

Heart valve disease presenting in adults: investigation and management

Cost-utility analysis: Transcatheter Mitral edge-to-edge repair for inoperable patients

NICE guideline NG208

Economic analysis report

November 2021

Final

*This analysis was developed by the
National Guideline Centre*

Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and, where appropriate, their carer or guardian.

Local commissioners and providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

NICE guidelines cover health and care in England. Decisions on how they apply in other UK countries are made by ministers in the [Welsh Government](#), [Scottish Government](#), and [Northern Ireland Executive](#). All NICE guidance is subject to regular review and may be updated or withdrawn.

Copyright

© NICE 2021. All rights reserved. Subject to Notice of rights.
ISBN: 978-1-4731-4301-2

Contents

1	Introduction	7
2	Methods	8
2.1	Model overview	8
2.1.1	Comparators	8
2.1.2	Population	8
2.2	Approach to modelling	8
2.2.1	Model structure: post-procedural consequences decision tree	9
2.2.2	Model structure: Long-term outcomes Markov model	10
2.2.3	Uncertainty	12
2.3	Model inputs	13
2.3.1	Summary table of model inputs	13
2.3.2	Baseline probabilities	17
2.3.3	Relative treatment effects	20
2.3.4	Utilities	21
2.3.5	Resource use and costs	23
2.4	Computations	30
2.5	Sensitivity analyses	31
2.5.1	Cost of a MitraClip procedure	31
2.5.2	Remove heart transplant	31
2.5.3	Use CtE data instead of COAPT	31
2.5.4	Utility benefits are persistent	31
2.5.5	Exponential distribution for mortality	32
2.5.6	Survival benefits last for the duration of the trial only	32
2.5.7	Exclude vascular complications	32
2.6	Model validation	33
2.7	Estimation of cost effectiveness	33
2.8	Interpreting results	33
3	Results	34
3.1	Base case	34
3.2	Sensitivity analyses	35
3.3	Threshold analysis	36
4	Discussion	38
4.1	Summary of results	38
4.2	Limitations and interpretation	38
4.3	Generalisability to other populations or settings	38
4.4	Comparisons with published studies	39
4.5	Conclusions	39

Appendices	43
Appendix A: Drugs included in the model	43

1 Introduction

Mitral valve regurgitation (MR) occurs when the mitral valve loses competency, allowing retrograde flow of blood from left ventricle into the atrium, which in turn reduced the efficiency of the heart. There are two different causes of MR: degenerative and functional. Degenerative or primary MR is caused by the deterioration of the valve itself whereas functional or secondary MR occurs when the valve is structurally normal, but its function is compromised by the leaflets which fail to coapt usually following a left ventricular enlargement.

Transcatheter Mitral Valve edge-to-edge repair is a minimally invasive technique used to treat patients with moderate-severe and severe mitral valve regurgitation (MR). It allows to treat patients who are unable to receive standard surgery due to the high risk associated with surgical repair or surgical replacement. The transcatheter procedure, differently from a standard surgery, is performed through a small incision in the groin where a tube is passed up through the leg vessel to the heart valve. The MitraClip device is delivered through the tube and positioned over the leaky mitral valve.

MitraClip was only recently commissioned by NHS England as the Commission through Evaluation (CtE)²⁸ study found the benefits of MitraClip to be largely sustained in the medium term. An economic evaluation comparing transcatheter Mitral Valve edge-to-edge repair with medical management found transcatheter repair to be cost effective¹². However, the study was considered of poor quality as treatment effects were informed by a prospective, single arm registry. Two recent randomized controlled trials (RCT) seemed to point to two different directions: MITRA-FR¹⁹ saw no significant benefit whereas COAPT²⁵ found improvements on mortality and rehospitalisation. It has been argued that the two studies differed for patient selection, medical management control and for the definition of the parameter of MR severity².

A cost-utility patient-level analysis on transcatheter mitral valve repair using COAPT data was performed from the perspective of the US healthcare system⁴. The study found MitraClip to be likely cost-effective according to US threshold.

Given the lack of cost-effectiveness analyses, an economic evaluation of transcatheter Mitral Valve edge-to-edge repair was considered of high priority and a decision model analysis was undertaken. The number of MitraClip interventions performed in England is still very low compared to other European countries; therefore, a strong recommendation may have a high impact on the current practice. Moreover, as the cost of a MitraClip procedure was estimated to be considerably high (£32,910)²⁸, a recommendation to offer it to inoperable patients may lead to a substantial resource impact for the NHS. Hence, the need of an economic evaluation assessing the cost-effectiveness of transcatheter Mitral Valve edge-to-edge repair with MitraClip in England appears to be strongly justified.

2 Methods

2.1 Model overview

A cost-utility analysis was undertaken where lifetime quality-adjusted life years (QALYs) and costs from a current UK NHS and personal social services perspective were considered. The analysis followed the standard assumptions of the NICE reference case for interventions with health outcomes in an NHS setting including discounting at 3.5% for costs and health effects¹³. An incremental analysis was undertaken.

2.1.1 Comparators

The following comparators were included in the analysis:

1. Transcatheter Mitral Valve edge-to-edge repair with MitraClip device plus guideline-based medical management
2. Guideline-based medical management only

It is assumed that patients in both arms receive the pharmaceutical medication provided by NICE guideline for chronic heart failure in adults (<https://www.nice.org.uk/guidance/ng106>). A full list of the drugs included is provided in Appendix A:. It is assumed that people in the control and intervention group do not differ in terms of medications prescribed.

In addition to the cost of drugs, it was agreed to include the recurrent cost of resynchronisation therapy (pacemaker check, echocardiography assessment and echocardiography-based optimisation).

2.1.2 Population

The population of the analysis was patients with severe secondary mitral valve regurgitation judged inoperable for standard mitral valve surgery.

Following the discussion with the GC, it appeared clear that whereas COAPT²⁵ enrolled mostly patients with severe MR, MITRA-FR¹⁹ enrolled a substantial number of patients with moderate MR. Moreover, many patients in MITRA-FR received the intervention in centres lacking adequate expertise, whereas, in COAPT, MitraClip was performed only in highly specialized medical centres. As the focus of the analysis is on patients with severe secondary mitral regurgitation and MitraClip in England would be performed only in high-volume centres similarly to COAPT, it was agreed to use the effectiveness data coming from COAPT in the analysis as it better reflects what would be found in practice in the NHS.

2.2 Approach to modelling

A two-part model was developed which included a decision tree to model post-procedural outcomes (up to 30 days) followed by a Markov model for long-term extrapolation of outcomes and costs.

The 30 days decision tree model reflects the immediate period following the intervention when several post-procedural consequences can occur. Estimates from an UK registry were used to populate the decision tree whereas the treatment effectiveness data came from the clinical effectiveness review. Further details on the decision tree model can be found in section 2.2.1.

The decision tree model only captures immediate consequences of the intervention, but the clinical review shows that differences in e.g., mortality are consistent even after 1 year. In order to extrapolate costs and outcomes beyond the period of 30 days, a Markov model was developed for each comparator using baseline data and relative treatment effects data from

COAPT study. People start in the decision tree and then move to the Markov model at the end of the 30-days period entering the corresponding Markov state determined by the final state of the decision tree model. The Markov model was then run for 30 repeated cycles of 1 year each. Time spent in each health states was calculated to determine costs and QALYs associated with each intervention. The comparison between the results of each intervention allowed us to identify the most cost-effective strategy. More details on the Markov model structure are described in section 2.2.2. To account for uncertainty, a probabilistic analysis was undertaken (see section 2.2.3 for further details).

Summary of key assumption:

- People are assumed to stick with their medication regime for the whole duration of their life unless they receive a heart transplant
- People who received a heart transplant withdraw from heart failure medication and take immunosuppressor medication for the duration of their life
- People in both arms can undergo one or more mitral valve re-intervention during their lifetime
- Re-intervention is always assumed to be a transcatheter Mitral Valve edge-to-edge repair in both arms
- People who had a stroke or received a heart transplant cannot undergo a re-intervention

2.2.1 Model structure: post-procedural consequences decision tree

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

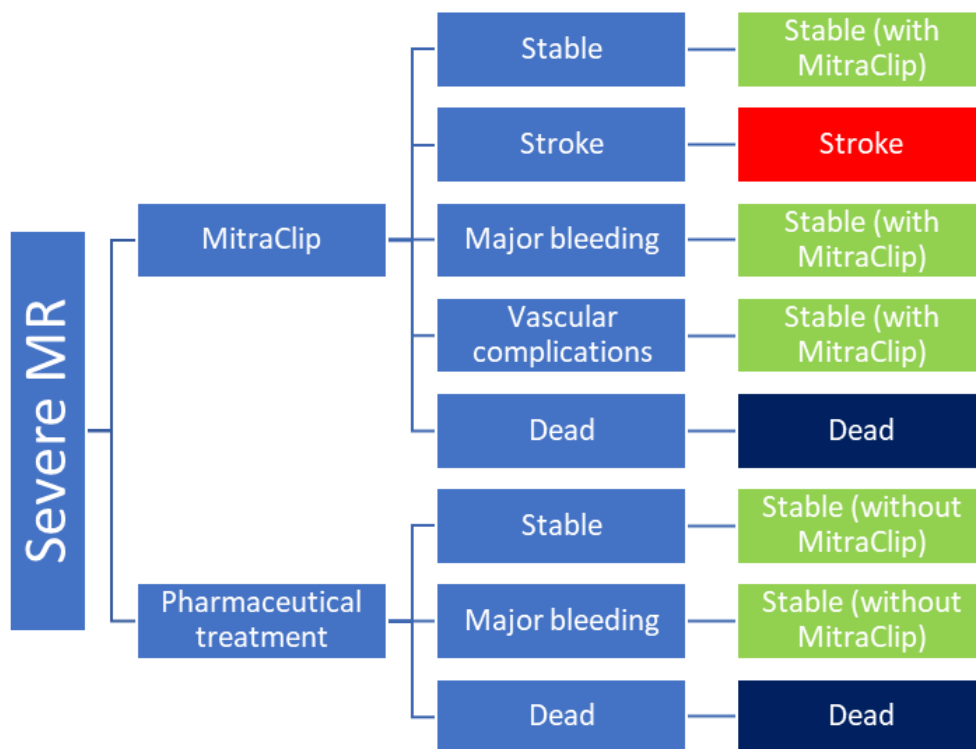
- mortality at 30 days
- Stroke
- Major bleeding
- Vascular complication

There was some uncertainty regarding the opportunity to include other outcomes as well. Acute kidney injury (AKI) needing renal replacement therapy was initially included as a short and long-term outcome but was eventually removed after a discussion with the clinical advisor suggested that AKI cannot be a consequence of a transcatheter Mitral Valve edge-to-edge repair intervention. The clinical evidence showed that people in the medical management arm do not experience most of the states of the MitraClip arm with the exception of major bleeding which has a positive probability to occur even in the medical arm.

