COST EFFECTIVENESS ANALYSIS OF TRANSCATHETER AORTIC VALVE IMPLANTATION

Ms Aileen Murphy*[+]; Prof Andrew Briggs*; Dr Elisabeth Fenwick*
*University of Glasgow [+] University College Cork

Aortic Stenosis (AS) is the most common form of valvular disease present in 2-4% of the adult population over 65 years of age (2008). It is a progressive, age-dependent, build up of calcium in the aortic valve and patients presenting with it have a poor diagnosis (Van Brabandt and Neyt 2008). Owing to the aging nature of the patient group, AS is becoming more prevalent, and predominately amongst elderly patients with significant co-morbidities. Even with medical management, life expectancy is poor, with mean survival only 2-3 years. Therefore replacement of the aortic valve is required. While Conventional Valve Replacement (CVR) can restore life expectancy to that close to the usual age, sex adjusted life expectancy it is a major operation which involves open heart surgery and is therefore only appropriate for a small group of patients with AS. Thus often patients are denied surgery.

An innovation in the treatment of AS is transcatheter aortic valve implantation (TAVI). 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 potential of the TAVI procedure is that it could deliver the benefits of CVR, increase life expectancy and alleviate AS, without the need for invasive nature of the CVR procedure. Subsequently TAVI could be of benefit two groups of patients. Firstly, those who currently receive CVR and but who could benefit from the avoidance of 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 indeed equivalent to CVR in terms of outcomes is very scarce. While many thousands of patients worldwide have successfully received the TAVI device, long term follow-up is still immature. This paper outlines a model for considering the potential benefits of TAVI for the health service in Scotland. The paper presents the development of a model of TAVI compared to CVR and medical management of AS that retains the flexibility to represent the uncertainties associated with the procedure and investigates the cost effectiveness of TAVI for the different patient groups.

MODELLING METHODS

Decision analytical modelling is used to develop a model to compare TAVI to CVR and medical management of AS. Decision analysis comprises of a set of analytical tools that are complementary to traditional cost benefit analysis and cost effectiveness analysis techniques (Briggs, Claxton, Sculpher, 2006). The likelihood of each consequence is presented as a probability, calculated from the inputs. As each consequence has a cost and output it is possible to calculate the expected cost and outcome of each option under evaluation. The purpose of such modelling is to allow for the variability and uncertainty associated with all decisions, (Briggs *et al*, 2006). This is important where uncertainty surrounding the parameters and decisions exist for a new technology such as TAVI where evidence is sparse.

Model Design

The model developed here is split into two time periods and employs separate models for each time period. The first considers the initial phase of treatment for a patient with AS, who could be managed medically, could receive a CVR or a TAVI procedure. This initial phase is considered to take the patient up to the point at which they have recovered from any procedure received and the outcome of any procedure (success or failure) is known. The second phase is then the longer term projection of costs and life-expectancy following the initial phase.

Short term modelling of the valve replacement procedures

The initial phase, the first 30 days or in hospital period, is modelled using a decision tree and is presented in Figure 1. Here three treatment options available for those suffering from aortic stenosis are represented; these are CVR, TAVI, and no valve replacement (medical management). Following valve replacement patients are at risk of operative mortality. For those who survive, the procedure may result in complications. In accounting for complications the model distinguishes between minor complications, which are assumed to resolve with appropriate medical care, and major complications which are assumed to result in failure of the valve implantation. Failure of the valve results in a state no better than their original manifestation of AS for the patient. For patients with minor or no complications, the procedure is assumed to be successful and they enjoy the benefits of successful valve replacement. Major disabling stroke is too included in the model, as an important health outcome it is considered equivalent to death in the model. This method avoids the need to model stroke outcomes in a complex fashion and retains the flexibility of the model while still considering stroke in the model.

Table 1 presents the transition probabilities which are employed in the decision tree model. As presented the operative mortality rates following valve replacement and the probability of having a major complication resulting in valve failure are assumed to be the same for CVR and TAVI. Major complications which result in valve failure include valve thromboembolism; major paravavular leak; endocarditis; cardiac tamponade and myocardial infarction. These estimates are calculated by averaging the absolute probabilities obtained from the literature[1] across CVR and TAVI giving the same probability of major complication in the base case. A simple weight is constructed from these probabilities so that the cost conditional on having an event can be computed. These 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. A similar approach is adopted for minor complications, although the base case assumption is that these vary between CVR and TAVI. Here the absolute probabilities obtained from the literature[1] relating to experiences for CVR and TAVI respectively were combined. Minor complications include access site events; vascular events and pacemaker implantation.

Those patients receiving TAVI follow the same pathway as those receiving CVR except for the fact that it is assumed that for some patients there is a risk that the TAVI procedure does not go to plan and that during the procedure the decision is made to convert to CVR. If this occurs then the outcomes are assumed to be equivalent to CVR. Finally, patients receiving no valve replacement are assumed to receive appropriate medical management for their condition.

[1] (Alsmady, et al. 2009); (Gilbert, Orr et al. 1999); (Gehlot, Mullany et al. 1996); (Milano, Guglielmi et al. 1998); (Eichinger et al 2008); (Aupart et al 2006); (Banbury et al 1998). † (Alsmady, et al. 2009); (Berry, Asgar et al. 2007); (Cribier, Eltchaninoff et al. 2004); (Webb, Pasupati et al. 2007); (Eltchaninoff, Tron et al. 2007); (Grube, Laborde et al. 2006); (Grube, Schuler et al. 2007); (Hanzel, Harrity et al.); (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).

With respect to disabling stroke, the base case scenario is where the risk of disabling stroke is the same across valve replacement procedures. To account for potential differences between TAVI and CVR a relative risk parameter for disabling stroke is included.

Table 2 presents in detail the complications associated with valve replacement for both procedures. Here also the probabilities of these complications and the associated costs of those events are presented.

In Table 3 then the costs of each branch on the decision tree are specified. These include the device cost, procedure cost and length of stay. With respect to the device cost, these are only approximately presented owing to the commercial nature of these data. The effect of varying this on cost to NHS Scotland of these devices is explored through the sensitivity anlaysis. Examining the procedural costs it is evident that there is a slight advantage towards TAVI. However it is in the length of stay where the cost advantages of TAVI are realised. As presented in Table 3, it is assumed that the length of stay for TAVI patients is significantly less than that for CVR. These savings are predominately in the more costly departments such as intensive care and high dependency units. The length of stay on the general ward however is similar between the two devices. Table 3 also presents the data on follow up care post hospital discharge. Here it is assumed the probability of needing cardiac rehabilitation and/or temporary nursing home care will b highest amongst patients receiving CVRs.

The impacts on utility from the valve related complications are presented in Table 4. As mentioned previously it is assumed that major disabling stroke is equivalent to death so is assigned a utility of 0. Applying the weights estimated in Table 2 for major and minor complications the utility toll for major and minor complications for CVR and TAVI is estimated. The utilities associated with having persistent AS or failed valve replacement and functioning valve replacement are estimated in Table 5 along with the utilities associated with the procedures. The former were estimated using the utility estimate per New York Heart Association (NYHA) class as per Maliwa et al (2003) and the proportion per class with functioning and failed valve replacement using data from the Revive Trials. These utility estimates are then applied to calculate the utility of being in each of the states: functioning valve replacement and failed valve replacement and/or persistent AS. The assigned utility tolls for the two procedures, CVR and TAVI, were 0.012 QALYS for 13 weeks and 0.0035 QALYS for 6 weeks respectively.

