerable scope for generating evidence for TAVI within these sorts of bounds.

4. Summary and research recommendations

Cost-effectiveness of TAVI is borderline for low and medium risk patients and subject to uncertainties. There are two short term uncertainties that are absolutely key to understanding the potential for TAVI to provide a cost-effective treatment for the NHS. The first is the extent to which the high acquisition cost of the device can be offset by the reduction in hospital length of stay, particularly in high dependency units. The second is the potential for TAVI to reduce the operative mortality rate. It has been suggested that TAVI could reduce the operative mortality to 50%. We have chosen a more conservative 10% reduction. If we had been more optimistic the TAVI point estimates for these groups would have been closer to the £30,000 per QALY mark (though still outside the range usually considered cost effective).

The cost-effectiveness of TAVI in patients currently ineligible for surgery appears more positive. This is largely due to the poor prognosis for AS patients who do not receive CVR, meaning that the potential patient benefit in this group is much higher. Nevertheless, with few costs to offset, the health service would have to find the full cost of the device, and this may prove a practical challenge in current resource constrained environments.

There are a number of limitations to the modelling we present in this report. The model provides a highly stylised version of the complexities of everyday clinical practice in this challenging patient group. In particular, the co-morbidities for patients with higher operative mortality risks are likely to increase, and this is not explicitly modelled at present. For the lower mortality risk patients eligible for conventional surgery, it is not clear that the QALY approach adequately captures patient preferences for the less invasive technique compared to conventional surgery. Nevertheless, decisions do have to be made and it is clear that the potential for TAVI to bring huge patient benefits should not be ignored. The appropriate question to ask is what further research could be performed to help improve decisions regarding TAVI in the future?

The value of information analysis attempts to summarise this potential. If all uncertainties in the model could be resolved, the 'value' of this is estimated to average around £2,742 per patient in terms of the reduced cost of this uncertainty associated with making the incorrect decision (either to reject a cost-effective technology or adopt a cost-ineffective one) at a ceiling ratio of £30,000. Even with a small population size, this high per-patient value of information provides enormous scope for further research. Several immediate opportunities exist that provide the potential for relatively low cost evidence generation. Firstly, a register of TAVI procedures has been created in England from the main centres undertaking the procedure. The number of patients on the register is approaching 1,000 and there is considerable scope to update the parameters of the model (both in terms of point estimates and confidence intervals) to reflect the experience of TAVI south of the border. This would mainly offer the opportunity to resolve short term uncertainties regarding operative mortality and LOS in hospital, but may also assist in the assessment of the long term equivalence of TAVI as the registry data matures. We are currently actively pursuing the opportunity to access these data.

Secondly, results have recently been published from a relatively short term (1 year) trial of TAVI in high risk patients in the US. Results from a trial in medium risk patients in the US are due to be published in 2011. The parameters in the model could be updated to take account of this new data on intermediate outcomes.

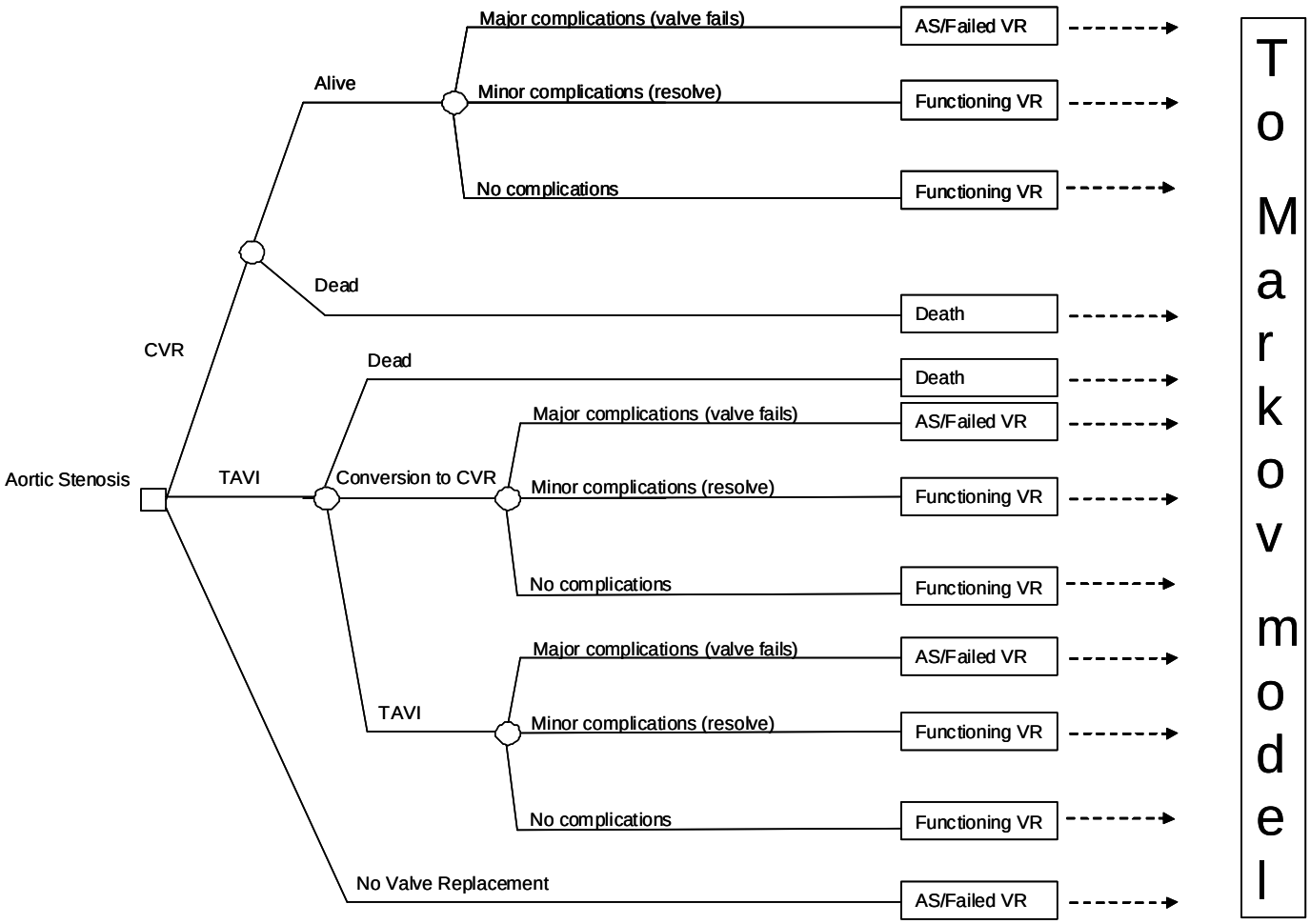
Thirdly, there is currently a proposed RCT being considered by the NIHR HTA programme to randomise 'medium' risk patients to receive either CVR or TAVI. Scottish Centres would have the opportunity to participate in this trial if TAVI was being conducted in Scotland. While there might be the temptation to 'let England do the trial' and effectively 'free-ride' on the back of the notion of information as a public good, this risks the political consequences of denying patients a treatment that may ultimately be shown to provide value for money during the period.

A potential method to provide access to TAVI for patients, while improving the evidence base, may be a Patient Access Scheme. Through the introduction of a Patient Access Scheme a risk-sharing system can be created between manufactures and the health care provider. This could, for example, mean that manufacturers only charge for the TAVI device if the procedure is successful. According to the model presented in this report this would account for approx 70% of cases. Such a scheme has the potential to reduce the cost of TAVI (while still maintaining the original reference price) thus improving its' cost effectiveness, while gathering further information.

Overall, given the potential for TAVI to be beneficial to patients, but also recognising the potential costs involved, we urge the SHTG to recommend that further evidence on TAVI is required before a robust decision can be made, but to recognise the potential role of the NHS in generating further evidence through participating in the planned HTA trial.

5. Figures & Tables

Figure 1 Short term decision tree



Note: No Valve Replacement (No AVR) represents medical management.