Data for complication risk were recovered from the UK CtE registry²⁸ as the committee agreed that, although the population in CtE was different from the population of the model, complication rates are affected by the intervention and not by the MR aetiology (see further discussion in section 2.3.2). Longer-term mortality and treatment effects were taken from the COAPT²⁵ trial as the committee agreed that this trial better represents what would be found in the NHS. However, since only MITRA-FR¹⁹ includes 30 days outcomes, data for major bleeding and vascular complications come from this study. It should be noted that the MITRA-FR trial might over-estimate these complications, since the interventions were performed in centres with little experience of conducting the procedure. Therefore, a sensitivity analysis was conducted that removes these complications altogether to demonstrate that the model results are not sensitive to these estimates.

Figure 1 shows the structure of the decision tree model. There are three final states patients can end up at the end of the 30 days period: stable, stroke or dead. Major bleeding and vascular complication are assumed to be only temporary states and, as such, result only in a temporary loss of utility and cost. Hence, people experiencing major bleeding or vascular complication end in the stable state and have no long-term consequence. Following the 30 days post-procedural period, people enter the Markov model in the same state they were at the end of the decision tree model.

Figure 1: Model structure: post-procedural consequences decision tree



2.2.2 Model structure: Long-term outcomes Markov model

In a Markov model, people exist in a set of mutually exclusive states describing what happens to the population over time. At each Markov cycle, assumed to be a 1-year period, patients can move to other states according to a set of transition probabilities defined between each of the health states.

The Markov model was developed to model long-term outcomes and extrapolate costs and consequences of the population over a lifetime time-horizon. Costs and outcomes were collected at each cycle for a period of 30 years after which most of the cohort were dead.

Following the discussion with the committee and clinical advisor it was agreed to include 7 health states:

- Stable (with or without MitraClip)
- Stroke
- Post-stroke
- Heart transplant first year
- Stable with heart transplant
- Re-intervention

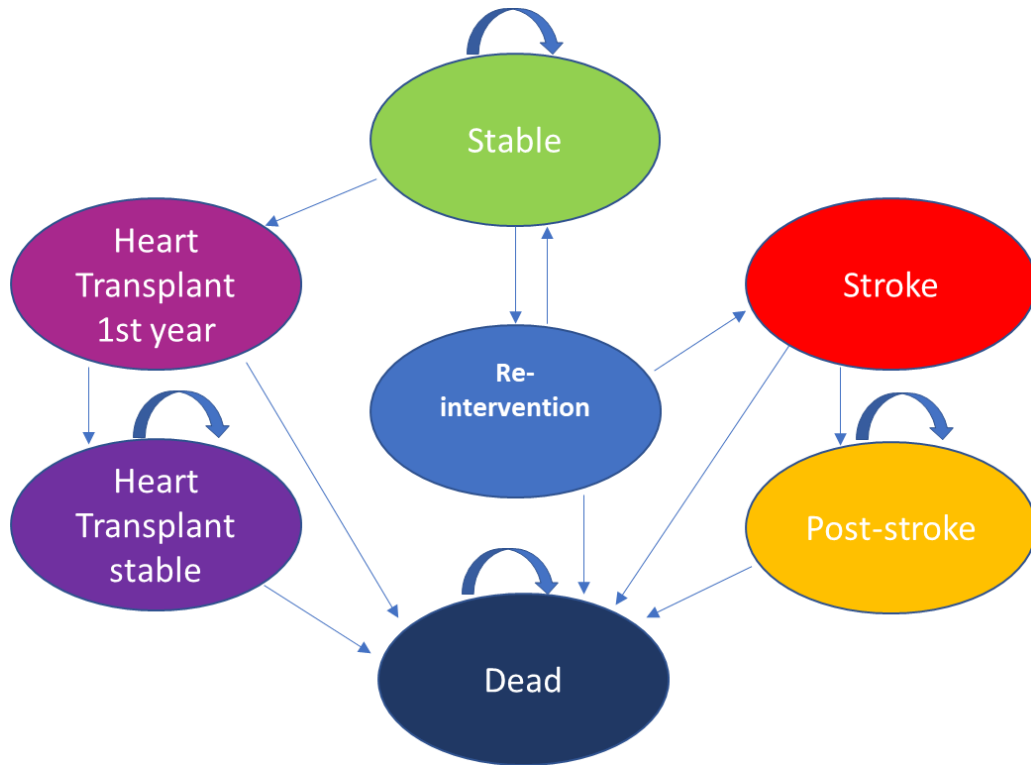
Those who are alive and in the stable state at the end of the decision tree model, enter the Markov model in the stable state. Those who experienced stroke enter the stroke state of the Markov model. Finally, those who have died during the 30 days of the decision tree enter the model in the dead state.

Figure 2 shows the structure of the Markov model. People in the stable state have a positive probability of transitioning to heart transplant or to reintervention. The model captures stroke as a post-procedural consequence. It does not capture strokes occurring at other times, as the rate is assumed to be the same in both arms. Therefore, it is not possible for someone in the stable state to transit to stroke in the Markov model. Heart transplant first-year, reintervention and stroke are all tunnel states meaning that people remain in those state for one cycle only before moving to the next state or to dead. Patients in the heart transplant first-year state move to stable with heart transplant whereas patients in the stroke state move to post-stroke. It was agreed to model heart transplant in two separated states to account for the high mortality people experience during the first year following surgery. Stable with heart transplant and post-stroke states were included to model long-term mortality, utility and costs associated with these two conditions. It is assumed that after someone ends up in one of these two states, they cannot experience another intervention and remain in such states until they die. This is an obvious simplification but one that will not affect the results substantively. Those who receive a heart transplant are unlikely to need a new mitral valve intervention after their surgery. People who have had a stroke might be at risk of having an additional mitral valve intervention but they represent a very small population (1%) so we do not expect this assumption to have a strong impact on the model. Dead is an absorbing state.

Reintervention is a tunnel state only occurring between full cycles. At the beginning of every cycle, people can move from the stable state to the reintervention state. People ending up in the reintervention state enter a decision tree model simulating post-procedural outcomes and costs of the re-intervention, which is always assumed to be a new MitraClip intervention. Hence, the decision tree model has the same structure described in chapter 2.2.1. After the decision tree has calculated costs and outcomes of the re-intervention, people re-enter the Markov model in the health states determined by the decision tree model. People in the medical management arm who receive a MitraClip intervention move to a new state, “stable with MitraClip”, with the same utility and mortality of patients in the MitraClip arm. It is assumed that people can undergo more than one reintervention during their lifetime.

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

Figure 2: Model structure: Long-term outcomes Markov model



2.2.3 Uncertainty

The model was built probabilistically to take account of the uncertainty around input parameter point estimates. A probability distribution was defined for each model input parameter. When the model was run, a value for each input was randomly selected simultaneously from its respective probability distribution; mean costs and mean QALYs were calculated using these values. The model was run repeatedly – 10,000 times for the base case - and results were summarised.

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

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

Parameter	Type of distribution	Properties of distribution
Baseline risks	Beta	Bounded between 0 and 1. As the sample size and the number of events were specified alpha and beta values were calculated as follows: <ul style="list-style-type: none"> • Alpha = (number of patients hospitalised) • Beta = (number of patients) – (number of patients hospitalised)
Hazard ratios Reintervention and hospitalisation rates SMRs	Lognormal	The natural log of the mean and standard error were calculated as follows: <ul style="list-style-type: none"> • Mean = $\ln(\text{mean cost}) - SE^2/2$ • SE = $[\ln(\text{upper 95\% CI}) - \ln(\text{lower 95\% CI})]/(1.96 \times 2)$

Parameter	Type of distribution	Properties of distribution
		$\sqrt{\ln \frac{SE^2 + mean^2}{mean^2}}$ <p>This formula includes a correction to ensure the mean generated in the probabilistic analysis will be the same as the reported mean³.</p>
Utilities	Beta	<p>Bounded between 0 and 1. Derived from mean and its standard error, using the method of moments.</p> <p>Alpha and Beta values were calculated as follows: Alpha = $mean^2 \times [(1 - mean) / SE^2] - mean$ Beta = $alpha \times [(1 - mean) / mean]$</p>
Utility decrements	Gamma	<p>Bounded at 0, positively skewed. Derived from mean and its standard error.</p> <p>Alpha and beta values were calculated as follows:</p> <ul style="list-style-type: none"> • Alpha = $(mean / SE)^2$ • Beta = $SE^2 / Mean$

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

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

- The cost-effectiveness threshold (which was deemed to be fixed by NICE)
- Health state costs (based on analyses that use unit costs from UK national sources)
- Drug costs (based on drug tariff which is known)
- Mortality probabilities for general population (based on UK national data)
- Utility score in the general population (based on the paper from Ara 2010¹)

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

2.3 Model inputs

2.3.1 Summary table of model inputs

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

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

Input	Data	Source	Probability distribution
Comparators	<ul style="list-style-type: none"> • MitraClip plus guideline-based medical management^(a) 		n/a

Input	Data	Source	Probability distribution
	<ul style="list-style-type: none"> Guideline-based medical management alone 		
Population	Adults with severe mitral regurgitation secondary to heart failure		n/a
Perspective	UK NHS & PSS	NICE reference case ¹³	n/a
Time horizon	Lifetime		n/a
Discount rate	Costs: 3.5% Outcomes: 3.5%	NICE reference case ¹³	n/a
Cohort settings			
Cohort size	1000		
Male start age	72	COAPT ²⁵	
Female start age	72	COAPT ²⁵	
Percentage of males entering the model	47.7%	COAPT ²⁵	
Percentage of females entering the model	52.3%	COAPT ²⁵	
MitraClip risks in 30 days decision tree model			
Mortality 30 days	6%	CtE ²⁸	Dirichlet
Stroke	1%	CtE ²⁸	Dirichlet
Major bleeding	1.5%	CtE ²⁸	Dirichlet
Vascular complication	3.5%	MITRA-FR ¹⁹	Beta
MitraClip risks in post 1-year Markov model			
Reintervention rate	CtE: 0.03 COAPT: 0.017	CtE ²⁸ COAPT ²⁵	Log-normal
Heart failure hospitalisation rate	0.755 per patient year	COAPT ²⁵	Log-normal
Heart transplant	0.05%	COAPT ²⁵	Beta
General population mortality	Age and sex dependent	ONS Life Tables 2016-2018 ²⁰	n/a
Medical management mortality	23.12% at 1 year 43% at 2 years 55.5% at 3 years	COAPT 3-years outcomes ¹⁰	n/a
Heart transplant mortality at first year	19%	UK cardiothoracic transplant audit ²⁷	n/a
Stroke relative survival	1-year: 0.818 (0.805-0.830) 2-year: 0.792 (0.778-0.806) 3-year: 0.768 (0.752-0.782) 5-year: 0.721 (0.703-0.738) 10-year: 0.624 (0.598-0.648)		Log-normal