Long term modelling of the valve replacement procedures

The second part of the model is represented using a Markov state transition model as represented in Figure 2. As per Figure 2, there are three states in the Markov model: functioning valve replacement; AS / failed valve replacement; or death. The outcome of the decision tree determines which of the three states the patient enters for the Markov Model and thus where the start the long term element of the model. Each cycle in the Markov model is 12 months long and the model is run until all patients have died. So for patients who enter into the Markov model in the successful valve replacement state they are at risk of a valve related event that could be fatal, or if non fatal, results in loss of the functioning of the valve meaning that they move to the 'failed valve replacement' state. Patients who enter the Markov model in the 'failed valve replacement' state remain here until they die.

Similar to the first phase the Markov model requires transition probabilities to direct the movement of patients between the states in each annual cycle. Table 5 presents the transition probability parameters which are utilised in the Markov model. As outlined above patients in the 'functioning valve replacement' state can have a valve related event (VRE) which maybe fatal or non fatal. There the probability of having a VRE is assumed to be 0.15 per annual cycle. Further more conditional on having a VRE it is expected that 52% of those events are fatal with the remaining 48% resulting in valve failure which moves the patient to the 'failed valve replacement' state. This is equivalent to valve failure and returning the patient to the original AS state. These probabilities were estimated by averaging the absolute probabilities obtained from the literature on valve replacement. VREs include valve thromboembolism; major paravavular leak; endocarditis and cardiac tamponade.

In addition to risk of VRE patients in the 'functioning valve replacement' state can die from natural causes. A natural mortality rate is estimated which follows the background age/sex mortality rates. To account for the fact that these patients have undergone valve replacements, so are likely to be at a higher risk of death than an average patient with the same age/sex background, a standardised mortality ratio of 1.5 is included for adjustment. For patients in the 'failed valve replacement' state the life expectancy is assumed to be only three years which equates to three cycles of the model. This yields a transition probability of 0.33 for probability of death from the 'failed valve replacement' state. Using the probabilities presented in Table 6, Table 7 presents the probabilities and costs of these VREs which result in failed valve replacement. Similar to the short term model the weighting factor is used to calculate the expected cost of a VRE conditional on the VRE occurring.

Table 8 presents the annual costs associated with being in each of the states in the Markov model. This includes the cost of hospitalisations, medication and permanent nursing home care. The costs of hospitalisations are calculated using estimates of the annual number of hospitalisations per NYHA class. Again using the Revive Trial data the proportion of patients in each NYHA class could be estimated to calculate this. A probability of requiring permanent nursing home care was assigned for those with a functioning valve and a failed valve given the patient characteristics (i.e. elderly with high risk of co-morbidities).

Finally Table 9 presents the utility scores associated with the VREs. These are estimated using a similar method to that used in estimating the utilities associated with complications in the short term model, where weights are applied. The utility scores for each state; 'functioning valve replacement' and 'failed valve replacement' state, are identical to those calculated in Table 5 for the short term model. Failed valve replacement is assumed to be equivalent to valve failure and returns the patient to the original AS state.

TAVI specific parameters

As outlined previously there is considerable uncertainty relating to the relative effectiveness of TAVI compared to CVR. While many thousands of patients worldwide (Vahanian, Alfieri et al. 2008) have successfully received the TAVI device, long term follow-up is still immature. So while the base case assumption throughout the model is that TAVI is comparable to CVR, flexibility is built into the model to allow for representation of differential outcomes for TAVI. Table 10 lists these TAVI specific parameters which afford such flexibility to the model.

Ratio parameters, initially set to unity, are used to present the relative impact of TAVI in terms of outcomes. Throughout the analysis of uncertainty this is varied to non-unity values in either direction to present alternative outcomes of TAVI when compared to CVR. 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.

ANALYSIS

In analysing the model three patients groups are considered. 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. The following sections presents the results across age-sex groups but the base case for the Low Risk group is assumed to be 60 year old males with an operative mortality of 5%. For medium risk patients the treatment choice is between the three technologies; they can receive CVR, TAVI and no

AVR. Here the base case is assumed to be 70 year old males with operative mortality of 15%. Finally high risk patients are those who are ineligible for conventional surgery so traditionally get medical management, so the choice is between TAVI and no AVR. Here the base case is 80 year old males with an operative mortality of 20%.

An initial cohort of 1,000 patients passes through each arm of the model, for each patient group. Throughout their journey through the model they accumulate costs and QALYs according to which path they take. The costs and QALYs are discounted accordingly at 4%. After twenty years all the patients have died at which time an average cost and QALY per patient can be calculated separately for each treatment option, for each age and sex group.

As the data used to populate the model is based on sample information and expert opinion there is significant uncertainty surrounding the parameters, especially those relating to TAVI for which long-term data is not available. Thus it was appropriate to apply probabilistic distributions to the parameters, for which there was uncertainty. Applying distributions to the parameters permits the realisation of the uncertainty distributions and these can be used to propagate the uncertainty surrounding the parameters throughout the model in order to obtain a distribution across the output parameters also. The expectation over the output parameters can then be used to represent an estimate for the decision model which incorporates uncertainty (Briggs et al 2006).

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 parameters as the confidence limits for these parameters are calculated on the log scale as the relative risks are made up of ratios. These were the 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 transition probabilities in the short term decision tree component of the model and probabilities of valve related events in the longer term Markov Model and risk of death from TAVI in the same. In addition Beta distributions were applied to the probability of hospitalisations and permanent nursing home care with a functioning and failed valve replacement. Here the Beta distribution was considered more appropriate than the normal distribution as probability parameters are constrained to having values between zero and one and a normal distribution may sample values less than zero or greater than one which are impossible values for probability parameters. Finally a Dirichlet distribution was applied to estimate the uncertainty surround the proportion of patients in each NYHA class to estimate the utility associated with having aortic stenosis, a failed valve replacement resulting in persistent aortic stenosis and functioning valve replacement. Following the application of probabilistic distributions to the parameters a Monte Carlo simulation is applied to propagate the uncertainty throughout the model. The uncertainty is then reflected in the in the distribution of the average overall costs and QALYs per patient.

The cost effectiveness analysis then involves two stages. The first stage focuses on the mean of the distributions. Whereby, the differential mean cost and QALYs between TAVI vs CVR; CVR vs No AVR and TAVI vs No AVR for each patient group is calculated. The mean cost and QALY estimates are examined for dominance, i.e. to see if one treatment offers higher mean QALYs at a lower mean cost. If neither treatment dominates the incremental cost effectiveness ratio of the more costly and more effective treatment is calculated. The incremental cost effectiveness ratio (ICER) is the ratio of mean differential costs to the differential mean QALYs. This computed ICER is comparable to decision maker's willingness to pay for additional health benefit e.g. QALYs across various areas in health care. The willingness to pay is indicated by the ceiling ratio.