Figure 2 Long term Markov model

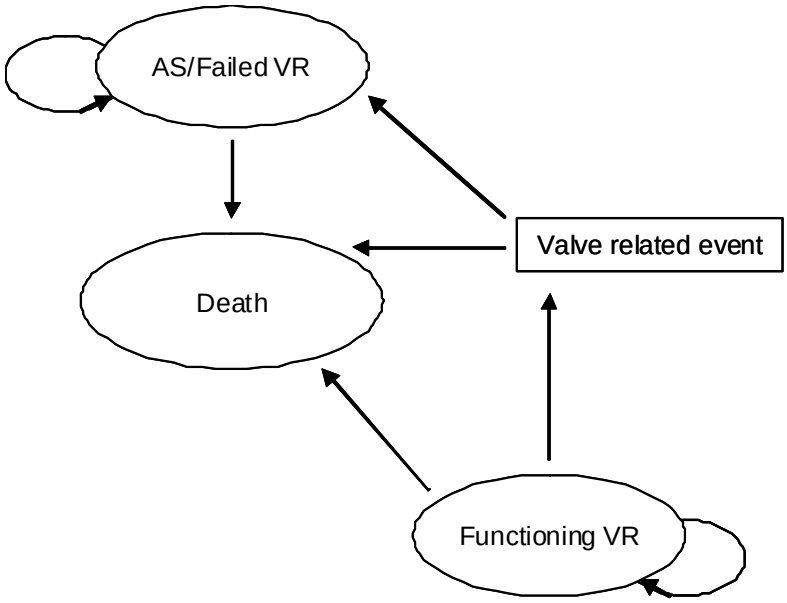


Figure 3 Incremental Cost Effectiveness Plane (low risk group): TAVI vs CVR

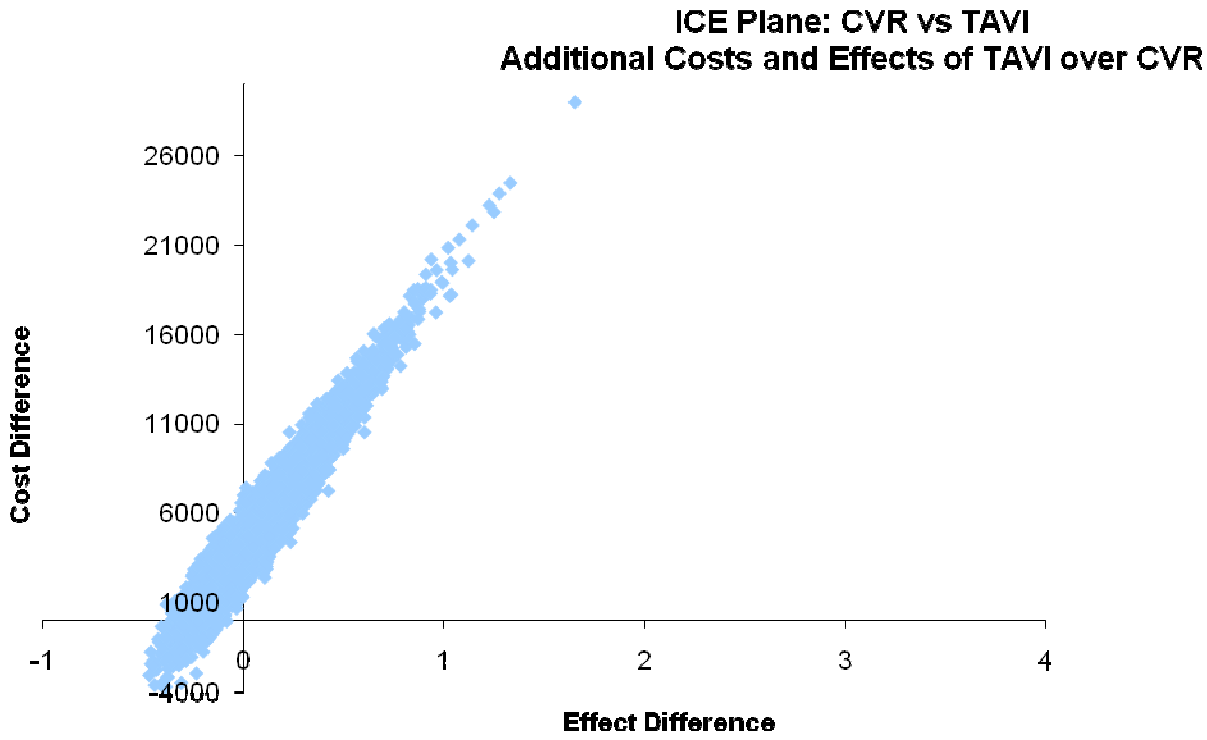


Figure 4 Cost Effectiveness Acceptability Curves (low risk group): TAVI vs CVR

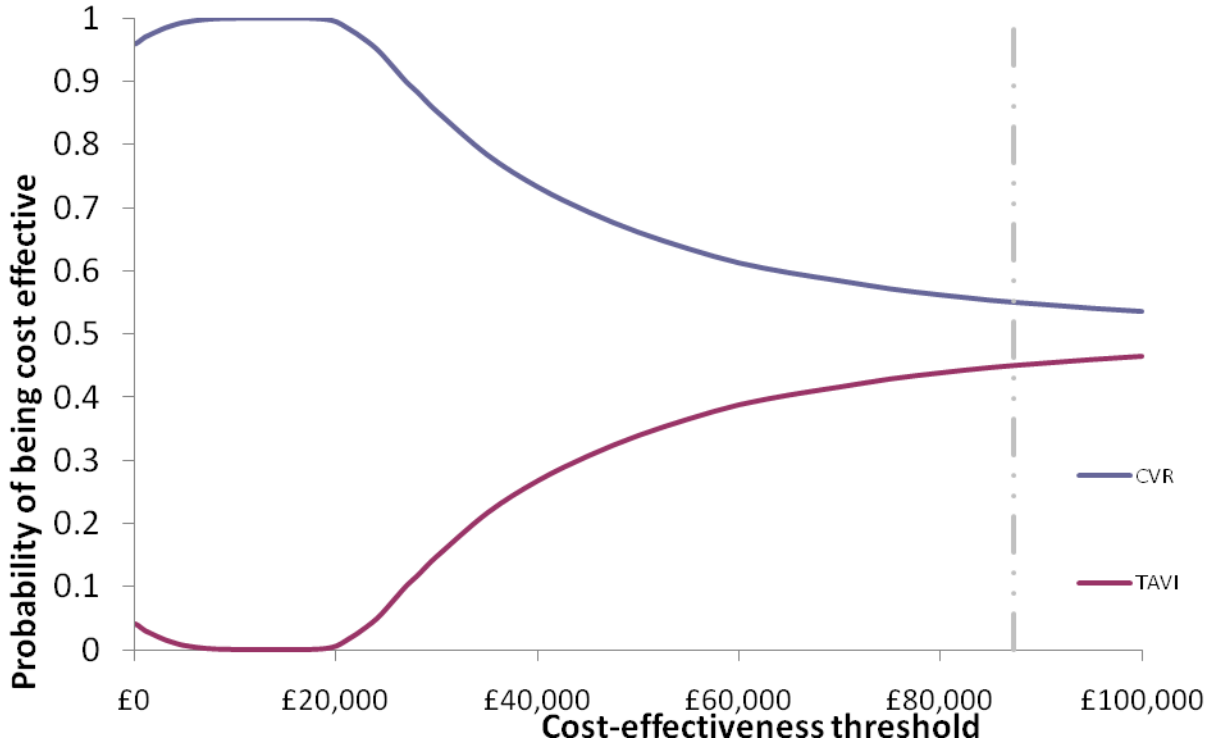


Figure 5 Incremental Cost Effectiveness Plane (medium risk group): TAVI vs CVR vs medical management