Input	Data	Source	Probability distribution
Heart transplant SMR	2.84 (2.82-2.87)	Suarez-Pierre 2020 ²⁶	Log-normal
Relative treatment effects 30 days MitraClip vs medical management			
Mortality 30 days HR	2.43 (0.63 to 9.4)	COAPT ²⁵	Log-normal
Major bleeding RR	1.83 (0.7 to 4.83)	Mitra-FR ¹⁹	Log-normal
Relative treatment effects post 1-year MitraClip vs medical management			
Mortality HR (3 years)	0.67 (0.52 to 0.85)	COAPT ¹¹	Log-normal
Need for re-intervention HR (3 years)	0.1 (0.05 to 0.2)	COAPT ¹¹	Log-normal
Rehospitalisation HR (3 years)	0.58 (0.48 to 0.72)	COAPT ¹¹	Log-normal
Heart transplant HR (2 years)	0.35 (0.09 to 1.32)	COAPT ²⁵	Log-normal
Health-related quality of life (utilities)			
Health states			
Medical management 1 year	0.64	SF-36 score from COAPT ¹⁶ converted into EQ-5d using the formula from Lawrence ⁸	Beta
Medical management 2 years	0.62		Beta
MitraClip 1 year	0.73		Beta
MitraClip 2 years	0.72		Beta
Dead	0	By definition	
Utility decrements			
Major bleeding	0.0199	Kaier 2016 ⁶	Gamma
Vascular complication	0.00695	Kaier 2016 ⁶	Gamma
Stroke	0.16	Luengo Fernandez 2013 ⁹	Gamma
Post-stroke	0.18	Luengo Fernandez 2013 ⁹	Gamma
Utility decrements duration			
Major bleeding	30 days	Assumed	n/a
Vascular complication	30 days	Assumed	n/a
Stroke	365	Assumed	n/a
Post-stroke	Permanently	Assumed	n/a
Costs			
Mitraclip intervention cost			
Lower case	£29,900	CtE ²⁸	n/a
Central case	£32,910	CtE ²⁸	n/a
Upper case	£34,500	CtE ²⁸	n/a

Input	Data	Source	Probability distribution
Pharmaceutical annual costs			
ACE	£25.52	Unit cost and dosing from British National Formulary ⁵ . Cost per mg and weighted average cost of classes calculated using Prescription Cost Analysis ¹⁷	n/a
ARB	£83.26		n/a
ARNI	£1,883.26		n/a
Beta Blockers	£37.08		n/a
MRA	£45.79		n/a
Diuretics	£13.66		n/a
Percentage of patients taking each drug			
ACE/ARB/ARNI	72.30%	CtE ²⁸	n/a
Beta Blockers	73.90%	CtE ²⁸	n/a
MRA	26.60%	CtE ²⁸	n/a
Diuretics	79.30%	CtE ²⁸	n/a
Patients taking ARB among those under ACE/ARB/ARNI	33.33%	COAPT ²⁵	n/a
Patients taking ARNI among those under ACE/ARB/ARNI	5.34%	COAPT ²⁵	n/a
Cardiac resynchronization therapy			
Cost of therapy	£250	NHS Reference Costs 2018-2019 ¹⁸	n/a
Patients in CRT	36.5%	COAPT ²⁵	n/a
Decision tree costs			
Major bleed	£1,971.51	NHS Reference Costs 2018-2019 ¹⁸	n/a
Vascular complication	£1,825.99	NHS Reference Costs 2018-2019 ¹⁸	n/a
Markov model costs			
Hospitalisation	£2,275.43	NHS Reference Costs 2018-2019 ¹⁸	n/a
Stroke	£18,948.01	Xu 2018 SSNAPP project ²⁹	n/a
Post-stroke	£6,727.25	Xu 2018 SSNAPP project ²⁹	n/a
Heart transplant			
Procedure cost	£55,117.42	NHS Reference Costs 2018-2019 ¹⁸	n/a
Antiproliferative (annual cost)	£115.07	Unit cost and dosing from British National Formulary ⁵ . Cost per mg and weighted average cost of classes calculated using Prescription Cost Analysis ¹⁷	n/a
Calcineurin inhibitors (annual cost)	£3,494.03		n/a
Corticosteroids (annual cost)	£334.09		n/a

Abbreviations: SMR = Standardized mortality ratio; HR = Hazard ratio; ACE = Angiotensin-converting-enzyme inhibitors; ARB = Angiotensin II Receptor Blockers; ARNI = Angiotensin receptor-neprilysin inhibitor; MRA = Aldosterone receptor antagonists

2.3.2 Baseline probabilities

The model was populated with baseline probabilities of people who received a MitraClip intervention. These probabilities mostly come from the Commissioning through Evaluation (CtE)²⁸ registry of 2018 for the decision tree model and from COAPT trial²⁵ in the Markov model. When running the model for people receiving guideline-based medical management, relative treatment effects obtained from the clinical review were applied to the baseline probabilities in order to obtain the probabilities of the control group. The relative treatment effects are discussed in section 2.3.4.

The availability of data and general issues

Post-procedural outcomes probability and the cost of the intervention were identified from the Commissioning through Evaluation (CtE) registry²⁸, which is the only registry reporting outcomes following a MitraClip intervention in the UK. CtE registry enrolled 199 patients with moderate or severe secondary or primary MR across three centres in England. The committee acknowledged two main issues associated with this registry.

Firstly, a large proportion (40%) of the enrolled patients have primary rather than secondary MR. Primary MR is rather different than secondary MR as it is associated with a better prognosis and survival. For most of the outcomes, e.g., the probabilities of adverse events or hospital readmission rate, the authors found no significant difference between patients with secondary and primary MR although they did not provide a subgroup analysis in the study. The committee noted that post-procedural outcomes depend only on the intervention and, as such, they should not vary across different types of patients. Hence, CtE was considered the appropriate source for short-term outcomes probability. On the other hand, reintervention and hospitalisation rate differ among people with primary or secondary MR. For this reason, the committee agreed to use instead the figures reported in COAPT in base case scenario, and test CtE outcomes in the sensitivity analysis.

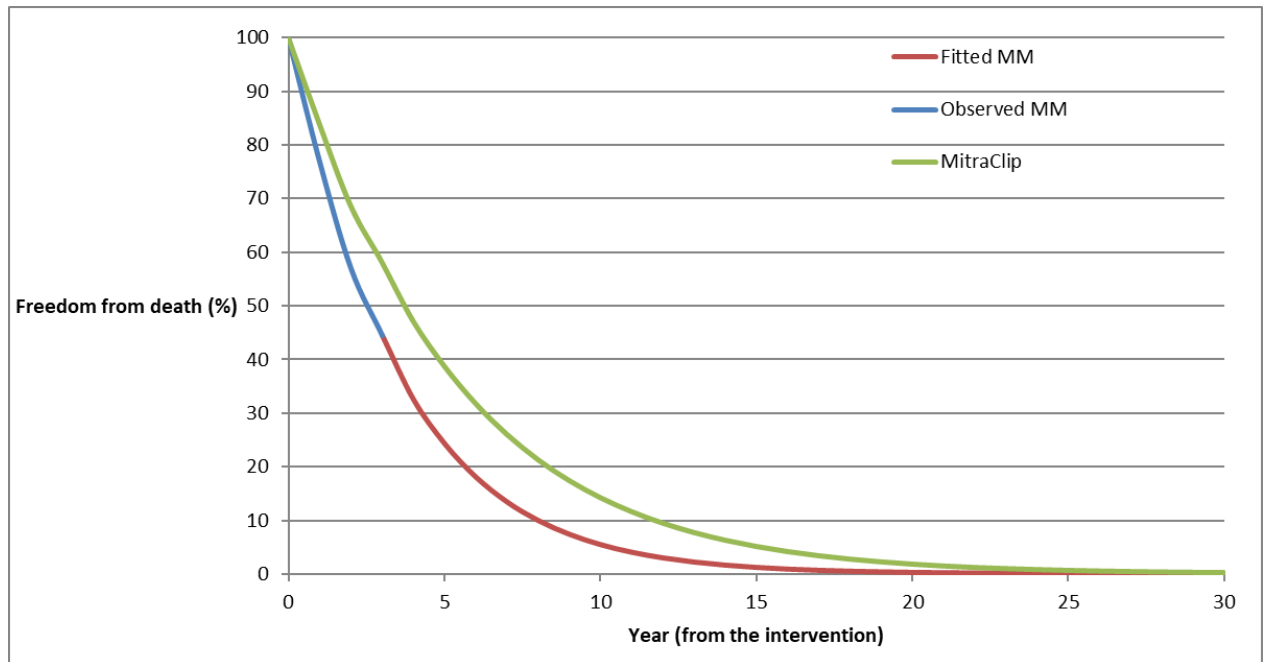
A second issue noted by the committee is that CtE participants were highly selected and, therefore, may not reflect the population that would be found in practice in UK. This appears to be the main reason why some of its outcomes, such as mortality, greatly differ from the ones found in other registries across Europe. As a result, the committee agreed to rely on other sources when extrapolating mortality data (see chapter on mortality).

Other relevant outcomes were not reported in CtE registry and had to be extracted from the trials included in the clinical review. Outcomes on heart transplant were recovered from COAPT study as this was the only study reporting the probability and hazard ratio of undergoing a heart transplant in the two years following the intervention. Likewise, the probability of experiencing a vascular complication at 30 days following a MitraClip intervention was informed using MITRA-FR trial as CtE reported no cases for this outcome.

Mortality

All-cause mortality was reported by the COAPT trial up to 3 years in the medical management arm¹⁰. A Weibull distribution was fitted to the observed survival curve to extrapolate mortality rates beyond the last follow-up adding, as a constraint, that almost all the cohort is dead at 10 years, as recommended by the Committee. The related hazard ratio from COAPT was then applied to the curve to obtain the survival curve in the MitraClip arm (see figure 3). In the sensitivity analysis an exponential distribution was tested instead of the Weibull for the extrapolation (see chapter 2.5 on the sensitivity analyses).