The second stage of the cost effectiveness analysis manages the uncertainty around the mean costs and QALYs of the treatments. Cost-effectiveness acceptability curves are employed for each of the patient groups using the base case (Briggs et al (1999); Fenwick et al (2001); Van Hout et al (1994)). Cost-effectiveness acceptability curves illustrate the probability that one treatment is the more cost effective given a range of willingness-to-pay values which decision makers may value additional QALYs at (Briggs et al (2004).

RESULTS

The results are presented by patient group (low, medium and high risk) across age-sex groups and the base case scenario is discussed in further details. Following this the value of further research for the population as a whole is considered (i.e. all patient groups). The population size for each of the patient groups in the UK as a whole and for Scotland (assuming proportionality) presented in Table 11.

Low risk patients – TAVI vs CVR

The results for low risk patients across the age/sex groups are presented in Table 12. Here it is evident that TAVI is both more costly and more effective than CVR across all age/sex sub-groups. The base case presented for the low risk group refers to a 60 year old male with an operative mortality of 5%. The results indicate that the benefit for TAVI is slight, and is chiefly driven by a reduction in the operative mortality rate.

The estimated ICER for the base case is £117,377 per QALY gained. This result is well above the level usually considered cost-effective in the United Kingdom of £20,000-£30,000 per QALY. It is however important to recognise the high degree of uncertainty that is associated with this result – indeed a 95% uncertainty interval cannot be defined. To analyse this uncertainty cost effectiveness acceptability curves (CEAC) which plot the probability of CVR and TAVI being cost effective at different values for the ceiling ratio are used. The CEAC for base case low-risk patients (60 year old males) between CVR and TAVI for the base case is illustrated in Figure 3. This CEAC illustrates that as the ceiling ratio increases the probability of CVR being cost effective decreases and the probability of TAVI being cost effective increases. While TAVI is not cost-effective at any point over the range shown on Figure 3, the CEAC does show that there is considerable uncertainty surrounding the cost-effectiveness of TAVI and CVR. This is illustrated by considering at a ceiling ratio of £30,000 per QALY the probability that CVR is cost-effective is 98% while the probability that TAVI is cost-effective is 2%.

It is important to note that small changes in the base case assumptions of the modelling could drastically change the interpretation of these results. For example, reducing the cost of the TAVI device by approximately £3,500 would make TAVI cost neutral, but with a slight health advantage due to the lower operative mortality. Similarly, greater reductions in operative mortality than the 10% assumed here, would give a much greater potential health gain, which would drastically reduce the ICER also.

Medium risk patients: TAVI vs CVR vs NO AVR

Medium risk patients are those who could receive any of the three treatment options. For the analysis of results for the medium risk patients the ICERs for CVR vs No AVR and TAVI vs CVR are considered. The mean costs and QALYs and ICERs for each age/sex group are presented in Table 13. These results demonstrate that TAVI is both more costly and more effective than CVR which is in turn more costly and more effective than No AVR across all age/sex sub-groups.

The base case presented for the medium risk group is 70 year old males with operative mortality of 15%. As presented in Table 13, the ICER for CVR vs no AVR for the base case is estimated as per £7,163 QALY gained. This estimated is well within the level usually considered cost-effective in the United Kingdom of £20,000 to £30, 000 per QALY. However, the ICER associated with TAVI compared to CVR for the base case is estimated as £69,988. This estimate is well above the usually accepted level of £20,000- £30,000 per QALY. As with the low risk group it is important to interpret this point estimate in the context of the large degree of uncertainty which is associated with the cost-effectiveness estimates such that a 95% interval for TAVI is not defined.

As with the low risk groups a CEAC is constructed to analyse uncertainty, this is presented in Figure 4, illustrating the cost effectiveness acceptability curve for CVR vs TAVI vs No AVR (base case – 70 year old males). Here as the ceiling ratio increases initially the probability of CVR being cost effective increases and the probability of no AVR being cost effective decreases while the probability that TAVI is cost-effective is 0. The dotted line illustrates the value of the ICER associated with CVR vs no AVR; this is the point beyond which CVR is cost-effective.

As the ceiling ratio continues to increase the probability of CVR being cost-effective decreases and the probability of TAVI being cost-effective increases while the probability that no AVR is cost-effective falls to 0. The second dotted line illustrates the value of the ICER associated with TAVI vs CVR, this is the point beyond which TAVI is considered cost-effective. The CEAC illustrates that depending on the value of the ceiling ratio there is a reasonable level of uncertainty surrounding the cost-effectiveness of TAVI, CVR and No AVR. For example at a ceiling ratio of £30,000 per QALY the probability that no AVR is cost-effective is 0%, while the probability that CVR is cost-effective is 96% and the probability that TAVI is cost-effective is 5%.

Again, in this medium risk patient group, it is clear that small changes to the base case assumptions of the model could alter the conclusions. Sensitivity analysis suggests a reduction of just over £4,000 (or 1/3 of the assumed price) 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.

High risk patients: TAVI vs No AVR

Finally for the high risk patient group where the cost effectiveness of TAVI vs No AVR is consider the results are presented in Table 14. These results demonstrate that TAVI is both more costly and more effective than no AVR across all age/sex sub-groups. The base case presented for the high risk group is a 80 year old male with an operative mortality of 20%. For this base case the ICER is estimated as £17,960 per QALY gained. This estimate is well within the level usually considered cost-effective in the United Kingdom of £20,000 to £30,000 per QALY.

As with the previous risk groups a CEAC is used to analyse the uncertainty surrounding the cost effectiveness of TAVI vs No AVR. The CEACs for TAVI vs no AVR for the base case (80 year old males) is presented in Figure 5. Here as the ceiling ratio increases the probability of TAVI being cost effective increases and the probability of no AVR being cost effective decreases. The dotted line illustrates the value of the ICER associated with TAVI vs no AVR, beyond this is the point TAVI is considered cost-effective. The CEAC illustrates that there is still some uncertainty surrounding the cost-effectiveness of TAVI and no AVR as illustrated by examining the scenario of a ceiling ratio of £30,000 per QALY. Here the probability that TAVI is cost-effective is 95%, while the probability that no AVR is cost-effective is 5%.

Compared to the other risk group scenarios considered above the potential for cost-effectiveness is clearer in this high-risk group due to the poor prognosis of patients which makes them ineligible for surgical valve replacement. However, with few costs to offset, the additional cost of TAVI in this patient group would be higher than that in the other groups.

Value of further research

As discussed in the introduction, TAVI is a relatively new technology for which little long term evidence exists. With further evidence generation the uncertainties in the model could be reduced. This is considered through an examination of the value of undertaking further research. This is estimated by determining the value of eliminating all the uncertainties within the model, i.e. estimating the expected value of perfect information (EVPI).