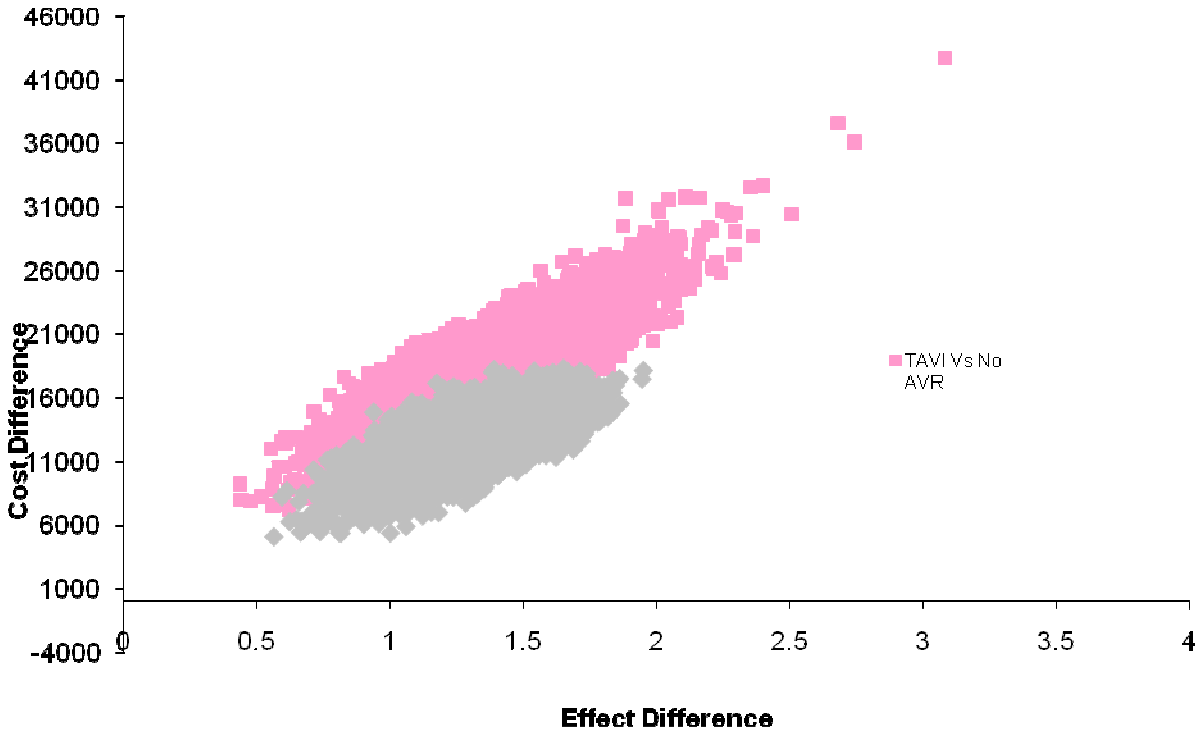


Figure 6 Incremental Cost Effectiveness Plane (medium risk group): CVR vs TAVI

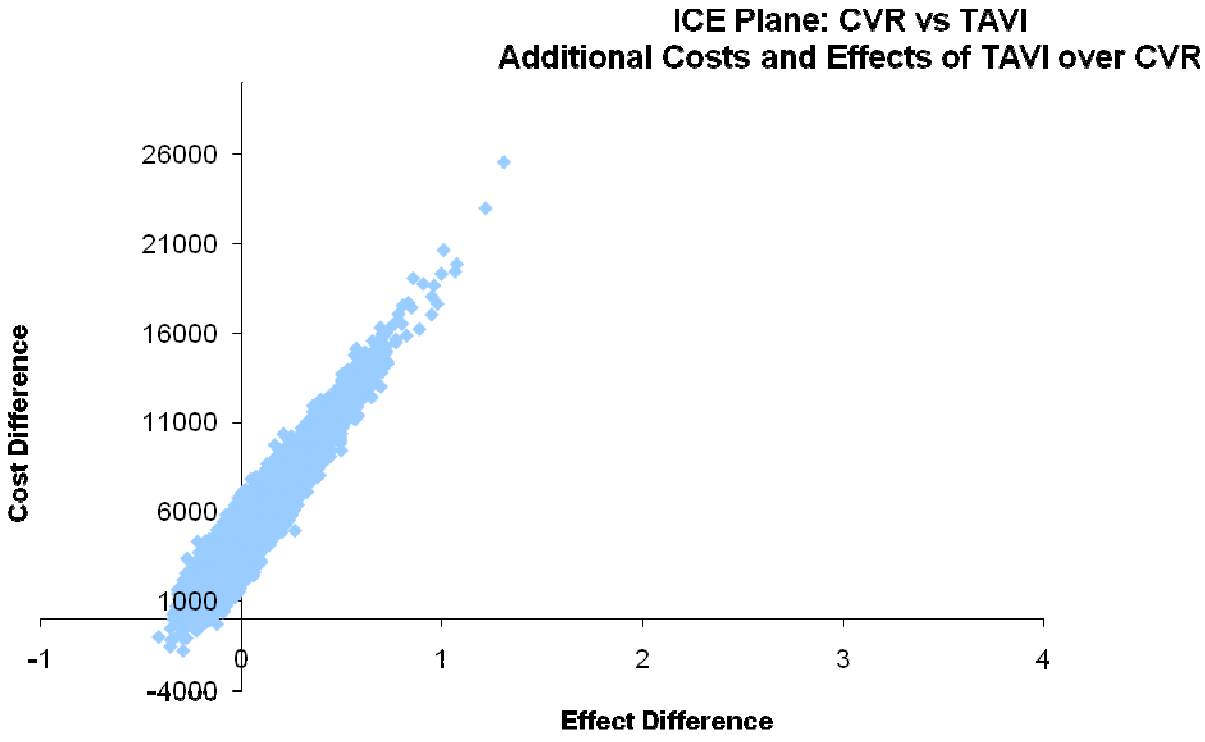


Figure 7 Cost Effectiveness Acceptability Curves (medium risk group): TAVI vs CVR vs medical management

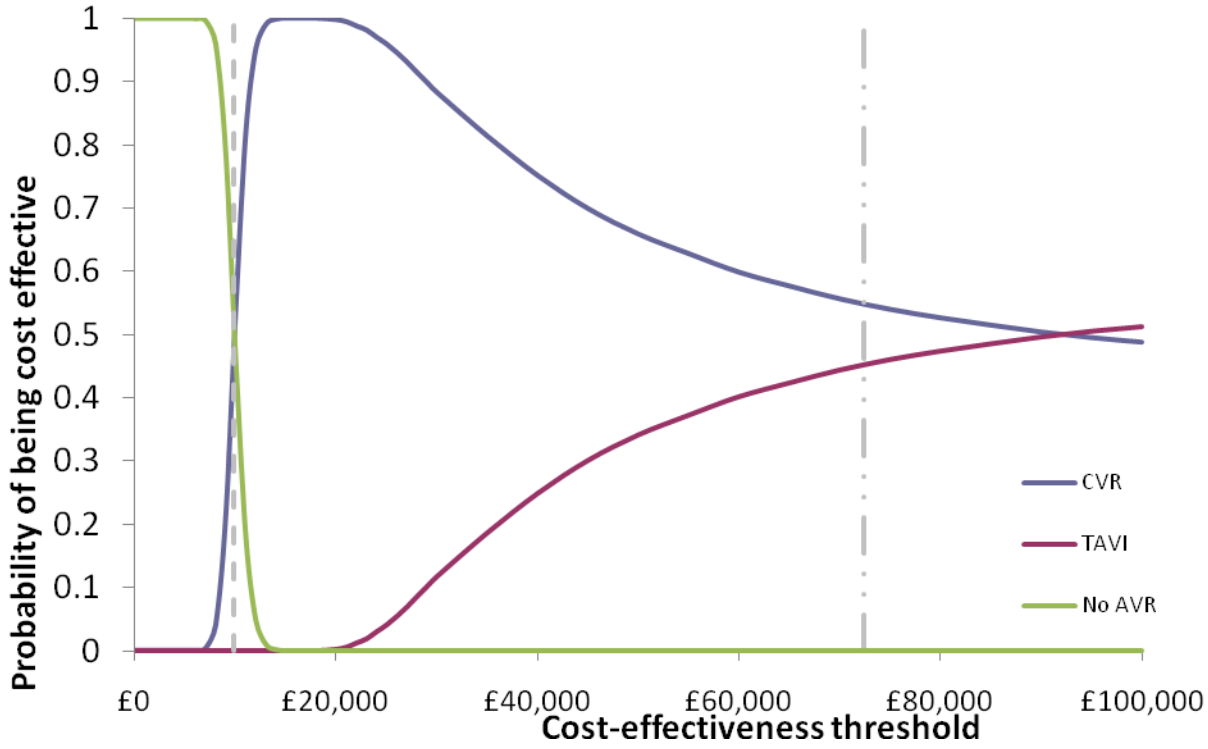


Figure 8 Incremental Cost Effectiveness Plane (high risk group): TAVI vs medical management