Figure 3: mortality in the MM and MitraClip arms (with fitted Weibull)



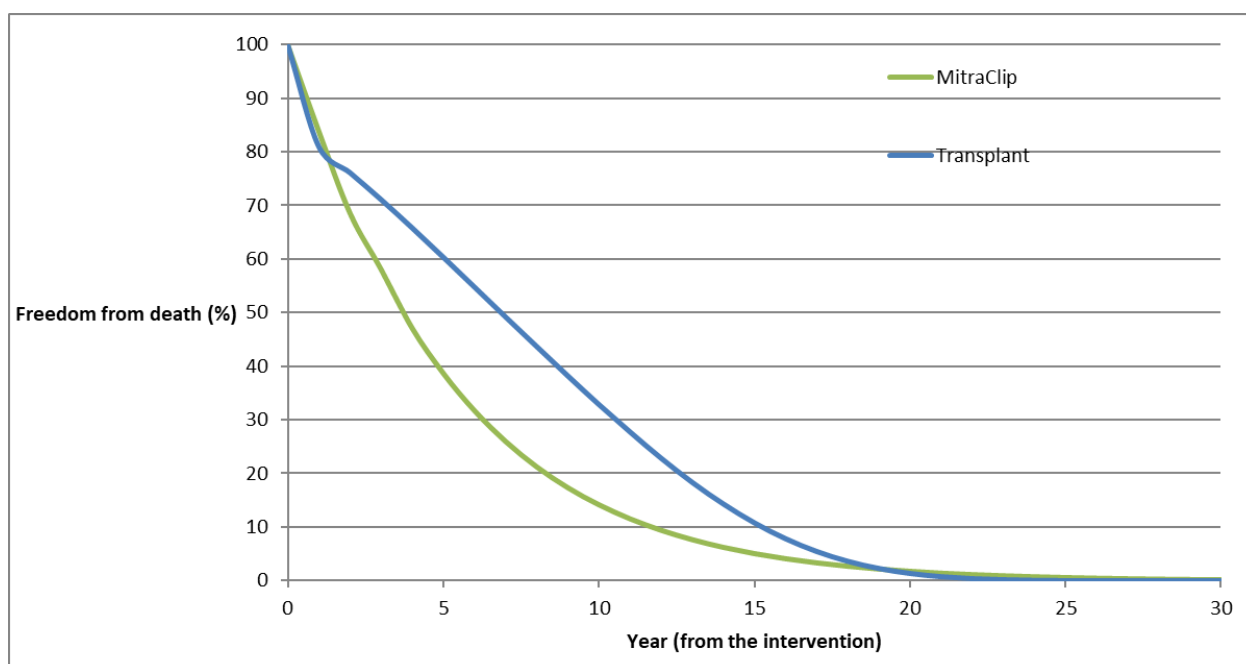
Mortality rates for people with heart transplant were sought from published literature. The mortality at the first year was recovered from the UK cardiothoracic transplant audit reporting survival in heart transplant patients in the UK. Mortality rates for the subsequent years were calculated by applying the standardized mortality ratio from the study of Suarez-Pierre²⁶ to the mortality rates of the general population. This study matched 31,883 heart transplant recipients to 159,415 non-institutionalized US residents to calculate standard mortality ratios between recipient and the general population. Table 3 illustrates data and sources used to calculate the mortality in heart transplant recipients.

Table 3: Mortality after heart transplant

Input	Data	Source
Mortality at 1 year	19%	UK cardiothoracic transplant audit ²⁷
SMR	2.84 (2.82-2.87)	Suarez-Pierre 2020 ²⁶

Figure 4 compares the mortality rate between people with MitraClip and people with a heart transplant. People with heart transplant exhibit a higher mortality during the first year following the intervention as a result of the higher probability of organ rejection but have a more favourable prognosis in the following years.

Figure 4: mortality after heart transplant vs MitraClip



To calculate the probability of dying for people in stroke or post-stroke states a recent French study based on the Dijon stroke registry was used²². The study reported the relative survival to the general population of people who had an ischemic stroke up to 10 years after the event (see table 4). Relative survival between the third and the fifth years and beyond the last follow-up was extrapolated assuming a linear relation over time. People in the stroke state are assigned the 1-year relative survival, whereas in the post-stroke state the probability of dying was calculated using the relative survival (either observed or extrapolated) related to the years beyond the first one.

Table 4: stroke relative survival

Input	Data	Source
1-year RS	0.818 (0.805 to 0.83)	Romain 2020 ²²
2-year RS	0.792 (0.778 to 0.806)	
3-year RS	0.768 (0.752 to 0.782)	
5-year RS	0.721 (0.703 to 0.738)	
10-year RS	0.624 (0.598 to 0.648)	

Gender population mortality was based on data from life tables for England 2018-2019. Cycle-specific general population mortality was calculated taking into account the age and gender split for the population entering the model and how this changed over time: not only mortality increases by age, but the gender split varies as well as males have a higher probability of dying than females and therefore die at a higher rate. As population mortality is not available beyond 100 years, the model applied the mortality rate for age 100 to those who are 100 years or older. Table 5 shows age and gender split data used in the model. This was obtained from the CtE registry²⁸

Table 5: Model population

Population	Model entry age	Percentage
Male	72	47.7%
Female	72	52.3%

Calibration of survival during the first three years

Although we had overall survival from both arms of the COAPT trial, for the model we needed mortality estimates specifically for people in the stable state, which was not reported.

To deal with this issue, for the first three cycles (until the last follow-up), the number of people in the dead state was not calculated through transition probabilities but directly assigned using the survival curve reported in the trial. This approach ensured that the number of people in the dead state perfectly matches the number reported in the trial. The number of people still alive in the stable state was calculated as the model cohort size minus the number of people in all the other states. Therefore, the mortality rate in the stable state was calculated implicitly. This approach was applied to both arms, such that the baseline survival and hazard ratios in the model were identical to those in the trial.

For the cycles beyond the third one, the number of people in the dead state was calculated using the standard approach of a Markov model, with transition probabilities based on the survival distribution curve extrapolated from COAPT.

2.3.3 Relative treatment effects

Relative treatment effects for transcatheter mitral valve repair compared to medical management were based on the clinical review.

The committee acknowledged that the two studies included in the clinical review were discordant as one study²⁵ found MitraClip to improve patients outcomes and survivability whereas the other¹⁹ found no significant difference between the intervention and the control group. The committee agreed that the two studies were considerably different as COAPT²⁵ enrolled mostly patients with severe MR assess by a cardiothoracic surgeon to be unsuitable for mitral valve surgery whereas in MITRA-FR trial¹⁹ the selection was less strict as many patients with moderate MR ended up being included as well. Table 6 shows that mean effective regurgitant area (EROA) is lower in MITRA-FR than in COAPT suggesting that a majority of patients in the COAPT study have a truly severe MR. Atianzar and colleagues investigated further the difference between the two trials². Their conclusion was that MitraClip is particularly effective when performed on patients with very severe MR but less effective or not effective at all when performed on patients with moderate MR.

Table 6: EROA in MITRA-FR and COAPT

Trail	EROA
COAPT	41 mm ²
MITRA-FR	31 mm ²

Giving the differences between the two studies, the committee agreed that pooling together the results of the two trials would not be preferable for the modelling analysis. Hence, it was agreed to use the findings of the COAPT trial only²⁵ as the patients enrolled in this study should better reflect the population of interest, which is people with severe MR and inappropriate for surgery.

The hazard ratios extracted from COAPT were applied to the baseline rates of people who underwent transcatheter mitral valve edge-to-edge repair to obtain the probabilities of patients in the medical management arm. The only exception was the relative risk for major bleeding, which was not an included outcome in COAPT and therefore had to be extracted from Mitra-FR. Table 7 shows the relative treatment effects included in the model.

Table 7: relative treatment effects

Input	Data	Source	Probability distribution
Relative treatment effects 30 days MitraClip vs medical management			
Mortality 30 days HR	2.43 (0.63 to 9.4)	COAPT ²⁵	Log-normal
Major bleeding RR	1.83 (0.7 to 4.83)	Mitra-FR ¹⁹	Log-normal
Relative treatment effects post 1-year MitraClip vs medical management			
Mortality HR (3 years)	0.67 (0.52 to 0.85)	COAPT ¹¹	Log-normal
Need for re-intervention HR (3 years)	0.1 (0.05 to 0.2)	COAPT ¹¹	Log-normal
Rehospitalisation HR (3 years)	0.58 (0.48 to 0.72)	COAPT ¹¹	Log-normal
Heart transplant HR (2 years)	0.35 (0.09 to 1.32)	COAPT ²⁵	Log-normal

2.3.4 Utilities

Health states

Utilities for people with MitraClip and under medical management were sought from the papers included in the clinical review. As discussed in chapter 2.3.4, the committee agreed to use relative treatment effects data from COAPT only as this trial better represents the population of interest of the model. Likewise, it was decided to collect utility scores from the same study.

COAPT trial measured utility score at baseline, 6 months, 12 months and 24 months after the intervention. Utility scores were measured in terms of SF-36 composite scores divided in SF-36 Mental Component Score (MCS) and SF-36 Physical Component Score (PCS). To convert these scores into EQ-5D scores, which are the preferable measures by NICE, mapping studies were sought using the database for mapping studies. No study on mapping SF-36 MCS and PCS into EQ-5D were found although several studies on mapping from SF-12 composite scores were available. As a comparative study suggests that SF-12 composite score and SF-36 composite score are very similar, with a correlation coefficient of 0.94⁷, it was decided to apply the algorithm from Lawrence et al.⁸ referring to how to map SF-12 composite scores into EQ-5D. The algorithm used is the following:

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

It is worth mentioning that the study used is based on a US population sample and therefore it may not reflect the UK population. To calculate the associated standard deviation a second algorithm included in the paper was used. The resulting EQ-5D scores and standard deviation used in the model are illustrated in table 8.

Table 8: utility scores

Time	MitraClip	Medical management
12 months	0.73 (0.18)	0.64 (0.20)
24 months	0.72 (0.19)	0.62 (0.18)

The committee anticipated that the quality of life benefits of MitraClip would not be persistent and probably decrease over time. Hence, it was assumed in the base case analysis that the improvement in EQ-5D of MitraClip would gradually decrease over a period of 5 years and that people in MitraClip and medical management arms would share the same utility score

beyond the fifth year. In the sensitivity analysis an alternative scenario where the quality of life improvement lasted for the duration of the life of the patients was tested (see 2.5.4)

Utility score for people with a heart transplant were sought from available literature. A paper was identified reporting SF-36 scores of people who received a range of solid organ transplantation (insert citation). The mapping algorithm described above was used to calculate the corresponding EQ-5D utility scores (see table 9):

Table 9: utility score after heart transplant

Follow-up	Mean
1 year	0.77 (0.05)
2 years	0.65 (0.05)
3 years	0.63 (0.04)

The utility scores obtained were compared to the utility score of the general UK population reported by Ara and Brazier¹ and an utility multiplier was calculated by dividing the utility score observed in the trials with the corresponding utility score in the general population. The multiplier was then multiplied for the utility scores of the general population at each year of age to calculate the utility score by age for people in the MitraClip and medical management arms. This methodology ensured that utility decreases with ageing as expected in the real world.

Utility decrements

Several short and long-term states result in a loss of utility for people experiencing such events. Utility decrements associated with these states were sought by looking at studies reporting patients' utility score after a heart valve intervention. A study from Kaier and colleagues⁶ reports the EQ-5D decrements following a range of post-procedural outcomes after a transcatheter aortic valve replacement (TAVI).

Following a discussion with the clinical advisor, it appeared that outcomes after TAVI are comparable with the ones after a MitraClip intervention although with some important differences: TAVI is performed through an artery whereas MitraClip through a vein. As a result, major bleedings after TAVI are more serious and can be life-threatening whereas they tend to be less important after a MitraClip intervention. Consequently, the committee agreed to use in the model the utility decrement caused by non-life-threatening major or minor bleeding instead of the one associated with very severe disabling bleeding.

Regarding vascular complication, the committee agreed that the loss of utility caused by vascular complication after TAVI or MitraClip should be similar and therefore, the estimation provided by Kaier⁶ was used in the model. As the study reported one-month change of EQ-5D, it was assumed that the events last for a period of 30 days.