In order to generate a Scottish specific value for further information over the lifetime of the technologies the annual Scottish population data for each risk subgroup is summed for a period of 10 years and discounted at 3.5%. A 10 year period was choose as this is the period over which a choice between TAVI, CVR and no AVR is considered a viable decision as advances in technology would not make the decision obsolete or invalid. The patient population for Scotland was estimated from UK figures assuming proportionality (SHTG, 2009). The EVPI across the risk groups is presented in Figure 6 for the Scottish population. This is estimate for the EVPI provides a maximum value for the return on further research and requires the assumption of information independence across the sub-groups. The results, presented in Figure 6, show that for the Scottish population the overall value of the EVPI is in the order of £0.2-£0.8 million for the range of ceiling ratios usually considered to be cost-effective in the United Kingdom of £20,000 to £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.

These EVPI calculations can be used to analyse the value of further research in improving decision making with respect to the provision of TAVI in the future. EVPI estimates that on average at £20,000 ceiling threshold, resolving all the uncertainties in the model has a 'value' of around £1,400 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).

CONCLUSIONS & RECOMMENDATIONS

The results of this study indicate that the cost-effectiveness of TAVI is borderline for low and medium risk patients and subject to large uncertainties. Two key short term uncertainties to understanding the potential for TAVI in providing a cost-effective treatment for the NHS of aortic stenosis exist. Firstly, the extent to which the high acquisition cost of the TAVI device can be offset by the reduction in hospital length of stay, particularly in costly high dependency units. Secondly, the potential for TAVI to reduce the operative mortality rate amongst aortic stenosis patients. It has been suggested that TAVI could reduce the operative mortality up to 50%. While a more conservative 10% reduction was chosen in this study, a more optimistic view point could result in the TAVI point estimates for these groups being around the £30,000 per QALY mark.

The cost-effectiveness of TAVI in the high risk patients who are ineligible for surgery appears more positive. This is largely due to the poor prognosis for aortic stenosis patients who do not receive CVR. This means 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, which may prove a practical challenge in current resource constrained environments.

A number of limitations to the modelling used in this study do exist. The model is 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, which is not explicitly modelled here. For the lower mortality risk patients who are eligible for conventional surgery, it is ambiguous if the QALY approach adequately captures patient preferences for the less invasive technique (TAVI) compared to conventional surgery. However, 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 question to ask then is what further research could be performed to help improve decisions regarding TAVI in the future?

The value of information analysis estimates the value of resolving all uncertainties to average around £1,400 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 £20,000. Even with a small population size, like that in Scotland, this high per-patient value of information provides enormous scope for further research. Thus given the potential for TAVI to be beneficial to patients, while appreciating the potential costs involved, the results of this study indicate that further evidence on TAVI is required before a robust decision can be made by decision makers about the provision of TAVI.