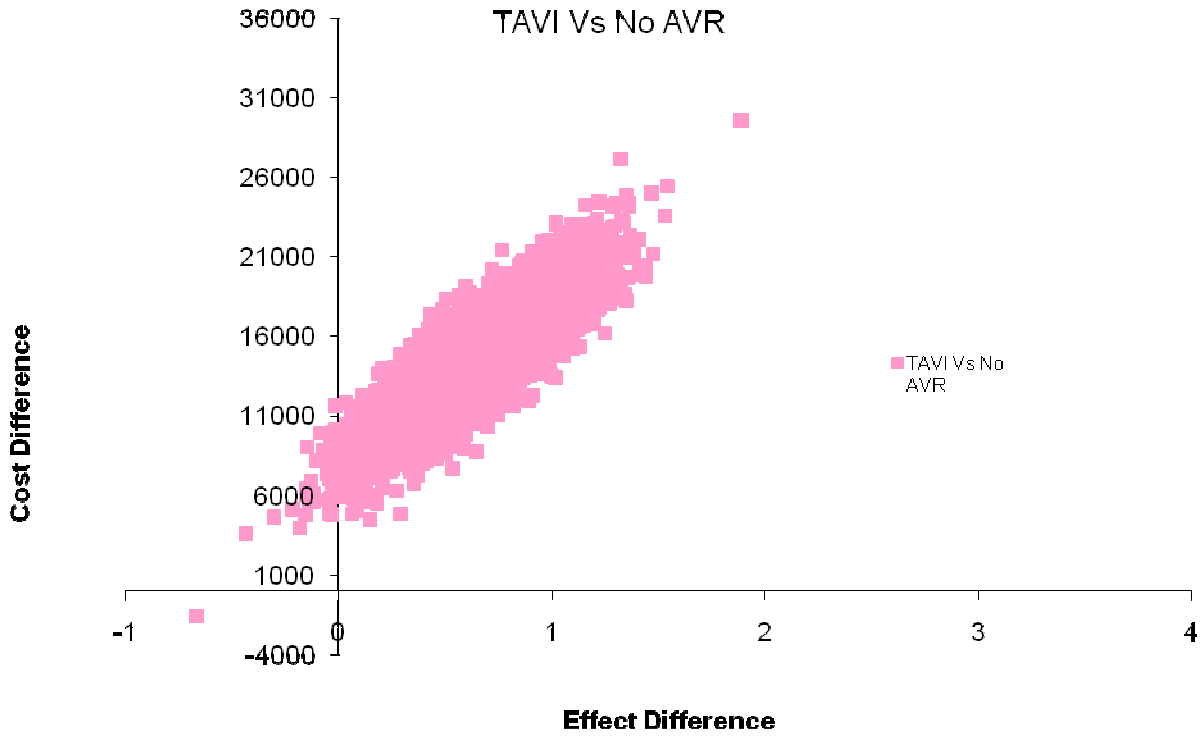


Figure 9 Cost Effectiveness Acceptability Curves (high risk group): TAVI vs medical management

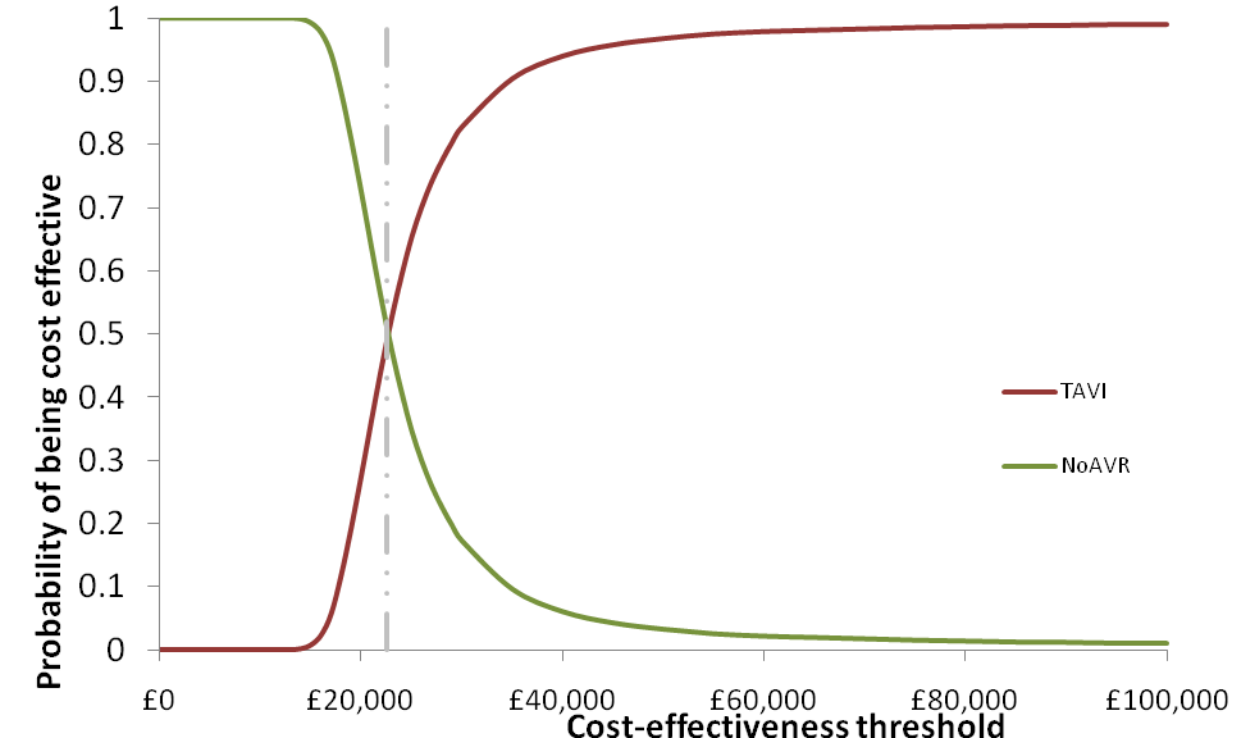
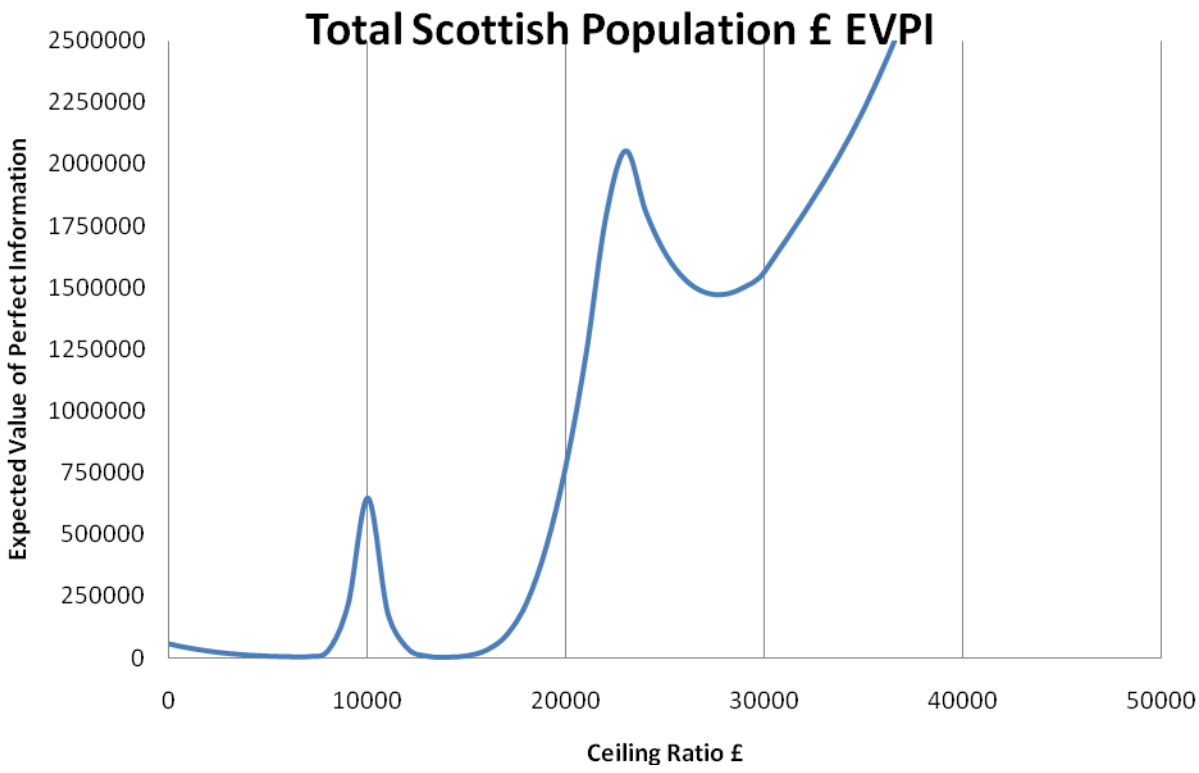


Figure 10 Expected Value of Perfect Information



NB Scale presented on the x-axis is restricted to a narrower range than previous figures in order to present the relevant range in more detail.