The loss of utility caused by a stroke was obtained from a different source as in Kaier only a small group of individuals experienced stroke (around 6). Hence, loss of utility due to stroke was calculated using Luengo-Fernandez study⁹ reporting the quality of life after a stroke using the ten-year results of the Oxford vascular study. To calculate the average utility score during the first year, it was assumed that the utility score increased at a constant rate each month. Hence, the loss of utility score caused by stroke during the first year was calculated by subtracting the annual average utility score in the stroke group from the corresponding annual average utility score in the control group. Likewise, to calculate the loss of utility score caused by post-stroke (>1 year), an average across the 5 years was calculated assuming, again, that the utility scores vary at a constant rate each year.

Table 10 illustrated the utility detriments associated with the health states included in the model, their assumed duration and sources.

Table 10: utility detriments

Condition	Utility detriments	Duration	Source
Major bleeding	0.0199	30 days	Kaier 2016 ⁶
Vascular complication	0.00695	30 days	Kaier 2016 ⁶
Stroke	0.16	1 year	Luengo-Fernandez 2013 ⁹
Post-stroke	0.179	Permanently	Luengo-Fernandez 2013 ⁹

2.3.5 Resource use and costs

2.3.5.1 Intervention costs

The cost of a MitraClip intervention was recovered from the CtE²⁸. The committee agreed that, although CtE enrolled people with mixed mitral regurgitation aetiology, this should not be reflected in their price estimation as the nature of the intervention is expected to be the same in primary and secondary mitral regurgitation alike. The authors estimated through a bottom-up approach the total cost of a transcatheter mitral valve repair intervention by including the pre-operative assessment costs, peri-operative and post-operative management costs at 2017/2018 prices. Three different estimations were provided representing a central case estimation, a low cost and a high cost scenario (see table 11). The central case estimation was used in the base case analysis whereas the high and low case scenarios were both tested in the sensitivity analysis (see section 2.5).

Table 11: cost of a MitraClip procedure

Scenario	Cost	Source
Central case	£32,910	CtE ²⁸
Low cost scenario	£29,000	CtE ²⁸
High cost scenario	£34,500	CtE ²⁸

2.3.5.2 Drugs and CRT therapy

The drugs included in the medical management were identified from the NICE chronic heart failure guideline and include ACEi (or ARBs if not tolerated), Beta-Blockers, MRA and diuretics. It was assumed that people would stick with their medication whether or not they receive the intervention. A list of the drugs for heart failure, dosages and their average cost per mg is shown in table 12. Dosages and unit costs of drugs were sought from the British National Formulary⁵ whereas the cost per mg was calculated using the Prescription Cost Analysis database¹⁷.

Table 12: heart failure drugs

Drug	Daily dosage (in mg)	Cost per mg	Cost per day
Ace inhibitors			
Ramipril	10	£0.01	£0.06
Captopril	150	£0.0008	£0.13
Enalapril	15	£0.0056	£0.08
Lisinopril	35	£0.0027	£0.09
Quinapril	40	£0.0137	£0.55
Fosinopril	40	£0.0081	£0.33
ARBs			
Candesartan	32	£0.0071	£0.23
Valsartan	320	£0.0035	£1.12
Losartan	150	£0.0013	£0.19
Beta blockers			
Bisoprol	10	£0.0089	£0.09
Carvedilol	50	£0.0049	£0.25
Nebivolol	10	£0.0403	£0.40
Diuretics			
Furosemide	40	£0.0009	£0.03
Bumetanide	0.5	£0.0866	£0.04
Torsemide	20	£0.0342	£0.68
MRA			
Eplerenone	50	£0.0058	£0.29
Spirolactone	50	£0.0018	£0.09
ARNI			
Sacubitril with valsartan	194	£0.0266	£5.16

The immunosuppression therapy drugs for people who received a heart transplant were sought from the British National Formulary⁵ and include antiproliferative, calcineurin inhibitors and corticosteroids (prednisolone). It was assumed that the 100% of the patients with a heart transplant would comply with their medication until the end of their life. Unit costs were recovered from the British National Formulary⁵ and the Prescription Cost Analysis¹⁷ was used to calculate the average cost per mg. The drugs included for each class are illustrated in table 13 together with their dosage, cost per mg and daily cost.

Table 13: immunosuppressive drugs

Drug	Daily dosage (in mg)	Cost per mg	Cost per day
Antiproliferative			
Azathioprine	134.58	£0.012	£0.16
Mycophenolate mofetil	3,0000	£0.0004	£1.33
Calcineurin inhibitors			
Ciclosporin	307.60	£0.0240	£7.37
Tacrolimus	5.77	£1.8042	£10.41
Corticosteroids			
Prednisolone	60	£0.0153	£0.92

To obtain the daily cost of the overall drug class, the Prescription Cost Analysis database¹⁷ was used to convert in “days of dosage” the quantity of drugs sold in England each year. Days of dosage was then used as a weight to calculate the weighted average cost of the classes of drugs. Table 14 illustrates each class of drugs together with their yearly cost and percentage of people taking them. This latter was recovered from the CtE registry²⁸ and COAPT trial²⁵.

Table 14: cost of drug classes

Drug class	Cost per year	Percentage of patients taking the drug	Source
Pharmaceutical management of heart failure			
ACE	£25.52	44.22%	Unit cost and dosage from BNF ⁵ . Weighted average cost per class calculated using PCA ¹⁷ . Percentage of patients from CtE and COAPT ²⁵ .
ARB	£83.26	24.22%	
Beta blockers	£37.08	73.90%	
MRA	£45.79	26.60%	
Diuretics	£13.66	79.30%	
ARNI	£1883.26	3.86%	
Immunosuppressive therapy			
antiproliferative	£115.07	100%	Unit cost and dosage from BNF ⁵ . Weighted average cost per class calculated using PCA ¹⁷ .
calcineurin inhibitors	£3,494.03	100%	
Corticosteroids	£334.09	100%	

A relevant proportion of patients with heart failure are under cardiac resynchronization therapy (CRT). To capture the recurrent cost associated with this therapy, it was assumed that patients under CRT routinely receive each year an echocardiogram and a consultant-led visit for pacemaker optimisation. More details can be seen in table 15.

Table 15: Cardiac resynchronization therapy

State	Cost	Source
Simple echocardiogram	£115	NHS Reference Costs 2018-2019 ¹⁸
Consultant led cardiac visit	£135	NHS Reference Costs 2018-2019 ¹⁸
Percentage of people on CRT	36.50%	COAPT ²⁵

2.3.5.3 Health states

Several health states are associated with a cost sustained by the NHS and social care. The sources of costs data were sought by reviewing existing models and by conducting a non-systematic review online. Costs were divided in short-term decision tree costs and long-term Markov states costs according to whether they are sustained immediately after the surgery or continuously over the years following the intervention.

Decision tree outcomes (major bleeding and vascular complications)

Two post-procedural outcomes, namely major bleeding and vascular complication are associated with a cost sustained by the NHS. These are states that affect patients only temporarily and consequently do not have long-term consequences implying that the associated costs occur only once, at the offsetting of the states, and are not repeated over time. The costs used in the model are reported together with their sources in table 16.

Table 16: Decision tree costs

State	Cost	Source
Major bleeding	£1,971.51	NHS Reference Costs 2018-2019 ¹⁸
Vascular complication	£1,825.99	NHS Reference Costs 2018-2019 ¹⁸

The cost of major bleeding was sought from the NHS Reference Cost database under the item gastrointestinal bleed. An average weighted by the number of attendances of NHS reference costs for all categories of non-elective long stay and short stay gastrointestinal bleed admission was used in the model (see table 17). The cost of gastrointestinal bleed without intervention with CC score between 0 and 4 was omitted as this category represent minor events.

Table 17: cost of major bleeding

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

Currency Code	Currency Description	Number of FCE's	National Average Unit Cost
Non-elective long stay			
	Intervention, with CC Score 8+		
FD03D	Gastrointestinal Bleed with Single Intervention, with CC Score 5-7	46	£2,360
FD03E	Gastrointestinal Bleed with Single Intervention, with CC Score 0-4	108	£1,089
FD03F	Gastrointestinal Bleed without Interventions, with CC Score 9+	2,213	£591
FD03G	Gastrointestinal Bleed without Interventions, with CC Score 5-8	8,830	£541
Weighted average			£1,971.51

The cost of vascular complication was sought by looking at International Classification of Diseases (ICD) codes related to various injuries to blood vessels around the body. The ICD code was then converted into an HRG code to find the associated cost for the public sector in the NHS References Costs. The associated HRG description was “peripheral vascular disorder” and the cost for the model was obtained by calculating the average non-elective long and short stay cost weighted by the number of attendances. This is shown in table 18.

Table 18: Cost of vascular complication

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

Currency Code	Currency Description	Number of FCE's	National Average Unit Cost
Non-elective long stay			
YQ50A	Peripheral Vascular Disorders with CC Score 15+	673	£852
YQ50B	Peripheral Vascular Disorders with CC Score 11-14	1,519	£710
YQ50C	Peripheral Vascular Disorders with CC Score 8-10	2,685	£597
YQ50D	Peripheral Vascular Disorders with CC Score 5-7	4,438	£541
YQ50E	Peripheral Vascular Disorders with CC Score 2-4	6,924	£452
YQ50F	Peripheral Vascular Disorders with CC Score 0-1	5,050	£350
Weighted average			£1,826

Long-term outcomes (Stroke and post-stroke)

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

To cost stroke and post-stroke the same approach used in the Acute Coronary Syndrome model was adopted. The cost was based on the work of Xu 2018²⁹ which estimated the total burden of stroke in UK to the NHS and social services. This was done using a patient simulation based on UK Sentinel Stroke National Audit Programme (SSNAP) data. The cost of stroke was reported in the study for 1 and 5 years (see table 19).

Table 19: burden of stroke

Health state	Cost	Source
Stroke 1 year	£23,052	Xu 2018 – SSNAP project inflated to 2017/18 ²⁹
Stroke 5 year	£47,023	Xu 2018 – SSNAP project inflated to 2017/18 ²⁹

Cost associated with NHS and social service were reported separately. The latter includes both publicly financed social service and privately funded social service. As the NICE reference case provides that the cost-effectiveness analysis is conducted from a public sector point of view only, non-publicly funded cost cannot be included in this analysis. A recent paper Patel 2019²¹ used the assumption that approximately 50% of the social cost is born by the NHS and, therefore, the same assumption was used in the model.

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

The costs used in the model related to stroke or post-stroke are summarized in table 20.

Table 20: cost of stroke and post-stroke

Health state	Cost	Source
Stroke	£18,948	Xu 2018 ²⁹ 1-year costs with 50% of social care costs removed and inflated to 2018/2019
Post-stroke	£6,727	Xu 2018 ²⁹ 5-year costs adjusted to remove 1 year cost and annualised; 50% of social care costs removed and inflated to 2018/2019

Hospitalisation

The cost of a cardiac hospitalisation episode was sought from the NHS Reference Costs 2018/2019 under the item “Heart failure or shock”. An average weighted for the level of activity was calculated and used in the model (see table 21).