Figure 1 Short Term Model - The Decision Tree

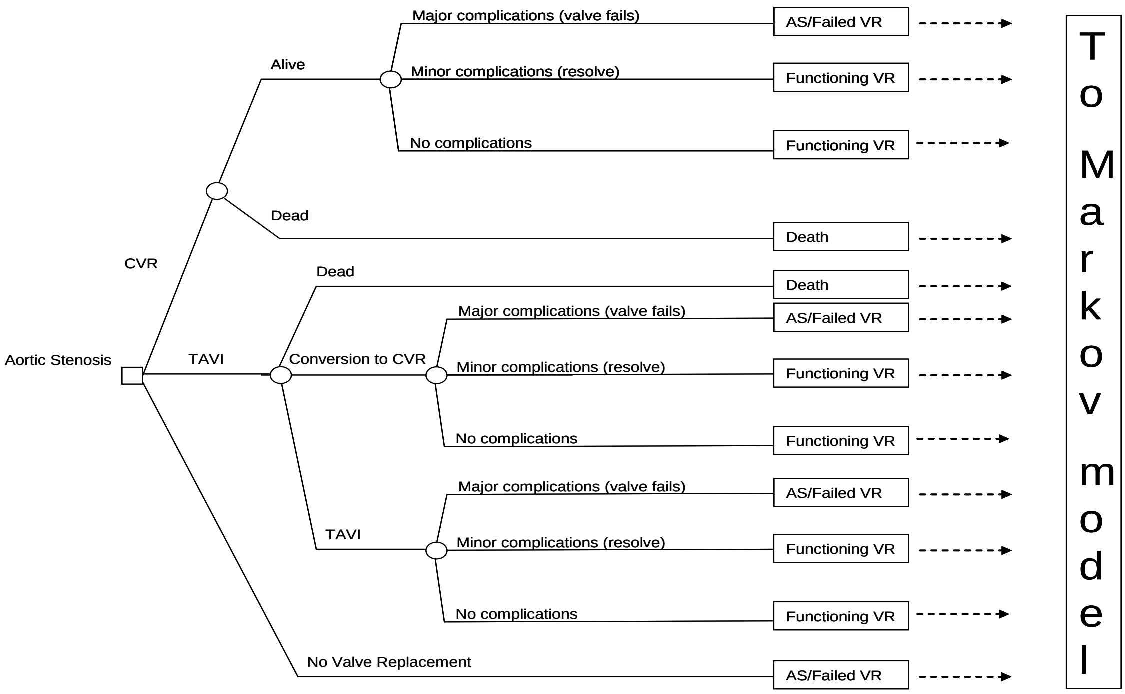

Figure 2 The Long Term Model

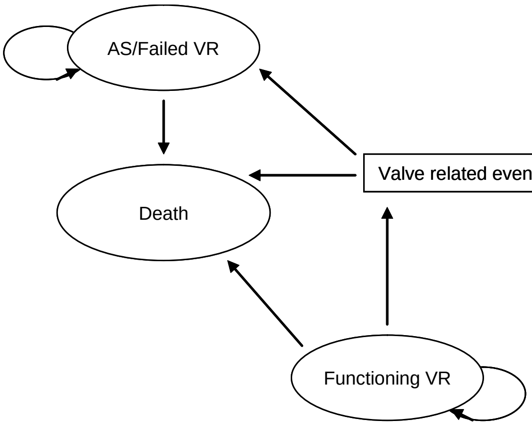

Figure 3 Cost Effectiveness Acceptability Curves: TAVI vs CVR

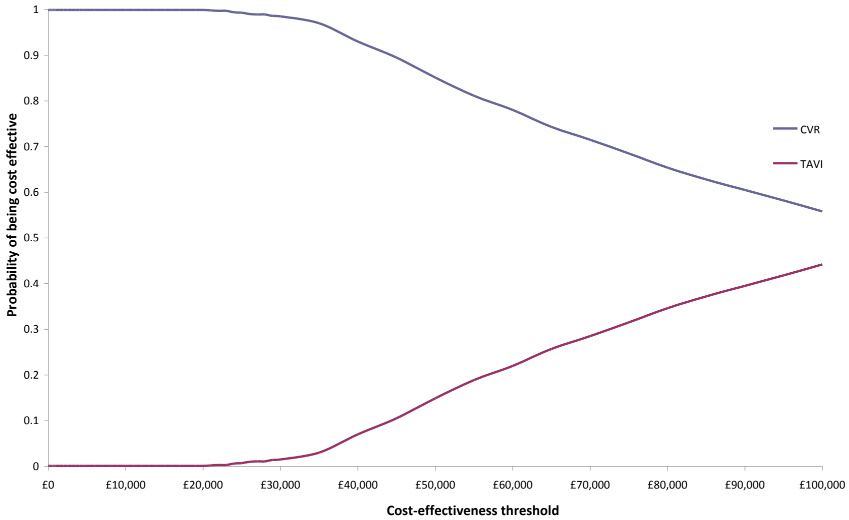

Figure 4 Cost Effectiveness Acceptability Curves: CVR vs TAVI vs No AVR

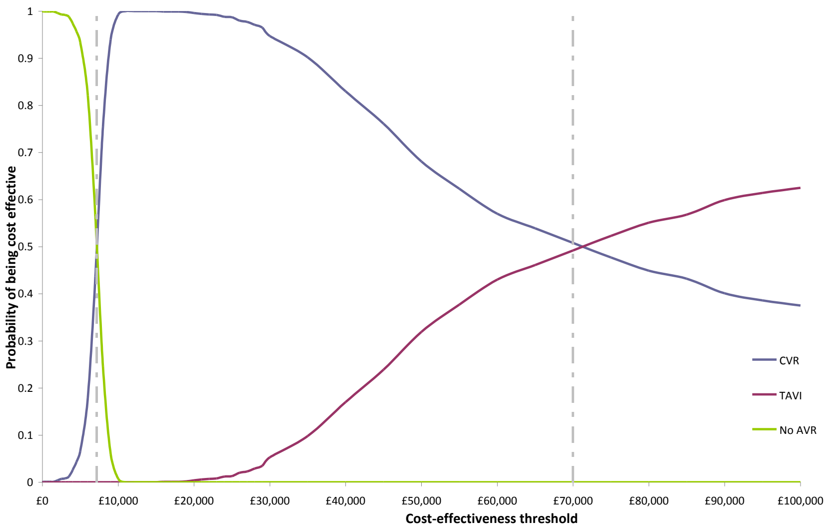

Figure 5 Cost Effectiveness Acceptability Curves: TAVI vs No AVR

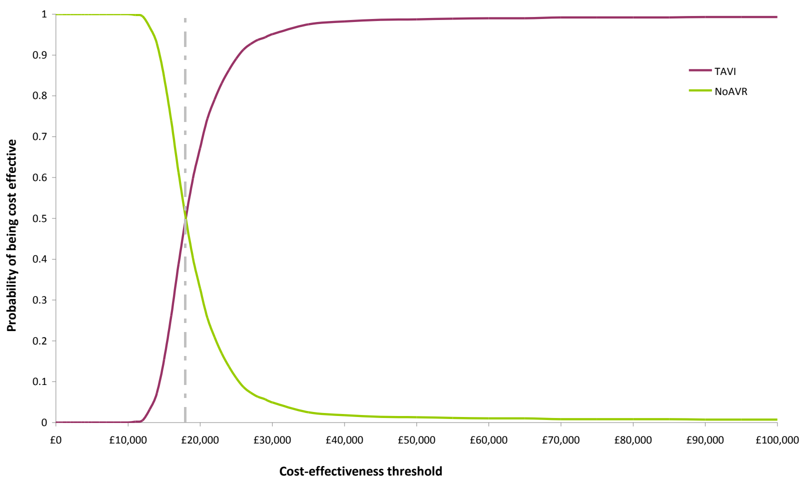

Figure 6 Expected Value of Perfect Information

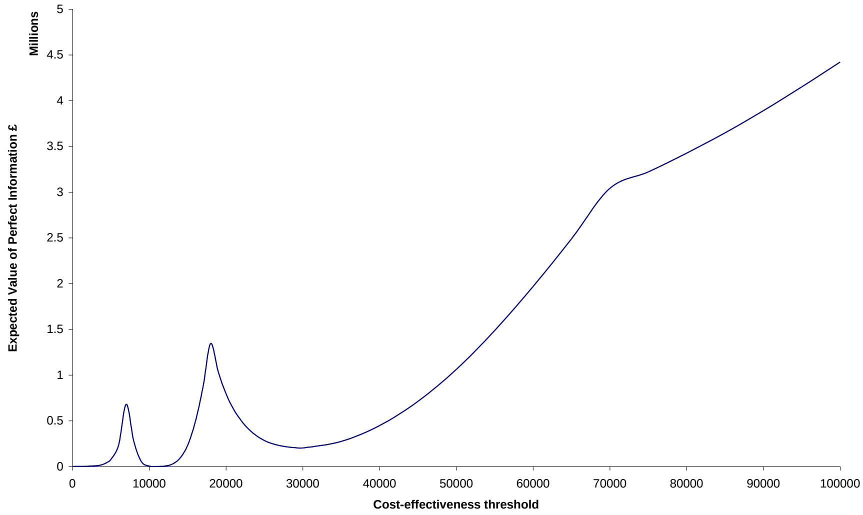

Table 1 Decision Tree Transition Probabilities

Description	Probability	Source
Operative mortality rates:		
Low risk	0.05	
Medium risk	0.15	+
High risk	0.20	
Major complication resulting in valve failure	0.06	* †
Minor complication following CVR	0.10	*
Minor complication following TAVI	0.15	†
Probability of converting from TAVI to CVR	0.04	†
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, Orr et al. 1999); (Gehlot, Mullany et al. 1996); (Milano, Guglielmi et al. 1998); (Eichinger et al 2008); (Aupart et al 2006); (Banbury et al 1998)
†(Berry, Asgar et al. 2007); (Cribier, Eltchaninoff et al. 2004); (Webb, Pasupati et al. 2007); (Eltchaninoff, Tron et al. 2007); (Grube, Laborde et al. 2006); (Grube, Schuler et al. 2007); (Hanzel, Harrity et al.); (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)

Table 2 Decision Tree Early Valve Related Events & Costs

Event		Probability CVR*	Probability TAVI†	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	0.01	0.17	£639	£107	£107
Major paravavular leak		0.01	0.01	0.17	£210	£35	£35
Endocarditis		0.01	0.01	0.08	£5,149	£429	£429
Cardiac tamponade		0.02	0.02	0.25	£630	£158	£158
Myocardial infarction		0.02	0.02	0.33	£1,683	£561	£561
	Total	**0.06**	**0.06**			**£1,289**	**£1,289**
Minor valve-related complications							
Access site events		0.01	0.02		£198	£20	£26
Vascular events		0.02	0.06		£198	£40	£79
Pacemaker implantation		0.07	0.07		£4,649	£3,254	£2,170
	Total	**0.10**	**0.15**			£3,314	£2,275

* (Alsmady, et al. 2009); (Gilbert, Orr et al. 1999); (Gehlot, Mullany et al. 1996); (Milano, Guglielmi et al. 1998); (Eichinger et al 2008); (Aupart et al 2006); (Banbury et al 1998).

† (Alsmady, et al. 2009); (Berry, Asgar et al. 2007); (Cribier, Eltchaninoff et al. 2004); (Webb, Pasupati et al. 2007); (Eltchaninoff, Tron et al. 2007); (Grube, Laborde et al. 2006); (Grube, Schuler et al. 2007); (Hanzel, Harrity et al.); (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 et al, 2005); (Kennon et al, 2008); (NHS Reference Costs, 2008).