Table 1 Decision Tree Transition Probabilities

Description	Probability	Source
Operative mortality rates:		
Low risk	0.05	
Medium risk	0.15	+
High risk	0.20	
Major complication resulting in valve failure	0.12	* †
Minor complication following CVR	0.19	*
Minor complication following TAVI	0.26	†
Probability of converting from TAVI to CVR	0.06	†
Probability of major disabling stroke	0.03	§

+ Choice of procedure is related to risk of operative mortality, therefore this parameter forms the basis of different scenarios in the modelling. In practice, operative mortality risk will depend on clinical assessment of the patient.

* Gilbert et al. (1999); Gehlot et al. (1996); Milano et al. (1998).

† (Berry, Asgar et al. 2007); (Cribier, Eltchaninoff et al. 2004) ; (Cribier, Eltchaninoff et al. 2006) ; (Descoutures, Himbert et al. 2008) ; Eltchaninoff et al. (2007); Grube et al. (2006); Grube et al. (2007); Hanzel et al. (2005); Lichtenstein et al. (2006); Marcheix et al. (2007); Sack et al. (2005); Svensson et al. (2008) ;Walther et al. (2007); Walther et al. (2008); Webb et al. (2006); Webb et al. (2007) ; Ye et al. (2009)

§ (Caswell, O'Brien et al. 2003; Melby, Zierer et al. 2007; Alsmady, Abu-Abeeleh et al. 2009); (Chikwe, Walther et al. 2003)

*†§See Appendix A for description

Table 2 Decision Tree Early Valve Related Events & Costs

Event	Probability CVR*	Probability TAVI†	Pooled + 0.01	Weight+	Event cost§	Cost CVR	Cost TAVI
Major disabling stroke	0.03	0.03			£11,450	£343.50	£343.50
Major valve related complications							
Valve thromboembolism	0.01	0.00	**0.01**	0.08	£639	£54	£54
Major paravavular leak	0.01	0.06	**0.04**	0.33	£210	£70	£70
Endocarditis	0.00	0.00	**0.01**	0.06	£5,149	£324	£324
Cardiac tamponade	0.00	0.06	**0.03**	0.28	£630	£178	£178
Myocardial infarction	0.00	0.05	**0.03**	0.24	£1,683	£400	£400
Total	**0.02**	**0.17**	**0.12**	**1.00**		**£1,025**	**£1,025**
Minor valve-related complications			weight CVR	weight TAVI			
Access site events	0.04	0.06	0.19	0.23	£198	£38	£45
Vascular events	0.03	0.14	0.14	0.53	£198	£28	£106
Pacemaker implantation	0.13	0.06	0.66	0.24	£4,649	£3,091	£1,116
Total	0.19	**0.26**				£3,158	**£1,267**

Source based on -

* (Gilbert 1999); (Gilbert 1999); (Milano, Guglielmi et al. 1998).

†Berry et al. (2007); Cribier et al. (2004); Criber et al. (2006); Descoutures et al. (2008); (Eltchaninoff, Tron et al. 2007);(Grube, Laborde et al. 2006);(Grube, Schuler et al. 2007); (Hanzel, Harrity et al. 2005) ;(Lichtenstein, Cheung et al. 2006); (Marcheix, Lamarche et al. 2007); (Sack, Naber et al. 2005); (Svensson, Dewey et al. 2008);(Walther, Simon et al. 2007); (Walther, Falk et al. 2008); (Webb, Chandavimol et al. 2006) ; (Webb, Pasupati et al. 2007) ; (Ye, Cheung et al. 2009)

+ Weights are calculated from the absolute probabilities such that costs can be presented as conditional on the event occurring. A Bayesian technique is used such that zero probabilities of events in the data are assigned a non-zero weight to allow for a small chance of such events occurring.

§ (Kalra, Evans et al. 2005);(Kennon 2008);(NHS 2008).

Table 3 Decision Tree Branch Costs

	Resource Use		Resource Cost			
	CVR	**TAVI**	**CVR**	**TAVI**	**NoAVR**	**Source**
Device Cost/Medical Management[2]			£2,000	£12,000	£16	Kennon et al (2008)
Procedure Cost			£3,580	£2,630		Kennon et al (2008)
Intensive Care Unit - £1,690/day	2 days	0.5 days	£3,380	£845		Expert opinion;
High Dependency Unit - £570/day	2 days	1.5 days	£1,140	£855		(Yan, Cao et al. 2010); Gelhot et al
General Ward - £210/day	6 days	6 days	£1,260	£1,260		(1996); (Straumann, Kiowski et al.
Hospital Stay Total	10 days	8 days	£5,780	£2,960		1994)
Probability of Cardiac Rehab at £2,940	0.90	0.10	£2,646	£294		Kennon et al (2008)
Probability of Temporary Nursing Home (14 days) at £61/day	0.5	0.23	£427	£196		(Netten 1996)
Post Discharge Total			£3,073	£490		
Total			£14,433	£18,080	£16	

[2] The costs of the CVR and TAVI devices are only presented as approximates at this stage, due to the commercial nature of these data.

Table 4 Decision Tree – Major complication utilities

Event	Probability CVR*	Probability TAVI†	Weight+	Event Utility	CVR Utility	TAVI Utility
Major disabling stroke**	0.03	0.03		0	0	0
Major valve related complications						
Valve thromboembolism	0.01	0.01	0.08	0.04	0.00	0.00
Major paravavular leak	0.04	0.04	0.33	0.04	0.01	0.01
Endocarditis	0.01	0.01	0.06	0.01	0.00	0.00
Cardiac tamponade	0.03	0.03	0.28	0.02	0.01	0.01
Myocardial infarction	0.03	0.03	0.24	0.04	0.01	0.01
Total	**0.12**	**0.12**			**0.03**	**0.03**
Minor valve-related complications						
Access site events	0.04	0.06		0.01	0.00	0.00
Vascular events	0.03	0.14		0.01	0.00	0.01
Pacemaker implantation	0.13	0.06		0.05	0.03	0.01
Total	**0.19**	**0.26**			**0.04**	**0.02**

* Gilbert et al. (1999); Gehlot et al. (1996); Milano et al. (1998).

† (Berry, Asgar et al. 2007); Cribier et al. (2004); Criber et al. (2006); Descoutures et al. (2008); Eltchaninoff et al. (2007); Grube et al. (2006); Grube et al. (2007); Hanzel et al. (2005); Lichtenstein et al. (2006); Marcheix et al. (2007); Sack et al. (2005); Svensson et al. (2008) ;Walther et al. (2007); Walther et al. (2008); Webb et al. (2006); Webb et al. (2007) ; Ye et al. (2009)

+ Weights are calculated from the absolute probabilities such that dis-utilities can be presented as conditional on the event occurring. A Bayesian technique is used such that zero probabilities of events in the data are assigned a non-zero weight to allow for a small chance of such events occurring.