Table 21: Cost of vascular complication

Currency Code	Currency Description	Number of FCE's	National Average Unit Cost
Non-elective long stay			
EB03A	Heart Failure or Shock, with CC Score 14+	23406	£3,909.61
EB03B	Heart Failure or Shock, with CC Score 11-13	28511	£3,139.47
EB03C	Heart Failure or Shock, with CC Score 8-10	24564	£2,532.67
EB03D	Heart Failure or Shock, with CC Score 4-7	18805	£2,169.60
EB03E	Heart Failure or Shock, with CC Score 0-3	2841	£2,169.93
Non-elective short stay			
EB03A	Heart Failure or Shock, with CC Score 14+	8201	£605.12
EB03B	Heart Failure or Shock, with CC Score 11-13	15330	£537.31
EB03C	Heart Failure or Shock, with CC Score 8-10	19200	£493.72
EB03D	Heart Failure or Shock, with CC Score 4-7	20862	£464.38
EB03E	Heart Failure or Shock, with CC Score 0-3	4857	£404.73
Weighted average			£1,948.21

The number of cardiac related hospital admissions occurring each year in the MitraClip and medical management arms was calculated using the associated annualized rate and hazard ratio reported in the COAPT study, which was multiplied by the number of people alive at each cycle. The rate of hospitalisation in the two arms are shown in table 22.

Table 22: Cardiac hospitalisation annual rate

Health state	Cardiac hospitalisation annual rate	Source
MitraClip	0.76	COAPT ²⁵
Medical management	1.54	COAPT ²⁵

2.4 Computations

The model was constructed in Microsoft Excel 2010 and was evaluated by a 1,000 cohort simulation. Time dependency was built in by cross referencing the cohorts age as a respective risk factor for mortality.

People started in the decision tree in the MitraClip or medical management arm. People then moved to the other health states (major bleeding, vascular complication, stroke and dead) based on probabilities of events occurring which was calculated from baseline risks and treatment effects. Those alive at the end of the decision tree at 30 days, entered the model and started in cycle 0. The health state they entered was determined by which health state they were in at the end of the 30 days decision tree. Those who did not experience any events or experienced only temporary events such as bleeding or vascular complication entered the “stable” health state in the Markov model. Those who had a stroke entered the “stroke” health state in the Markov model. Mortality transition probabilities in the Markov model depend on the health states people are in and were recovered using a Weibull function fitted with the observed data from COAPT trial.

Hazard ratio was applied to the mortality rate of medical management arm to obtain the mortality rate in the MitraClip arm. Rates were then converted to probabilities using the following formula:

$$\text{Transition Probability (P)} = 1 - e^{-rt}$$

Where
 r =selected rate
 t =cycle length (1 year)

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

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

Discounting formula:

$$\text{Discounted total} = \frac{\text{Total}}{(1+r)^n}$$

Where:
 r =discount rate per annum
 n =time (years)

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

2.5 Sensitivity analyses

In addition to the probabilistic sensitivity analysis, a range of one-way sensitivity analyses were undertaken. These are the following:

1. Vary the cost of a MitraClip procedure
2. Remove heart transplant
3. Use CtE data instead of COAPT for reintervention and hospitalisation
4. Assume that utility benefits are persistent
5. Use an exponential distribution instead of a Weibull to extrapolate mortality
6. Assume that survival benefits last for the duration of the trial only
7. Exclude vascular complications

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

2.5.1 Cost of a MitraClip procedure

As discussed in chapter 2.3.6.1, CtE reports three different estimations of the cost of a MitraClip procedure. These are reported in table 23.

Table 23: cost of a MitraClip procedure

Scenario	Cost	Source
Central case	£32,910	CtE ²⁸
Low cost scenario	£29,000	CtE ²⁸
High cost scenario	£34,500	CtE ²⁸

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

2.5.2 Remove heart transplant

The committee noted that heart transplant may have a significant impact in the analysis as it is associated with considerable and long-term costs and improved health outcomes. For this reason, it was decided to investigate the role of heart transplant in the model by testing a scenario where heart transplants are completely removed from the model.

2.5.3 Use CtE data instead of COAPT

As discussed in chapter 2.3.3, CtE registry enrolled very selected patients with mixed MR aetiology and as such, it was not considered suitable for extracting baseline probabilities which are believed to be affected by the aetiology of mitral regurgitation. Hence, although for all probabilities related to the intervention CtE was considered appropriate by the committee as those are not affected by MR aetiology, for other baseline risks, such as reintervention and hospitalisation, the committee agreed to use the figures reported by COAPT trial.

Nevertheless, a sensitivity analysis using the figures reported from CtE for hospitalisation and reintervention was undertaken to investigate the impact of using a different source for these two outcomes.

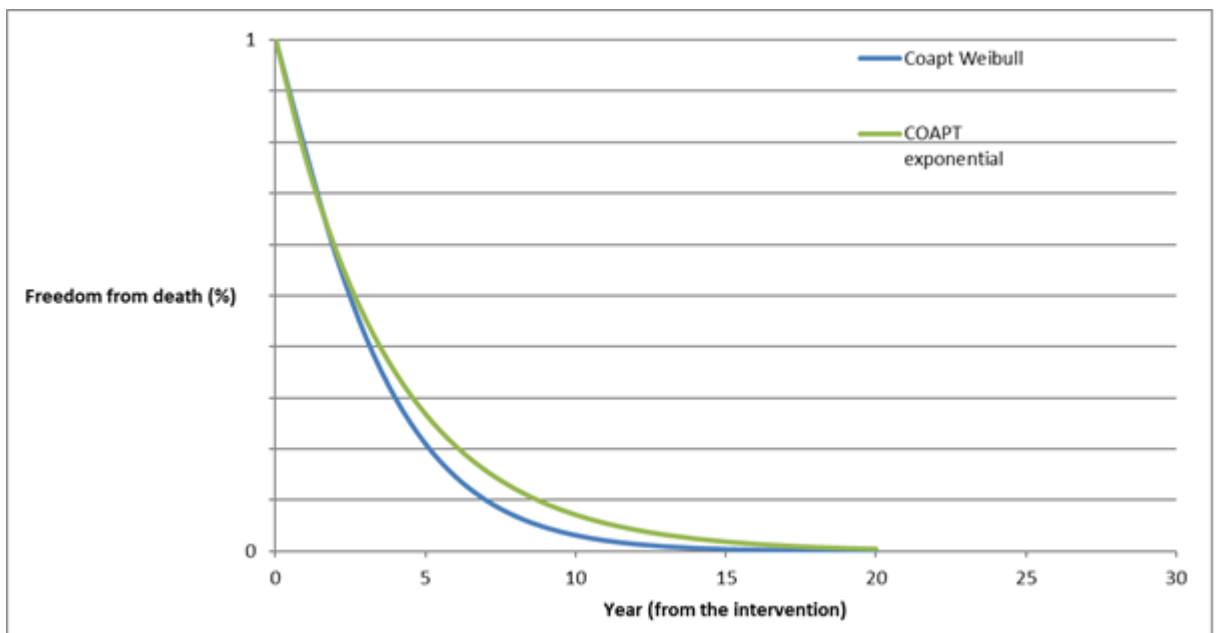
2.5.4 Utility benefits are persistent

In the base case analysis, utility scores were assumed to gradually decrease over a period of 5 years, as anticipated by the committee. In the sensitivity analysis we tested an alternative scenario where the benefits in terms of quality of life of MitraClip were persistent and lasted for the duration of the life of the patients.

2.5.5 Exponential distribution for mortality

Two different distributions were used to extrapolate the mortality rate beyond the last follow-up of the COAPT trial: an exponential and a Weibull distribution. The first was obtained through R studio by fitting a curve to the observed data points from COAPT. The committee noted that the exponential curve was likely under-estimating the number of deaths as people with severe heart failure rarely survive after 10 years from the diagnosis. For this reason, a second curve, a Weibull, was fitted based on the observed points and on the assumption that most of the cohort were dead at 10 years. This last curve was used in the base case-scenario. Figure 5 compares the exponential and Weibull curves.

Figure 5: Exponential and Weibull curves



In the sensitivity analysis the exponential curve was used as an alternative approach to extrapolate mortality beyond the last follow-up.

2.5.6 Survival benefits last for the duration of the trial only

The committee acknowledged that it is currently unknown whether MitraClip survival benefits would last for the lifetime of the patients. Follow-up studies based on COAPT showed that survival benefits are consistent at least 3 years after the intervention suggesting that they may be persistent over time. Nevertheless, a sensitivity analysis was conducted where the benefits lasted for the duration of the trial only. Results of this are presented in section 3.2.

2.5.7 Exclude vascular complications

As discussed in chapter 2.2.1, vascular complication rates were taken from Mitra-FR trial as CtE did not report this outcome. Mitra-FR failed to find significant improvement with MitraClip as it was conducted in centres lacking sufficient expertise. Therefore, it is possible that vascular complications are over-estimated by Mitra-FR as, in the UK, MitraClip would be conducted only on high-volume centres with high expertise. Therefore, a sensitivity analysis was conducted where these complications were removed altogether to assess whether these highly affect the model. Results can be seen in section 3.2

2.6 Model validation

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

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

2.7 Estimation of cost effectiveness

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

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

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

Cost effective if:
• ICER < Threshold

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

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

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

Cost effective if:
• Highest net benefit

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

2.8 Interpreting results

NICE sets out the principles that committees should consider when judging whether an intervention offers good value for money¹³⁻¹⁵. In general, an intervention was considered to be cost effective if either of the following criteria applied (given that the estimate was considered plausible):

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

3 Results

3.1 Base case

Table 24 illustrates the number of events occurring in the two arms for a cohort of 1,000 people.

Table 24: events for 1,000 people (deterministic)

Events	MitraClip strategy	Medical management (MM) Strategy	Difference (MitraClip minus MM)
Vascular complications	44	0	44
Major bleeding	5	4	2
Stroke	15	5	11
Hospitalisation	3,990	4,402	-411
Reintervention	91	324	-233
Heart transplant	57	79	-22

The MitraClip strategy results in more people experiencing complications such as vascular complication, bleeding and stroke. On the other hand, MitraClip is associated with less hospitalisation, less reinterventions and less heart transplants.

MitraClip was overall more expensive but resulted in more QALYs gained. Table 26 offers a breakdown of the costs per patients of the two strategies.

Table 25: cost breakdown (per patient, probabilistic)

Cost category	MitraClip strategy	Medical management (MM) Strategy	Difference (MitraClip minus MM)
MitraClip	£32,910	£0	£32,910
Heart failure drugs	£1,058	£442	£616
Vascular complications	£48	£0	£48
Bleeding	£29	£21	£9
Stroke	£417	£122	£296
Hospitalisation	£6,515	£8,897	-£2,382
Reintervention	£2,573	£12,480	-£9,907
Heart transplant	£1,232	£1,694	-£462
Immunosuppressive drugs	£474	£723	-£249
Total cost	£45,257	£24,378	£20,879

The difference in costs is mostly driven by the cost of the procedure, which amounts to £32,910 in the base case scenario. However, MitraClip generates savings downstream by reducing the number of people undergoing a mitral valve reintervention, needing a heart transplant or having a hospitalisation episode for cardiac reasons. Overall, MitraClip strategy is more expensive than medical management with a differential cost equal to £26,505.