Table 3 Decision Tree Branch Costs

	Resource Use		Resource Cost			
	CVR	**TAVI**	**CVR**	**TAVI**	**NoAVR**	**Source**
Device Cost/Medical Management			£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 (2009); Gelhot et al (1996);
General Ward - £210/day	6 days	6 days	£1,260	£1,260		Straumann et al (1994)
Hospital Stay Total	10 days	8 days	£5,780	£2,960		
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 et al (2002)
Post Discharge Total			£3,073	£490		
Total			£14,433	£18,080	£16	

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	0.02	0.02	0.17	0.04	0.01	0.01
Major paravavular leak	0.02	0.02	0.17	0.04	0.01	0.01
Endocarditis	0.01	0.01	0.08	0.01	0.00	0.00
Cardiac tamponade	0.03	0.03	0.25	0.02	0.01	0.01
Myocardial infarction	0.04	0.04	0.33	0.04	0.01	0.01
Total	**0.12**	**0.12**			**0.03**	**0.03**
Minor valve-related complications						
Access site events	0.01	0.02		0.01	0.000	0.000
Vascular events	0.02	0.06		0.01	0.000	0.001
Pacemaker implantation	0.07	0.07		0.05	0.004	0.004
Total	**0.1**	**0.15**			**0.004**	**0.004**

* (Gilbert, Orr et al. 1999); (Gehlot, Mullany et al. 1996); (Milano, Guglielmi et al. 1998); (Eichinger et al 2008); (Aupart et al 2006); (Banbury et al 1998).

† (Berry, Asgar et al. 2007); (Cribier, Eltchaninoff et al. 2004); (Webb, Pasupati et al. 2007); (Eltchaninoff, Tron et al. 2007); (Grube, Laborde et al. 2006); (Grube, Schuler et al. 2007); (Hanzel, Harrity et al.); (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 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.

Table 5 Decision Tree Branch Utilities

Event / State		Proportion	Utility	Duration	Reference
Utility by NYHA Class					
	I		0.85		Maliwa 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 et al (2007)
Disutility following CVR			0.012	13 weeks	Rao et al (2007)

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

Definition	Probability[1]	Source
Probability valve related event	0.15	Table 7
Probability VRE fatal	0.52	*
Mortality from natural causes	mr	Standard lifetables
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

*(Gilbert, Orr et al. 1999); (Gehlot, Mullany et al. 1996); (Milano, Guglielmi et al. 1998); (Eichinger et al 2008); (Aupart et al 2006); (Banbury et al 1998).

Table 7 Probability and Cost of Valve Related Events

	Unit Cost	Probability	Weighting Factor	Total Costs	Probability References	Cost References
Hospitalisations	£3,316	0.03	0.20	£663.20	(Gilbert, Orr et al. 1999); (Gehlot, Mullany et al. 1996); (Milano, Guglielmi et al. 1998); (Eichinger et al 2008); (Aupart et al 2006); (Banbury et al 1998).	Kennon et al (2008)
Valve thromboembolism	£639	0.04	0.27	£170.40		Kennon et al (2008)
Major paravavular leak	£210	0.03	0.20	£42.00		Kennon et al (2008)
Endocarditis	£5,149	0.04	0.27	£1,373.07		NHS Reference Cost (2008)
Cardiac tamponade	£630	0.01	0.07	£42.00		NHS Reference Cost (2008)
Total		**0.15**		**£2,290.67**		

Table 8 Cost of Functioning & Failed Valve Replacement Health States

	Unit Cost	Failed VR or persisting Aortic Stenosis	Functioning Valve Replacement	References
Annual probability of Hospitalisations		0.53*	0.07*	Ahmed 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
Major Late Valve Related Events				
hospitalisations	0.03	0.21	0.019	0.004
valve thromboembolism	0.04	0.29	0.04	0.012
major paravavular leak	0.02	0.14	0.04	0.006
endocarditis	0.04	0.29	0.01	0.003
cardiac temponade	0.01	0.07	0.02	0.001
Utility of major late valve related events				**0.025**

Probabilities Sources: 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; Henzel et al (2005); Lichtenstein et al 2006; Ye et al 2007; Walther et al 2007; Walther et al 2008; Svensson et al 2008; Grube et al 2007; Grube et al 2006; Marcheix et al 2007; Berry et al 2007. **Disutilities Source:** (Sullivan and Ghushchyan 2006)

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	27,492	3.75	31,232	3.78	£117,377
70	25,445	3.18	29,116	3.21	£131,223
80	22,834	2.47	26,517	2.49	£148,631
Females (age, yrs)					
60	28,141	3.93	31,791	3.96	£124,307
70	26,437	3.46	30,115	3.49	£114,112
80	23,807	2.73	27,486	2.76	£145,320

*Operative mortality risk assumed to be 5%

Table 13 Cost Effectiveness Results of Probabilistic Results: TAVI vs CVR vs No AVR 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	29668	3.42	25176	3.35	13886	1.52	£6,176	£66,367
70	27732	2.90	23262	2.83	13902	1.53	£7,163	£69,988
80	25375	2.25	20953	2.20	13908	1.52	£10,400	£95,901
Females (age, yrs)								
60	30159	3.58	25721	3.51	13896	1.53	£5,965	£63,935
70	28685	3.17	24229	3.10	13948	1.53	£6,523	£69,190
80	26272	2.50	21867	2.45	13952	1.53	£8,602	£86,536

*Operative mortality risk assumed to be 15%

Table 14 Cost Effectiveness Results of Probabilistic Results: TAVI vs No AVR for high operative mortality risk patients*

Patient Group	TAVI		No AVR		ICER
	Costs (£)	QALYs	Costs(£)	QALYs	
Males (age,yrs)					
60	28,867	3.24	13,991	1.53	£8,705
70	27,116	2.76	13,929	1.53	£10,714
80	24,840	2.14	14,016	1.54	£17,960
Females (age, yrs)					
60	29,412	3.39	14,099	1.54	£8,277
70	27,993	2.99	13,903	1.53	£9,601
80	25,757	2.38	13,949	1.53	£13,896

*Operative mortality risk assumed to be 20%

References

Alsmady, M. M., M. A. Abu-Abeeleh, et al. (2009). "Early and Mid-term Evaluation of Aortic Valve Replacement." European Journal of Scientific Research **33**(3): 502-508.

Astor, B. C., Kacmarek, R.G., Hefflin, B., Daley, W.R. (2000). "Mortality after aortic valve replacement: Results from a nationally representative database." Ann Thorac Surg **70**: 1939-45.

Aupart, M. R., A. Mirza, et al. (2006). "Perimount pericardial bioprosthesis for aortic calcified stenosis: 18-year experience with 1133 patients." J Heart Valve Dis **15**(6): 775–6.

Banbury, M. K., D. M. Cosgrove 3rd, et al. (1998). "Long-term results of the Carpentier-Edwards pericardial aortic valve: a 12-year follow-up." The Annals of thoracic surgery **66**(6 Suppl): S73.

Berry, C., A. Asgar, et al. (2007). "Novel therapeutic aspects of percutaneous aortic valve replacement with the 21F CoreValve Revalving TM System." Catheterization and Cardiovascular Diagnosis **70**(4): 610-616.