**Major disabling stroke is assumed equivalent to death, thereby incurring a utility of 0 (a disutility of 1).

Table 5 Decision Tree Branch Utilities

Event / State	Proportion	Utility	Duration	Reference
Utility by NYHA Class				
I		0.85		(Maliwa, van der Heijden et al. 2003)
II		0.71		
III		0.57		
IV		0.43		
Utility of Aortic Stenosis				
I	0.01	0.01		Revive Trials
II	0.09	0.06		
III	0.57	0.32		
IV	0.34	0.15		
Utility of Aortic Stenosis		**0.54**		
Utility of Functioning Valve Replacement				
I	0.59	0.50		Revive Trials
II	0.28	0.20		
III	0.10	0.06		
IV	0.03	0.01		
Utility of Functioning Valve Replacement		**0.77**		
Disutility following TAVI		0.0035	6 weeks	(Rao, Aziz et al. 2007)
Disutility following CVR		0.012	13 weeks	(Rao, Aziz et al. 2007)

Table 6 Probabilities for the Markov Model (1 year cycle length)

Definition	Probability[1]	Source
Probability valve related event	0.17	Table 7
Probability VRE fatal	0.22	*
Mortality from natural causes	mr	Standard life tables
Relative risk of death due to aortic stenosis (smrAS)	1.5	Assumption
Mortality from failed valve replacement and/or aortic stenosis	mr * smrAS	
Probability death from AS state	0.33	Expert Opinion – based on the assumption that without a valve replacement patients live approximately 3 years

*Gilbert et al. (1999); Milano et al. (1998); (Eichinger, Hettich et al. 2008) ; (Aupart 2006).

Table 7 Probability and Cost of Valve Related Events (CVR and TAVI)

	Unit Cost	Probability	Weighting Factor	Total Costs	Probability References	Cost References
Hospitalisations	£3,316	0.06	0.32	£1,069.64	Gilbert et al. (1999); Milano et al. (1998); Eichinger et al. (2008); Aupart et al. (2006).	Kennon et al. (2008)
Valve thromboembolism	£639	0.07	0.39	£251.01		Kennon et al. (2008)
Major paravavular leak	£210	0.02	0.09	£19.10		Kennon et al. (2008)
Endocarditis	£5,149	0.02	0.14	£700.94		((NHS) 2008)
Cardiac tamponade	£630	0.01	0.06	£36.24		((NHS) 2008)
Total		**0.17**		**£2,076.93**		

Table 8 Cost of Functioning & Failed Valve Replacement Health States

	Unit Cost	Failed VR or persisting Aortic Stenosis	Functioning Valve Replacement	Probability References	Cost References
Hospitalisations					
Annual cost of Hospitalisations		0.53*	0.07*	(Ahmed, Aronow et al. 2006)	
Cost of hospitalisation	£3,316	£1,757.48	£232.12		Kennon et al (2008)
Probability permanent nursing home care		0.50	0.1	Kennon et al (2008)	
Cost of nursing home care	£11,133	£5,566.50	£1,113.30		Netten et al (2002)
Routine Drug Therapy		£188	£188		Kennon et al (2008)
		£7,511.98	**£1,533.42**		

Table 9 Utility of Late Valve Related Events

Event	Probability	Weighting Factor	Utility Hit	Total Utility Hit	Probabilities Source	Disutilities Source
Major Late Valve Related Events						
hospitalisations	0.06	0.32	0.019	0.006	Gilbert et al. (1999); Milano et al. (1998); Eichinger et al. (2008); Aupart et al. (2006).	(Sullivan and Ghushchyan 2006)
valve thromboembolism	0.07	0.39	0.04	0.016		
major paravavular leak	0.02	0.09	0.04	0.004		
Endocarditis	0.02	0.14	0.01	0.001		
cardiac tamponade	0.01	0.06	0.02	0.001		
	0.17	1				
				0.028		

Table 10 TAVI Specific Parameters

Parameter	Base Case
Relative stroke risk	1.0
Relative risk of operative mortality with TAVI	0.9
Relative risk of major complications causing valve failure	1.0
Relative risk of valve related events causing valve failure	1.0
Relative cost of procedure	0.73
Relative cost of hospital stay	0.51
Relative cost of post-discharge care	0.16

Table 11 Annual Population Estimates

Patient Group	UK*	Scotland
		5: 70 million
Low risk patients currently getting conventional valve replacement	3,000	214
Medium risk patients currently getting either no AVR or CVR	2,250	161
High risk patients currently not getting valve replacement	2,750	196
Total	**8000**	**571**

***(SHTG 2009)**

Table 12 Cost Effectiveness Results: TAVI vs. CVR for low operative mortality risk patients*

Patient Group	CVR		TAVI		ICER
	Costs (£)	QALYs	Costs(£)	QALYs	
Males (age,yrs)					
60	31,516	3.65	36,375	3.71	£87,293
70	29,218	3.15	33,999	3.20	£98,178
80	26,185	2.50	30,886	2.54	£115,474
Females (age, yrs)					
60	32,170	3.80	37,005	3.85	£89,628
70	30,380	3.41	35,205	3.46	£92,255
80	27,388	2.76	32,117	2.80	£110,034

*Operative mortality risk assumed to be 5%

Table 13 Cost Effectiveness Results: TAVI vs. CVR vs. medical management for medium operative mortality risk patients*

Patient Group	TAVI		CVR		No AVR		ICER (£/QALY) CVR vs No AVR	ICER (£/QALY) TAVI vs CVR
	Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)	QALYs		
Males (age,yrs)								
60	34,385	3.36	28,775	3.27	13,984	1.532	£8,528	£61,978
70	32,200	2.90	26,728	2.82	13,968	1.531	£9,880	£72,412
80	29,420	2.30	24,005	2.24	13,933	1.529	£14,159	£83,666
Females (age, yrs)								
60	34,961	3.49	29,356	3.40	13,900	1.530	£8,259	£61,735
70	33,334	3.14	27,786	3.05	13,957	1.535	£9,086	£65,737
80	30,557	2.54	25,091	2.47	14,015	1.532	£11,850	£76,881

*Operative mortality risk assumed to be 15%

Table 14 Cost Effectiveness Results: TAVI vs. medical management for high operative mortality risk patients*

Patient Group	TAVI		No AVR		ICER
	Costs (£)	QALYs	Costs(£)	QALYs	
Males (age,yrs)					
60	33,369	3.18	13,958	1.530	£11,764
70	31,384	2.75	13,976	1.532	£14,277
80	28,654	2.18	13,971	1.532	£22,603
Females (age, yrs)					
60	33,893	3.31	13,921	1.528	£11,223
70	32,391	2.97	13,919	1.528	£12,799
80	29,681	2.40	13,976	1.532	£18,077

*Operative mortality risk assumed to be 20%

Appendix A

Point Estimate Calculation Description

A review of the literature revealed 18 papers reporting short term results for TAVI and five papers reporting short and longer term results for patients with CVR. The results from these studies are presented in Table A1. The results from the literature are broken into major valve related events causing valve failure within 30 days; minor valve related events within 30 days which do not result in valve failure; probability of major disabling stroke within 30 days; probability of converting to CVR during the TAVI procedure and major valve related events in the follow up period. For each event the number of cases per study is pooled across all studies and divided by the total number of patients to give the probability of that event occurring. The total number of patients is pooled across all studies presenting that event, under the assumption that unless specifically expressed with a zero where an event is not reported by a study it is not collected, rather than simply not occurring in the study.

As outlined previously (in the main body of the report) a small amount is added to the data for each event in order to adjust for those with an observed zero probability to allow for the small chance of such events occurring. These final probabilities then are reported in Tables 1, 2 and 4 in the main report.