The results of the analysis of the base case scenario are presented in the following table.

Table 26: Base case cost-effectiveness results (probabilistic)

Year	MitraClip	Medical management	MitraClip minus Medical management
Mean costs	£45,257	£24,378	£20,879
Mean QALYs	2.91	2.22	0.691
Incremental cost per QALY gained	-	-	£30,175
Incremental net monetary benefit at £20,000 per QALY	-	-	-£7,041
Incremental net monetary benefit – at £30,000 per QALY	-	-	-£121
Probability cost-effective at £20,000 per QALY	3%	97%	-
Probability cost-effective at 30,000 per QALY	48%	52%	-

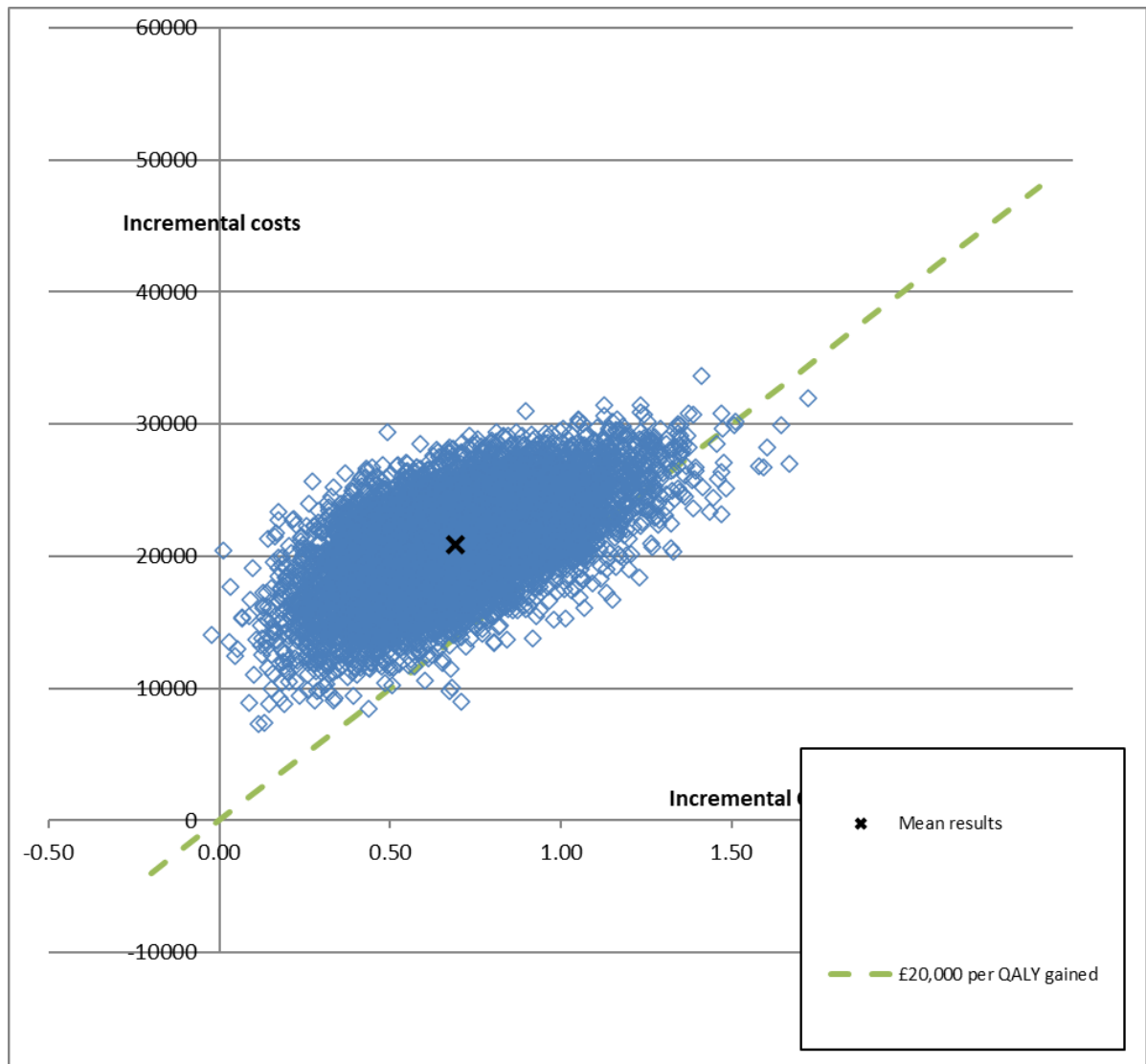
3.2 Sensitivity analyses

The sensitivity analyses showed that the results are sensitive to the cost of a MitraClip intervention, on the assumptions on utility and benefits, and on the distribution used to extrapolate mortality after the third year. The deterministic results of the sensitivity analysis are presented in table 27.

Table 27: One-way sensitivity analyses (deterministic)

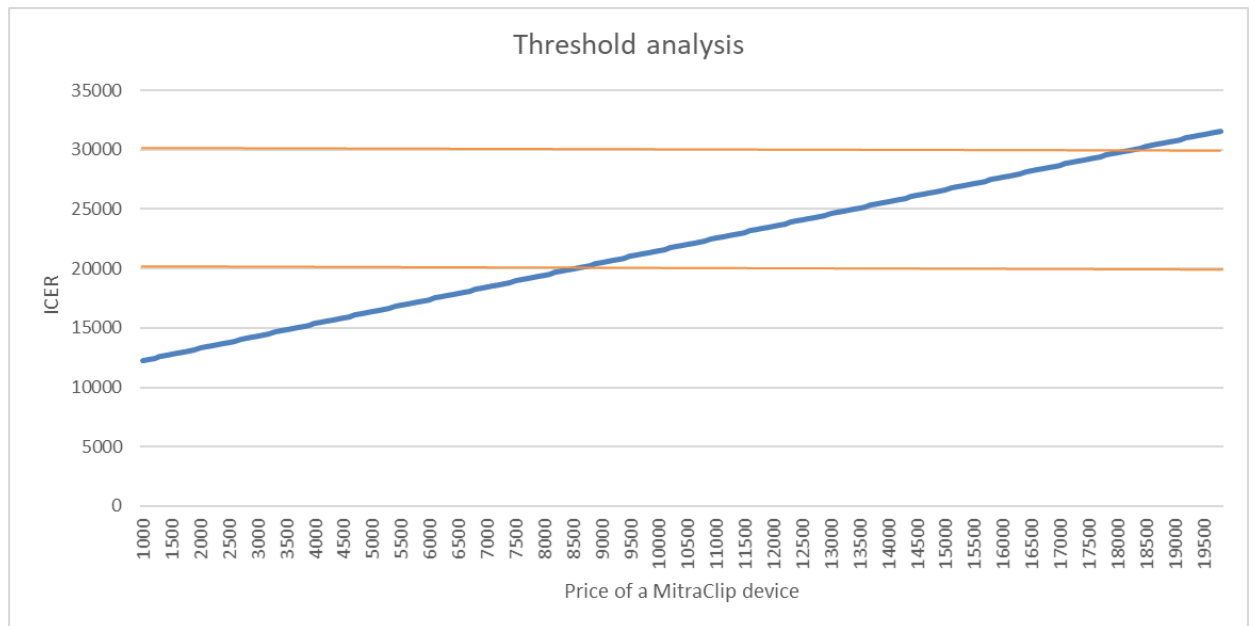
Scenario	Incremental costs	Incremental QALYs	Incremental cost per QALY gained
Deterministic base case	£21,738	0.69	£31,581
Probabilistic base case	£20,879	0.69	£30,175
Lower case MitraClip cost	£19,609	0.69	£28,488
Upper case MitraClip cost	£22,863	0.69	£33,215
No transplant	£21,738	0.7	£30,829
CtE data for reintervention	£18,276	0.56	£32,399
Utility benefits are persistent	£21,739	0.78	£27,990
Exponential distribution for mortality	£21,683	0.73	£29,480
Benefits last for the duration of the trial only	£21,078	0.51	£41,426
Exclude vascular complication	£21,705	0.69	£31,532

The scatterplot in figure 6 shows the results of the probabilistic analysis. All the points lie in the north-east quadrant and most of them are above the NICE threshold line of £20,000 per QALY gained suggesting that MitraClip is unlikely to be cost effective at a threshold of £20,000.

Figure 6: Probabilistic analysis scatterplot

3.3 Threshold analysis

A threshold analysis on the price of a MitraClip device was conducted to determine the threshold value of the price at which MitraClip becomes cost-effective at a threshold of £30,000 and £20,000. This was achieved through excel by varying the price of the device from £1,000 to £20,000 and looking at the corresponding incremental cost effectiveness ratio. The results are shown in figure 7.

Figure 7: Price threshold analysis

The results of the analysis demonstrate that MitraClip intervention becomes cost effective at a threshold of £30,000 when the price drops below £18,200 (equal to a price discount of 8%) and at a threshold of £20,000 when the price drops below £8,600 (equal to a discount of 56%). This analysis assumed that the initial price of a MitraClip device is £19,800 as reported in the NHS Supply Chain Catalogue.

4 Discussion

4.1 Summary of results

One original cost-utility analysis found that percutaneous edge-to-edge repair with MitraClip device in an inoperable population is not cost effective compared to medical management at a £30,000 per QALY threshold or £20,000 per QALY threshold (ICER: £30,175 per QALY gained).

4.2 Limitations and interpretation

This analysis demonstrated that mitral edge-to-edge repair with a MitraClip device has a cost per QALY gained slightly above the threshold of £30,000 in patients with severe secondary MR with a probability of 48% of being cost effective at a threshold of £30,000 per QALY and of 3% at a threshold of £20,000 per QALY.

This model is subject to some limitations. Firstly, mortality data were not available after the third years of the intervention and had to be extrapolated using a distribution function. The sensitivity analysis showed that the results are highly sensitive to the distribution assumed, with the exponential curve estimating a relatively high life expectancy and the Weibull curve giving a more conservative estimation. For the base case analysis, the committee decided to use the more conservative estimate of QALYs gained given by the Weibull curve.

This analysis is an intention-to-treat analysis and, therefore, some people in the medical management arm received MitraClip. This is in contrast with a similar economic analysis, which did not allow cross over between the arms²⁴. It is possible, therefore, that this analysis under-estimates the real QALYs gained associated with MitraClip but also under-estimates the incremental costs.

The committee acknowledged that the COAPT trial was performed under ideal conditions as patients were constantly monitored throughout the trial, guidance based medical management was ensured and MitraClip interventions were performed in high-volume centres by experienced surgeons. By contrast Mitra-FR seemed to show that when the intervention is done in centres that lack adequate expertise, the intervention may end up being less successful. It is anticipated that in the NHS, this would only be implemented in specialised centres.