Braunwald, E., Ed. (2002). Harrison's Advances in Cardiology, McGraw-Hill.

Briggs, A. and M. Sculpher (1998). "An Introduction to Markov Modelling for Economic Evaluation." PharmacoEconomics **13**(4): 397-409.

Briggs, A. H., K. Claxton, et al. (2006). Decision modelling for health economic evaluation. Oxford :, Oxford University Press.

Buxton, M. J., M. F. Drummond, et al. (1997). "Modelling in Economic Evaluation: An Unavoidable Fact of Life." Health Economics **6**(3): 217-227.

Canoui-Poitrine, F., G. Jeanblanc, et al. (2009). "Cost Effectiveness of Sirolimus-Eluting Stents Compared with Bare Metal Stents in Acute Myocardial Infarction: Insights from the TYPHOON Trial." Applied Health Economics and Health Policy **7**: 19-29.

Centre, N. H. S. (2006). Computed tomography (CT) angiography for the diagnosis and management of coronary artery disease. Horizon Scanning Technology Briefing, University of Birmingham.

Chessa, A. G., R. Dekker, et al. (1999). "Correlations in Uncertainty Analysis for Medical Decision Making: An Application to Heart-valve Replacement." Med Decision Making **19**(3): 276-286.

Comptroller, A. G. (2005). Reducing Brain Damage: Faster access to better stroke care. Health. London, National Audit Office.

Cribier, A., H. Eltchaninoff, et al. (2006). "Treatment of Calcific Aortic Stenosis With the Percutaneous Heart Valve: Mid-Term Follow-Up From the Initial Feasibility Studies: The French Experience." J Am Coll Cardiol **47**(6): 1214-1223.

Cribier, A., H. Eltchaninoff, et al. (2006). "Treatment of calcific aortic stenosis with the percutaneous heart valve mid-term follow-up from the initial feasibility studies: the French experience." Journal of the American College of Cardiology **47**(6): 1214-1223.

Cribier, A., H. Eltchaninoff, et al. (2004). "Early experience with percutaneous transcatheter implantation of heart valve prosthesis for the treatment of end-stage inoperable patients with calcific aortic stenosis." J Am Coll Cardiol **43**(4): 698-703.

Dalziel, K., L. Segal, et al. (2006). "A Mediterranean diet is cost-effective in patients with previous myocardial infarction." Journal of Nutrition **136**(7): 1879.

Descoutures, F., D. Himbert, et al. (2008). "Contemporary surgical or percutaneous management of severe aortic stenosis in the elderly." Eur Heart J: ehn081.

Drummond, M. F. (1997). Methods for the economic evaluation of health care programmes. Oxford ; New York :, Oxford University Press.

Eichinger, W. B., I. M. Hettich, et al. (2008). "Twenty-year experience with the St. Jude Medical Biocor bioprosthesis in the aortic position." The Annals of thoracic surgery **86**(4): 1204-1210.

Eltchaninoff, H., C. Tron, et al. (2007). "Aortic bioprosthesis implanted percutaneously: three year follow up." Archives des maladies du coeur et des vaisseaux **100**(11): 901.
Gehlot, A., C. J. Mullany, et al. (1996). "Aortic valve replacement in patients aged eighty years and older: early and long-term results." The Journal of Thoracic and Cardiovascular Surgery **111**(5): 1026.
Gilbert, T., W. Orr, et al. (1999). "Surgery for aortic stenosis in severely symptomatic patients older than 80 years: experience in a single UK centre." British Medical Journal **82**(2): 138.
Grube, E., J. C. Laborde, et al. (2006). "Percutaneous implantation of the CoreValve self-expanding valve prosthesis in high-risk patients with aortic valve disease: the Siegburg first-in-man study." Circulation **114**(15): 1616.
Grube, E., G. Schuler, et al. (2007). "Percutaneous Aortic Valve Replacement for Severe Aortic Stenosis in High-Risk Patients Using the Second- and Current Third-Generation Self-Expanding CoreValve Prosthesis: Device Success and 30-Day Clinical Outcome." Journal of the American College of Cardiology **50**(1): 69-76.
Hanzel, G. S., P. J. Harrity, et al. "Retrograde percutaneous aortic valve implantation for critical aortic stenosis." Catheterization and Cardiovascular Diagnosis **64**(3): 322-326.
Health, D. o. (2008). NHS reference costs 2006-07. N. r. c. 2006-07. London, UK, Department of Health (UK).
Heidenreich, P. A., F. A. Masoudi, et al. (1999). "Echocardiography in patients with suspected endocarditis: a cost-effectiveness analysis* 1." The American Journal of Medicine **107**(3): 198-208.
Iung, B., A. Cachier, et al. (2005). "Decision-making in elderly patients with severe aortic stenosis: why are so many denied surgery?" Eur Heart J **26**(24): 2714-2720.
Kalra, L., A. Evans, et al. (2005). "A randomised controlled comparison of alternative strategies in stroke care." Health Technol Assess **9**(18): 1-94.
Kennon, K., Mathur, Rothman (2008). Percutaneous Aortic Valve Replacement. Clinical and Economic Considerations.
Kuntz, K. M., J. Tsevat, et al. (1996). "Cost-effectiveness of routine coronary angiography after acute myocardial infarction." Circulation **94**(5): 957.
Lamotte, M., L. Annemans, et al. (2007). "A health economic evaluation of concomitant surgical ablation for atrial fibrillation." European Journal of Cardio-Thoracic Surgery **32**(5): 702-710.
Lee, T. T., N. A. Solomon, et al. (1997). "Cost-effectiveness of screening for carotid stenosis in asymptomatic persons." Annals of internal medicine **126**(5): 337.
Legrand, V., J. Beckers, et al. (1991). "Long-term follow-up of elderly patients with severe aortic stenosis treated by balloon aortic valvuloplasty. Importance of haemodynamic parameters before and after dilatation." Eur Heart J **12**(3): 451-457.
Lehtonen, J. M., Hippeläinen, M., Kattainen, E., Kouri, J., Kujala, J. (2009). "Speed and quality in Coronary Artery Bypass Graft (CABG) surgery: is there a connection? ." Health Care Management Science **12**(2): 1572-9389
Leon, M. G., Susheel, K., Williams, M., Oz, M., Smith, C., Steward, A., Schwartz., A., Collins, M., Mosses, J.W. (2006). "Transcatheter Aortic Valve Replacement in Patients with Critical Aortic Stenosis: Rationale, Device Descriptions, Early Clinical Experiences and Persepectives." Thoracic and Cardiovascular Surgery **18**.
Lichtenstein, S. V., A. Cheung, et al. (2006). "Transapical transcatheter aortic valve implantation in humans: initial clinical experience." Circulation **114**(6): 591.
Majeed, A., Aylin , P., (2005). "The ageing population of the United Kingdom and cardiovascular disease " British Medical Journal **331**.
Maliwa, M. A., G. van der Heijden, et al. (2003). "Quality of life and NYHA class 30 years after mechanical aortic valve replacement." Cardiovascular surgery **11**(5): 381-387.
Marcheix, B., Y. Lamarche, et al. (2007). "Surgical aspects of endovascular retrograde implantation of the aortic CoreValve bioprosthesis in high-risk older patients with