Appendix A
Table A1 Point Estimate Calculations

	Study	n	alpha	beta	probability
Major disabling stroke	Alsmady et al (2009)				0.031
	Chikwe et al (2003)				0.034
	Meldby et al (2007)				0.03
	Caswell et al (2003)				0.03
					0.031
Probability of Converting to CVR	Criber et al 2006				
	Criber et al 2004				
	Eltchaninoff et al 2007				
	Sack et al 2005				
	Webb et al 2007	49	1	48	0.02
	Webb et al 2006				
	Descoutures et al 2008	11	1	10	0.09
	Hanzel et al				
	Lichtenstein et al 2006				
	Ye et al 2009				
	Walther et al 2007	57	2	55	0.04
	Walther et al 2008	46	3	43	0.07
	Svensson et al 2008	37	2	35	0.05
	Grube et al 2007	76	6	70	0.08
	Grube et al 2006	22	2	20	0.09
	Marcheix et al 2007				
	Berry et al 2007				
		298			**0.06**
MAJOR VALVE RELATED EVENTS - TAVI					
Valve thromboembolism					
	Criber et al 2006				
	Criber et al 2004				
	Eltchaninoff et al 2007				
	Sack et al 2005				
	Webb et al 2007				
	Webb et al 2006				
	Descoutures et al 2008				
	Hanzel et al				
	Lichtenstein et al 2006				
	Ye et al 2009	26	0	26	0.00
	Walther et al 2007				
	Walther et al 2008				
	Svensson et al 2008	37	0	37	0.00
	Grube et al 2007				
	Grube et al 2006	22	0	22	0.00
	Marcheix et al 2007				
	Berry et al 2007				
		85		**0**	**0.00**

Table A1 Continued

Study	n	alpha	beta	Probability
Major paravalvular leak				
Criber et al 2006	34	5	29	0.15
Criber et al 2004				
Eltchaninoff et al 2007	34	5	29	0.15
Sack et al 2005				
Webb et al 2007				
Webb et al 2006				
Descoutures et al 2008	11	1	10	0.09
Hanzel et al				
Lichtenstein et al 2006				
Ye et al 2009				
Walther et al 2007				
Walther et al 2008				
Svensson et al 2008	37	2	35	0.05
Grube et al 2007	76	0	76	0.00
Grube et al 2006	22	0	22	0.00
Marcheix et al 2007	10	1	9	0.10
Berry et al 2007				
	224	**14**		**0.06**
Endocarditis				
Criber et al 2006				
Criber et al 2004				
Eltchaninoff et al 2007				
Sack et al 2005				
Webb et al 2007	49	0	49	
Webb et al 2006	18	0	18	
Descoutures et al 2008				
Hanzel et al				
Lichtenstein et al 2006				
Ye et al 2009				
Walther et al 2007				
Walther et al 2008				
Svensson et al 2008				
Grube et al 2007	76	0	76	0.00
Grube et al 2006	22	0	22	0.00
Marcheix et al 2007	10	0	10	0.00
Berry et al 2007				
	175	**0**		**0.00**

Table A1 Continued

Study	n	alpha	beta	probability
Cardiac tamponade				
Criber et al 2006				
Criber et al 2004				
Eltchaninoff et al 2007				
Sack et al 2005				
Webb et al 2007	49	1	48	0.02
Webb et al 2006				
Descoutures et al 2008	11	1	10	0.09
Hanzel et al				
Lichtenstein et al 2006				
Ye et al 2009				
Walther et al 2007				
Walther et al 2008				
Svensson et al 2008				
Grube et al 2007	76	6	70	0.08
Grube et al 2006	22	1	21	0.05
Marcheix et al 2007				
Berry et al 2007				
	158	**9**		**0.06**
Myocardial infarction				
Criber et al 2006	34	0	34	0.00
Criber et al 2004				
Eltchaninoff et al 2007				
Sack et al 2005				
Webb et al 2007	49	1	48	0.02
Webb et al 2006	18	0	18	0.00
Descoutures et al 2008	11	0	11	0.00
Hanzel et al				
Lichtenstein et al 2006				
Ye et al 2009	26	1	6	0.14
Walther et al 2007	57	4	53	0.07
Walther et al 2008				
Svensson et al 2008	37	6	31	0.16
Grube et al 2007	76	1	75	0.01
Grube et al 2006	22	0	22	0.00
Marcheix et al 2007	10	0	10	0.00
Berry et al 2007				
total	**340**	**13**		**0.05**

Table A1 Continued

	Study	n	alpha	beta	probability
MAJOR VALVE RELATED EVENTS - CVR					
	Valve thromboembolism				
	Gilbert et al (1999)	82			
	Geholt et al (1996)	287			
	Milano et al (1998)	328	7	321	0.02
		328	**7**		**0.01**
	Major paravalvular leak				
	Gilbert et al (1999)				
	Geholt et al (1996)				
	Milano et al (1998)	328	2	326	0.01
		328	**2**		**0.01**
	Endocarditis				
	Gilbert et al (1999)				
	Geholt et al (1996)	287	2	285	0.01
	Milano et al (1998)	328	1	327	0.00
		615	**3**		**0.00**
	Cardiac tamponade				
	Gilbert et al (1999)	82			
	Geholt et al (1996)	287			
	Milano et al (1998)	328			
		0	**0**		**0.00**
	Myocardial infarction				
	Gilbert et al (1999)	82	0		0.00
	Geholt et al (1996)	287			
	Milano et al (1998)	328			
		82	**0**		**0.00**

Table A1 Continued

	Study	n	alpha	beta	probability
MINOR VALVE RELATED EVENTS - TAVI					
	Access site events				
	Criber et al 2006				
	Criber et al 2004				
	Eltchaninoff et al 2007				
	Sack et al 2005				
	Webb et al 2007	49	2	47	0.04
	Webb et al 2006				
	Descoutures et al 2008				
	Hanzel et al				
	Lichtenstein et al 2006				
	Ye et al 2009	26	0	26	0.00
	Walther et al 2007				
	Walther et al 2008				
	Svensson et al 2008				
	Grube et al 2007				
	Grube et al 2006				
	Marcheix et al 2007	10	3	7	0.30
	Berry et al 2007				
		85	**5**		**0.06**
	Vascular Events				
	Criber et al 2006				
	Criber et al 2004	5	1	0	0.20
	Eltchaninoff et al 2007				
	Sack et al 2005				
	Webb et al 2007	49	2	0	0.04
	Webb et al 2006	18	2	47	0.11
	Descoutures et al 2008	11	6	5	0.55
	Hanzel et al				
	Lichtenstein et al 2006				
	Ye et al 2009	26	2	0	0.08
	Walther et al 2007				
	Walther et al 2008				
	Svensson et al 2008				
	Grube et al 2007				
	Grube et al 2006	22	5	0	0.23
	Marcheix et al 2007	10	2	8	0.20
	Berry et al 2007	11	1	8	0.09
		152	**21**		**0.14**

Table A1 Continued

	Study	n	alpha	beta	probability
	Pacemaker				
	Criber et al 2006	34	0		0.00
	Criber et al 2004				
	Eltchaninoff et al 2007				
	Sack et al 2005				
	Webb et al 2007	49	1		0.02
	Webb et al 2006				
	Descoutures et al 2008				
	Hanzel et al				
	Lichtenstein et al 2006				
	Ye et al 2009				
	Walther et al 2007				
	Walther et al 2008	46	2	44	0.04
	Svensson et al 2008				
	Grube et al 2007	76	1	75	0.01
	Grube et al 2006				
	Marcheix et al 2007	10	3	7	0.30
	Berry et al 2007	11	3	8	0.27
	Yan et al 2010	1173	73	1100	0.06
		1399	**83**		**0.06**
MINOR VALVE RELATED EVENTS - CVR					
	Access site events				
	Gilbert et al (1999)				
	Geholt et al (1996)				
	Eichinger et al (2008)	431	16	415	0.04
	Aupart et al (2006)				
	Milano et al (1998)				
		431	**16**		**0.04**
	Vascular Events				
	Gilbert et al (1999)	82	4	78	0.05
	Geholt et al (1996)				
	Eichinger et al (2008)				
	Aupart et al (2006)	725	18	707	0.02
	Milano et al (1998)				
		807	**22**		**0.03**
	Pacemaker implantation				
	Gilbert et al (1999)	82	11	71	0.13
	Geholt et al (1996)	278	35	243	0.13
	Eichinger et al (2008)				
	Aupart et al (2006)				
	Milano et al (1998)				
		360	**46**		**0.13**