4.3 Generalisability to other populations or settings

This analysis is based on inoperable patients who have severe secondary MR as reflected by the participants of COAPT trial. People with less than severe MR, such as the participants enrolled in the Mitra-FR trial, would benefit less and it is likely that the intervention would not be cost effective for these patients.

Other analyses based on a mixed population with primary and secondary MR found MitraClip to be cost effective^{12, 23} suggesting that in people where mitral regurgitation is the primary health issue, a MitraClip intervention may be highly effective in reducing the symptoms and increasing quality of life. It is expected therefore that the same analysis conducted on a mixed aetiology population or on patients with primary MR only would give even more favourable results.

Given the very high cost of the intervention, it is unlikely that percutaneous edge-to-edge repair would be cost effective compared with standard mitral valve surgery in patients who are eligible for surgery.

In the COAPT trial, the rate of heart transplant surgery was lower in the MitraClip arm than in the medical management arm. It is possible that for some people on the heart transplant list, MitraClip is a cost-effective alternative to heart transplant. However, the relative costs and benefits in this subpopulation are uncertain.

4.4 Comparisons with published studies

A UK cost-utility¹² analysis based on a population with mixed primary and secondary mitral regurgitation found MitraClip to be cost effective at £22,153 per QALY gained. The analysis was not based on a randomized trial but on a non-randomised registry with a control group obtained retrospectively. Furthermore, the population studied had mixed primary and secondary MR. A second Japanese study²³ based on a mixed primary and secondary MR population found an even lower incremental cost per QALY gained: £13,549. Likewise, this analysis was not based on a RCT but on a propensity score matching study. Overall, compared to this analysis, these two studies seem to suggest that MitraClip is even more cost effective in a population with mixed aetiology which is biologically reasonable as people with primary MR are expected to benefit more from a MitraClip intervention.

Two different economic evaluations based on the COAPT trial were identified in the literature^{4, 24}. The first took a US perspective⁴. Although the differences between the US health care system and the UK NHS in terms of costs do not allow to make a meaningful comparison, the health outcomes can be still compared. Over a lifetime horizon, the US analysis estimated an increase in life expectancy of 1.13 years and in QALYs of 0.82. This is in line with the results of the guideline analysis which found MitraClip to increase life expectancy by 1.18 years and QALYs by 0.69. A second analysis based on COAPT was conducted from the UK NHS perspective²⁴. This analysis reported an ICER of £30,057 per QALY gained which is very close to the incremental cost per QALY gained of £30,175 found in this model.

4.5 Conclusions

This economic evaluation demonstrated that mitral edge-to-edge repair with MitraClip device is slightly above £30,000 per QALY gained for treating severe mitral regurgitation in inoperable patients with secondary mitral regurgitation.

References

1. Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. *Value in Health*. 2010; 13(5):509-518
2. Atianzar K, Zhang M, Newhart Z, Gafoor S. Why did COAPT win While MITRA-FR failed? Defining the appropriate patient population for MitraClip. *Interventional Cardiology Review*. 2019; 14(1):45-47
3. Barendregt JJ. The effect size in uncertainty analysis. *Value in Health*. 2010; 13(4):388-391
4. Baron SJ, Wang K, Arnold SV, Magnussen K, Whisenant B, Brieke A et al. Cost-effectiveness of transcatheter mitral valve repair versus medical therapy in patients with heart failure and secondary mitral regurgitation: Results from the COAPT trial. *Circulation*. 2019; 140(23):1881–1891
5. Joint Formulary Committee. *British National Formulary (BNF)*. 77th ed. London. British Medical Association and The Royal Pharmaceutical Society of Great Britain,. 2019. Available from: <https://bnf.nice.org.uk/>
6. Kaier K, Gutmann A, Baumbach H, von Zur Mühlen C, Hehn P, Vach W et al. Quality of life among elderly patients undergoing transcatheter or surgical aortic valve replacement- a model-based longitudinal data analysis. *Health and Quality of Life Outcomes*. 2016; 14(1):109
7. Lacson E, Jr., Xu J, Lin S-F, Dean SG, Lazarus JM, Hakim RM. A comparison of SF-36 and SF-12 composite scores and subsequent hospitalization and mortality risks in long-term dialysis patients. *Clinical journal of the American Society of Nephrology : CJASN*. 2010; 5(2):252-260
8. Lawrence WF, Fleishman JA. Predicting EuroQoL EQ-5D preference scores from the SF-12 Health Survey in a nationally representative sample. *Medical Decision Making*. 2004; 24(2):160-169
9. Luengo-Fernandez R, Gray AM, Bull L, Welch S, Cuthbertson F, Rothwell PM et al. Quality of life after TIA and stroke: ten-year results of the Oxford Vascular Study. *Neurology*. 2013; 81(18):1588-1595
10. Mack M, Abraham WT, Lindenfeld J, Stone GW. COAPT - three-year outcomes from a randomized trial of transcatheter mitral valve leaflet approximation in patients with heart failure and secondary mitral regurgitation Cardiovascular Research Foundation, 2019. Available from: <https://www.acc.org/education-and-meetings/image-and-slide-gallery/~media/A47D36E64F6D44FCA03AE5B84065B0AC.pdf>
11. Mack MJ, Lindenfeld J, Abraham WT, Kar S, Lim DS, Mishell JM et al. 3-Year Outcomes of Transcatheter Mitral Valve Repair in Patients With Heart Failure. *Journal of the American College of Cardiology*. 2021; 77(8):1029-1040
12. Mealing S, Feldman T, Eaton J, Singh M, Scott DA. Everest II High Risk Study based UK cost-effectiveness analysis of MitraClip in patients with severe Mitral Regurgitation ineligible for conventional repair/replacement surgery. *Journal of Medical Economics*. 2013; 16(11):1317-1326
13. National Institute for Health and Care Excellence. *Developing NICE guidelines: the manual [updated 2020]*. London. National Institute for Health and Care Excellence,

2014. Available from:
<http://www.nice.org.uk/article/PMG20/chapter/1%20Introduction%20and%20overview>
14. National Institute for Health and Care Excellence. The NICE Charter. 2020. Available from: <https://www.nice.org.uk/about/who-we-are/our-charter> Last accessed: 10/03/2020.
 15. National Institute for Health and Care Excellence. The principles that guide the development of NICE guidance and standards. 2020. Available from: <https://www.nice.org.uk/about/who-we-are/our-principles> Last accessed: 10/03/2020.
 16. NCT. Cardiovascular outcomes assessment of the mitraclip percutaneous therapy for heart failure patients with functional mitral regurgitation (The COAPT Trial) (COAPT). 2019. Available from: <https://clinicaltrials.gov/ct2/show/study/NCT01626079> Last accessed: 03 November 2020.
 17. NHS Business Services Authority. Prescription cost analysis (PCA) data. 2018. Available from: <https://www.nhsbsa.nhs.uk/prescription-data/dispensing-data/prescription-cost-analysis-pca-data> Last accessed: 05/01/2021.
 18. NHS Improvement. National cost collection guidance 2019. 2019. Available from: https://improvement.nhs.uk/documents/4883/National_cost_collections_19.pdf Last accessed: 05/01/21.
 19. Obadia JF, Messika-Zeitoun D, Leurent G, Lung B, Bonnet G, Piriou N et al. Percutaneous repair or medical treatment for secondary mitral regurgitation. *New England Journal of Medicine*. 2018; 379(24):2297-2306
 20. Office for National Statistics. National life tables: UK. 2020. Available from: <https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/nationallifetablesunitedkingdomreferencetables> Last accessed: 05/01/2021.
 21. Patel A, Berdunov V, King D, Quayyum Z, Wittenberg R, Knapp M. Current, future & avoidable costs of stroke in the UK. London. Stroke Association, 2019. Available from: https://www.stroke.org.uk/sites/default/files/jn_1819.144a_current_future_avoidable_costs_of_stroke_0.pdf
 22. Romain G, Mariet AS, Jooste V, Duloquin G, Thomas Q, Durier J et al. Long-term relative survival after stroke: The Dijon Stroke Registry. *Neuroepidemiology*. 2020; 54(6):498-505
 23. Sakamaki H, Nakao K, Matsumoto T, Inoue S. Cost-effectiveness analysis of percutaneous mitral valve repair with the MitraClip delivery system for patients with mitral regurgitation in Japan. *Journal of Medical Economics*. 2019; 22(12):1312-1320
 24. Shore J, Russell J, Frankenstein L, Candolfi P, Green M. An analysis of the cost-effectiveness of transcatheter mitral valve repair for people with secondary mitral valve regurgitation in the UK. *Journal of Medical Economics*. 2020:1-20
 25. Stone GW, Lindenfeld J, Abraham WT, Kar S, Lim DS, Mishell JM et al. Transcatheter mitral-valve repair in patients with heart failure. *New England Journal of Medicine*. 2018; 379(24):2307-2318
 26. Suarez-Pierre A, Lui C, Zhou X, Giuliano K, Etchill E, Almaraz-Espinoza A et al. Long-term survival following heart transplantation: A population-based nested case-control study. *The Annals of Thoracic Surgery*. 2020:<https://doi.org/10.1016/j.athoracsur.2020.1005.1163>

27. The Royal College of Surgeons of England. UK Cardiothoracic Transplant Audit in patients who received a transplant between 1st July 1995 and 31st March 2012: Annual report: UKCTA Steering Group. 2012. Available from: <https://www.rcseng.ac.uk/library-and-publications/rcs-publications/docs/cardiothoracic-transplant/>
28. Willits I, Keltie K, Urwin S, Cole H, Craig J, de Belder M et al. Nice observational data unit (ODU) - Commissioning through Evaluation (CtE) Percutaneous mitral valve leaflet repair for mitral regurgitation (MitraClip): final linked data report. Newcastle and York External Assessment Centre (NY EAC), 2018. Available from: <https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2019/04/Percutaneous-mitral-valve-leaflet-repair-for-mitral-regurgitation-Commissioning-through-Evaluation-Report.pdf>
29. Xu XM, Vestesson E, Paley L, Desikan A, Wonderling D, Hoffman A et al. The economic burden of stroke care in England, Wales and Northern Ireland: Using a national stroke register to estimate and report patient-level health economic outcomes in stroke. *European Stroke Journal*. 2018; 3(1):82-91

Appendices

Appendix A: Drugs included in the model

Table 29: List of drugs included in the model

Drug category	Drug name
Ace inhibitors	ramipril
Ace inhibitors	captopril
Ace inhibitors	enalapril
Ace inhibitors	lisinopril
Ace inhibitors	quinapril
ARB	Candesartan
ARB	Valsartan
ARB	Losartan
Beta Blockers	Bisoprolol
Beta Blockers	Carvedilol
Beta Blockers	Nebivolol
Diuretics	Furosemide
Diuretics	Bumetanide
Diuretics	Torasemide
MRA	Eplerenone
MRA	Spirolactone
ARNI	Sacubitril with valsartan
Antiproliferative	Azathioprine
Antiproliferative	Mycophenolate mofetil
calcineurin inhibitors	Ciclosporin
calcineurin inhibitors	Ciclosporin
Corticosteroids	Prednisolone