severe symptomatic aortic stenosis." The Journal of Thoracic and Cardiovascular Surgery **134**(5): 1150-1156.
Milano, A., C. Guglielmi, et al. (1998). "Valve-related complications in elderly patients with biological and mechanical aortic valves." The Annals of thoracic surgery **66**(6 Suppl): S82.
Nashef, S. A. M., F. Roques, et al. (1999). "European system for cardiac operative risk evaluation (EuroSCORE)." Eur J Cardiothorac Surg **16**(1): 9-13.
Netten, A. and L. Curtis (2002). Unit costs of health and social care, University of Kent at Canterbury, Personal Social Services Research Unit Canterbury.
NICE (2005). Dual chamber pacemakers for symptomatic bradycardia due to sick sinus syndrome and/or atrioventricular block. Technology Appraisal London, NICE.
NICE (2008). Transcatheter Aortic Valve Implantation for Aortic Stenosis. Interventional Procedure Guidance Scotland, NHS Quality Improvement Scotland. **266**.
NICE (2008). Understanding NICE guidance: Catheter Insertion of New Aortic Valve to Treat Aortic Stenosis. NHS, NHS.
Nkomo, V. T., J. M. Gardin, et al. (2006). "Burden of valvular heart diseases: a population-based study." The Lancet **368**(9540): 1005-1011.
Philips, Z., L. Bojke, et al. (2006). "Good practice guidelines for decision-analytic modelling in health technology assessment: a review and consolidation of quality assessment." PharmacoEconomics **24**(4): 355-71.
Post, P. N., A. M. Stiggelbout, et al. (2001). "The utility of health states after stroke: a systematic review of the literature." Stroke **32**(6): 1425.
Rao, C., O. Aziz, et al. (2007). "Cost effectiveness analysis of minimally invasive internal thoracic artery bypass versus percutaneous revascularisation for isolated lesions of the left anterior descending artery." British Medical Journal **334**(7594): 621.
Roques, F., Michel, P., Goldstone, A.R, Nashef, S.A.M. (2003). "The Logistic EuroScore." European Heart Journal **24**: 1-2.
Rosen, A. B., V. G. Fowler Jr, et al. (1999). "Cost-effectiveness of transesophageal echocardiography to determine the duration of therapy for intravascular catheter-associated Staphylococcus aureus bacteremia." Annals of internal medicine **130**(10): 810.
Sack, S., C. Naber, et al. (2005). "Percutaneous heart valve implantation in the aortic position." Herz **30**(5): 433.
Scottish Health Technologies Group (2009) Response to query on transcatheter aortic valve implantation (TAVI). Paper 6. 12th February 2009.
Sheldon, T. A. (1996). "Problems of using modelling in the economic evaluation of health care." Health Economics **5**(1).
Sonnenberg, F. A. and J. R. Beck (1993). "Markov Models in Medical Decision Making: A Practical Guide." Med Decis Making **13**(4): 322-338.
Sonnenberg, F. A. and J. R. Beck (1993). "Markov models in medical decision making: a practical guide." Medical Decision Making **13**(4): 322.
Stewart, S., N. Murphy, et al. (2003). "The current cost of angina pectoris to the National Health Service in the UK." British Medical Journal **89**(8): 848.
Sullivan, P. W. and V. Ghushchyan (2006). "Preference-based EQ-5D index scores for chronic conditions in the United States." Medical Decision Making **26**(4): 410.
Svensson, L. G., T. Dewey, et al. (2008). "United States Feasibility Study of Transcatheter Insertion of a Stented Aortic Valve by the Left Ventricular Apex." Ann Thorac Surg **86**(1): 46-55.
Tsevat, J., L. Goldman, et al. (1993). "Stability of time-tradeoff utilities in survivors of myocardial infarction." Medical Decision Making **13**(2): 161.
Vahanian, A., O. Alfieri, et al. (2008). "Transcatheter valve implantation for patients with aortic stenosis: a position statement from the European Association of Cardio-Thoracic Surgery (EACTS) and the European Society of Cardiology (ESC), in collaboration with the European Association of Percutaneous Cardiovascular Interventions (EAPCI)." Eur Heart J **29**(11): 1463-1470.

Vahanian, A., Alfieri, O., Al-Attar N, Antunes M, Bax J, Cormier B, et al. (2008). "Transcatheter valve implantation for patients with aortic stenosis: a position statement from the European Association of Cardio-Thoracic Surgery (EACTS) and the European Society of Cardiology (ESC), in collaboration with the European Association of Percutaneous Cardiovascular Interventions (EAPCI)." European Heart Journal **29**(11): 1463-70.

Vahanian A, A. O., Al-Attar N, Antunes M, Bax J, Cormier B, et al. (2008). "Transcatheter valve implantation for patients with aortic stenosis: a position statement from the European Association of Cardio-Thoracic Surgery (EACTS) and the European Society of Cardiology (ESC), in collaboration with the European Association of Percutaneous Cardiovascular Interventions (EAPCI)." European Heart Journal **29**(11): 1463-70.

Van Brabandt, H. and M. Neyt (2008). Percutaneous Heart Valve Implantation in Congenital and Degenerative Valve Disease. A Rapid Health Technology Assessment. KCE Reports 95C. Brussels, Belgium, Belgian Health Care Knowledge Centre. **95C**.

Walther, T., V. Falk, et al. (2008). "Transapical minimally invasive aortic valve implantation; the initial 50 patients." European Journal of Cardio-Thoracic Surgery **33**(6): 983-988.

Walther, T., P. Simon, et al. (2007). "Transapical Minimally Invasive Aortic Valve Implantation: Multicenter Experience." Circulation **116**(11_suppl): I-240-245.

Webb, J. G., M. Chandavimol, et al. (2006). "Percutaneous aortic valve implantation retrograde from the femoral artery." Circulation **113**(6): 842.

Webb, J. G., Chandavimol, M., Thompson, C.R., Ricci, D.R., Carere, R.G., Munt, B., Buller, C.E., Pasupati, S., Lichtenstein, S. (2007). "Percuntaneous transarterial aortic valve replacement in selected high-risk patients with aortic stenosis. ." Circulation **116**.

Webb, J. G., S. Pasupati, et al. (2007). "Percutaneous Transarterial Aortic Valve Replacement in Selected High-Risk Patients With Aortic Stenosis." Circulation **116**(7): 755-763.

Webb, J. G. A., Lukas,; Masson, Jean-Bernard; Bugami, Saad., A. (2009). "A New Transcather Aortic Valve and Percutaneous Valve Delivery System." Journal of the American College of Cardiology **53**(20).

Ye, J., A. Cheung, et al. (2009). "Transapical transcatheter aortic valve implantation: 1-year outcome in 26 patients." The Journal of Thoracic and Cardiovascular Surgery **137**(1): 167-173.

Zegdi, R., Ciobotaru, V., Noghin, M., Sleilaty, G., Lafont, A., Latrémouille, C., Deloche, A., Fabiani, J.N. (2008). "Is it reasonable to treat all calcified stenotic aortic valves with a valved stent? Results form a human anatomic study in adults." Journal of the American College of Cardiology **51**.