Table A1 Continued

	Study	n	alpha	beta	probability
LATE VALVE RELATED EVENTS					
	Hospitalisations				
	Gilbert et al (1999)	84	8	76	0.10
	Milano et al (1998)	328	23	305	0.07
	Eichinger et al (2008)	431	56	375	0.13
	Aupart et al (2006)	1101	22	1079	0.02
		1944	**109**		**0.06**
	Valve thromboembolism				
	Gilbert et al (1999)				
	Milano et al (1998)	328	18	0	0.05
	Eichinger et al (2008)	431	70	361	0.16
	Aupart et al (2006)	1101	39	1062	0.04
		1860	**127**		**0.07**
	Major paravavular leak				
	Gilbert et al (1999)				
	Milano et al (1998)	328	2	326	0.01
	Eichinger et al (2008)	431	10	421	0.02
	Aupart et al (2006)				
		759	**12**		**0.02**
	Endocarditis				
	Gilbert et al (1999)	84	1	83	0.01
	Milano et al (1998)	328	3	325	0.01
	Eichinger et al (2008)	431	18	413	0.04
	Aupart et al (2006)	1101	24	1077	0.02
		1944	**46**		**0.02**
	Cardiac tamponade				
	Gilbert et al (1999)	84			
	Milano et al (1998)	328		328	
	Eichinger et al (2008)	431		431	
	Aupart et al (2006)	1101		1101	
		0	0		0.00

Appendix B

Probabilistic Sensitivity Analysis

Table B1 Parameter Statistics and Distributions for Probabilistic Sensitivity Analysis

Description	Parameter name	*Mean*	*Std error*	*alpha*	*beta*	*n*	*distribution*
Decision Tree Transition Probabilities							
Probability of converting from TAVI to CVR	pconverting_to_CVR	0.06		17	281	298	Beta
Probability of major stroke	pmajorstroke	0.03		14	441	455	Beta
Decision Tree Early Valve Related Events - Probabilities							
Major valve related complications							
Valve thromboembolism		0.01		7	406	413	*beta*
Major paravavular leak		0.04		16	536	552	*beta*
Endocarditis		0.01		3	787	790	*beta*
Cardiac tamponade		0.03		9	149	158	*beta*
Myocardial infarction		0.03		13	409	422	*beta*
	rfailed	**0.12**					
Minor valve related complications CVR							
Access site events		0.04		16	415	431	*beta*
Vascular Events		0.03		22	785	807	*beta*
Pacemaker implantation		0.13		46	314	360	*beta*
	rminor_vre_CVR	**0.19**					
Minor valve related complications TAVI							
Access site events		0.06		5	80	85	*beta*
Vascular Events		0.14		21	131	152	*beta*
Pacemaker implantation		0.06		83	1316	1399	*beta*
	rminor_vre_TAVI	**0.26**					
Major valve related complications - COSTS							
Valve thromboembolism		639.00	100.00				*normal*
Major paravavular leak		210.00	50.00				*normal*
Endocarditis		5149.00	300.00				*normal*
Cardiac tamponade		630.00	95.00				*normal*
Myocardial infarction		1683.00	300.00				*normal*
Minor valve related complications -COSTS							
Access site events		198.00	48.00				normal
Vascular Events		198.00	48.00				normal
Pacemaker implantation		4649.00	500.00				Normal

Table B 1 continued

Description	Parameter name	*Mean*	*Std error*	*alpha*	*beta*	*n*	*distribution*
Decision Tree Early Valve Related Events -UTILTY							
Major valve related complications							
Valve thromboembolism		0.04	0.01				normal
Major paravavular leak		0.04	0.01				normal
Endocarditis		0.01	0.00				normal
Cardiac tamponade		0.02	0.01				normal
Myocardial infarction		0.04	0.01				normal
Minor valve related complications UTILITY							
Access site events		0.01	0.00				normal
Vascular Events		0.01	0.00				normal
Pacemaker implantation		0.05	0.00				normal
Decision Tree Branch Costs CVR - 30 days: Resource Use							
Device Cost/ Medical Management							
Intensive Care Unit		2.00	0.19				normal
High Dependency Unit		2.00	0.12				normal
General Ward		6.00	0.04	90.00	10.00	100.00	normal
Probability of cardiac rehab		0.90		50.00	50.00	100.00	Beta
Probability of Temporary Nursing home (14 days)		0.50					Beta
Decision Tree Branch Costs CVR - 30 days: Resource Costs							
Device Cost/ Medical Management		3380.00	300.00				normal
Intensive Care Unit		1690.00	300.00				normal
High Dependency Unit		570.00	200.00				normal
General Ward		210.00	50.00				normal
Probability of cardiac rehab		2940.00	500.00				normal
Probability of Temporary Nursing home (14 days)		854.00	50.00				normal
utility associated with having persistent aortic stenosis or a failed valve replacement	uAS						Dirichlet
utility associated with having a functioning valve replacement	uFnVR						Dirichlet

Table B1 Continued

Description	Parameter name	*Mean*	*Std error*	*alpha*	*beta*	*n*	*distribution*
Late Valve Related Events:							
Late Valve Related Events: PROBABILITIES							
Hospitalisations		0.06		109	1835	1944	beta
Valve thromboembolism		0.07		127	1733	1860	Beta
Major paravavular leak		0.02		12	747	759	Beta
Endocarditis		0.02		46	1898	1944	Beta
Cardiac tamponade		0.01		0	0	0	Beta
	platevre	0.17					
Late Valve Related Events: COSTS							
Hospitalisations		3316.00	500.00				normal
Valve thromboembolism		639.00	100.00				normal
Major paravavular leak		210.00	50.00				normal
Endocarditis		5149.00	300.00				normal
Cardiac tamponade		630.00	95.00				normal
Late Valve Related Events: UTILITIES							
Hospitalisations		0.02	0.01				normal
Valve thromboembolism		0.04	0.01				normal
Major paravavular leak		0.04	0.01				normal
Endocarditis		0.01	0.00				normal
Cardiac tamponade		0.02	0.01				Normal

Table B2 Range Surrounding Point Estimates in Probabilistic Sensitivity Analysis

	Point Estimate	*Range*	
		2.5% Percentile	*97.5% Percentile*
Decision Tree Transition Probabilities			
Major complications resulting in valve failure	0.12	0.07	0.171
Minor complication following CVR	0.12	0.093	0.341
Minor complication following TAVI	0.26	0.191	0.327
Probability of converting from TAVI to CVR	0.06	0.034	0.087
Probability of major stroke	0.03	0.016	0.048
Decision Tree Costs			
Expected Cost of major stroke	£343.50	188.514	549.252
Expected Cost of major valve related events	£1,025.44	644.545	1645.903
Expected cost of minor valve related events with CVR	2320.949	1627.252	3099.365
Expected cost of minor valve related events with TAVI	£1,266.62	901.705	1778.507
Expected Cost of TAVI procedure	£2,630.00	1980.078	3338.999
Expected cost of LOS TAVI	£2,960.00	2023.831	4098.773
Expected cost of post discharge care TAVI	£490.42	328.02	675.791
Decision Tree Utilities			
Expected utility associated with having a major valve related event resulting in valve failure	0.032	0.024	0.041
Expected utility associated with having a minor VRE following CVR			
Expected utility associated with having a minor VRE following TAVI	0.029	0.023	0.036
Expected utility associated with having persistent aortic stenosis or a failed valve replacement	0.02	0.016	0.024
Expected utility associated with having a functioning valve replacement	0.54	0.522	0.55
MARKOV MODEL Transition Probabilities			
Probability valve related event	0.17	0.145	0.183
Probability VRE fatal	0.22	0.183	0.268
Relative risk of death due to aortic stenosis (rrsmrAS)	1.5	0.954	2.245
Probability death from AS state	0.33	0.244	0.43

Table B2 Continued

	Point Estimate	*Range*	
		2.5% Percentile	*97.5% Percentile*
MARKOV MODEL COSTS			
Expected Cost of late valve related event	2076.93	1762.114	2602.174
Expected cost of failed valve replacement/persisting as including hospitalisations, drugs, permanent nursing home care	7511.98	7101.806	7918.777
Expected cost of functioning valve replacement as including hospitalisations, drugs, permanent nursing home care	1533.42	1296.639	1782.074
MARKOV MODEL UTILITIES			
Expected disutility associated with late non fatal valve related events	0.03	0.021	0.036
TAVI Specific Parameters			
Excess Stroke Risk	1	0.819	1.202
RRomTAVI	0.9	0.737	1.093
Rrmajorcomplications_TAVI	1	0.819	1.212
Rrvre_TAVI	1	0.566	1.75
relative cost of procedure	0.73	0.595	0.882
relative cost of hospital stay	0.51	0.421	0.623
relative cost of post-discharge care	0.16	0.131	0.193

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