Healthcare Improvement Scotland | SHTG Advice on health technologies

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In response to an enquiry from the National Advisory Committee on Heart Disease

MitraClip® transcatheter mitral valve repair in patients with moderate-to-severe or severe mitral regurgitation who are not eligible for surgery

Advice for NHSScotland

MitraClip® transcatheter mitral valve repair should be considered for patients with moderate-to-severe (grade 3+) or severe (grade 4+) mitral regurgitation who are not eligible for open mitral valve repair surgery. Decisions should be made by a multi-disciplinary team with experience of performing this procedure, taking into account individual patients' level of risk, comorbidities, preferences and quality of life.

The annual procedure volume per centre for MitraClip® should be maximised to support optimal patient outcomes and ensure clinical experience with this complex procedure is achieved and retained.

NHSScotland is required to consider the Scottish Health Technologies Group (SHTG) advice.

What were we asked to look at?

The National Advisory Committee on Heart Disease asked us to look at a transcatheter cardiac intervention, the MitraClip® mitral valve repair system, in patients with moderate-to-severe or severe mitral regurgitation who are at high surgical risk or inoperable.

Why is this important?

Left untreated, moderate or severe mitral regurgitation can lead to heart failure, serious cardiac arrhythmias and death. The symptoms of chronic mitral regurgitation and associated heart failure confer a substantial physical, emotional and social burden on patients. Severe symptoms may prevent patients from performing everyday tasks and simple activities, such as climbing a set of stairs. Current treatments for severe mitral regurgitation include medical management and surgical repair or replacement of the mitral valve. However some patients are at such high surgical risk that they cannot undergo traditional surgical repair or replacement of the mitral valve. The MitraClip® System offers a transcatheter approach to repairing the mitral valve, thereby avoiding the risks associated with open heart surgery and cardiopulmonary bypass.

What was our approach?

We produced SHTG Advice based on an updated review* of published evidence on the clinical effectiveness, cost effectiveness and safety of MitraClip® transcatheter mitral valve repair in patients with moderate-to-severe or severe mitral regurgitation and high surgical risk. Information on our SHTG Advice product can be found here.

What next?

The National Services Division will use the SHTG Advice when considering the provision of MitraClip® transcatheter mitral valve repair in NHSScotland. The National Advisory Committee on Heart Disease will also consider this advice.

*The MitraClip System was previously assessed by SHTG in Evidence Note 58 (published 2016).

Key points from the evidence review

- Two randomised controlled trials (RCTs) compared MitraClip® plus medical therapy with medical therapy alone in patients with functional mitral regurgitation. These trials reported contrasting findings.
    - The COAPT trial reported statistically significant differences favouring the MitraClip® group for heart failure related hospitalisation (hazard ratio (HR) 0.53, 95% confidence interval (CI) 0.40 to 0.70, p<0.001), heart failure related mortality (HR 0.43, 95% CI 0.27 to 0.67, p<0.001), quality of life scores (mean difference (MD) 16.1, 95% CI 11.0 to 21.2, p<0.001) and distance on the 6 minute walk test (MD 57.9m, 95% CI 32.7m to 83.1m, p<0.001).
    - The MITRA-FR trial found no statistically significant differences in a composite of death from any cause and hospitalisation for heart failure at 12 months (odds ratio (OR) 1.16, 95% CI 0.73 to 1.84, p=0.53), all-cause mortality (HR 1.11, 95% CI 0.69 to 1.77) or hospitalisation for heart failure (HR 1.13, 95% CI 0.81 to 1.56).
    - The most common adverse events in these trials were failure of the device implantation procedure (4.2% in MITRA-FR) and unplanned mitral valve interventions (3.3% in COAPT).
- In a systematic review of six observational studies incorporating patients with functional mitral regurgitation compared with mainly historical comparator groups, MitraClip® was associated with significant reductions in all-cause mortality (OR 0.79, 95% CI 0.68 to 0.92) and hospitalisation for heart failure (OR 0.73, 95% CI 0.59 to 0.91) at a median follow-up of 1.1 years. Heterogeneity was high in these analyses.
- An English registry (n=199, 60% patients with functional mitral regurgitation and 40% with degenerative mitral regurgitation) reported in-hospital mortality of 5% (95% CI 2.4% to 9.0%), an in-hospital major complication rate of 8.2%, and 1-year mortality of 11.6% (95% CI 7.5% to 16.8%). This registry also reported significant improvements in health-related quality of life up to 12 months after MitraClip® implantation based on the EQ5D tool.
- A survey of a small convenience sample (n=20, unknown aetiology) of MitraClip® patients in NHS England indicated positive patient experiences, including perceived improvements in symptoms and quality of life.
- Two meta-analyses of single-arm observational studies comparing outcomes in patients with functional versus degenerative mitral regurgitation treated with MitraClip® concluded that outcomes were similar for patients with mitral regurgitation of either aetiology who received MitraClip®. Heterogeneity was high in these analyses.
- In patients with degenerative mitral regurgitation, single-arm observational studies reported reductions in mitral regurgitation severity (2 studies, n=169), approximately 24% mortality at 1 year follow-up (2 studies, n=3,079), improved quality of life (1 study, n=127) and reduced hospitalisation for heart failure (1 study, n=127).

- In the four primary studies incorporating patients with degenerative mitral regurgitation, the most common adverse events were major or life-threatening bleeding (3.9%), minor bleeding (5%), major bleeding (12.6%) and partial clip detachment (2.5%), respectively.
- Two retrospective studies reported that hospitals with an annual MitraClip® procedure volume of ≥4 or ≥10 were associated with significant reductions in a composite of in-hospital mortality and complications compared with hospitals performing fewer procedures per annum.
- The indicative cost for the MitraClip® System is £16,500 plus VAT, regardless of the number of clips required, and excluding other consumables. In NHS England the MitraClip® procedure was estimated to cost £32,560 (range £28,800 to £34,100) per patient, although there is currently no agreed tariff in Scotland.
- Three economic analyses based on observational data reported incremental cost effectiveness ratios (ICERs) that suggest MitraClip® is cost effective at commonly used willingness-to-pay thresholds (£20,000 to £30,000 per quality adjusted life year (QALY)). These analyses were not UK-based and may therefore not generalise to Scotland. *De novo* economic analyses are currently being planned in England.

SHTG Committee considerations

- The Committee discussed potential explanations for the contrasting results in the COAPT and MITRA-FR trials. Additional explanations proposed by the Committee and clinical experts in attendance at the meeting included differences in standard care in the USA (COAPT) and France (MITRA-FR) during the trials; varying baseline levels of cardiology team experience; and longer follow-up in the COAPT trial (24 months versus 12 months).
- The Committee discussed the importance of clearly indicating which mitral regurgitation aetiologies should be included in the advice. Consequently, evidence available on the use of MitraClip® in patients with degenerative mitral regurgitation should be considered alongside the new randomised evidence for functional mitral regurgitation.
- The Committee agreed that the lack of effective alternative treatments for patients with degenerative mitral regurgitation should be considered when formulating advice on MitraClip®. It was acknowledged that there was a lack of randomised studies of MitraClip® in this patient group.
- The current estimate of 10 MitraClip® procedures per year in Scotland was noted and estimates of future patient volume were discussed. It was agreed that population changes and increased access to this procedure may impact significantly on predicted patient numbers.

Contents

Definitions

Degenerative mitral regurgitation (DMR): primary mitral regurgitation due to structural incompetence of the mitral valve leaflets and supporting apparatus[1].

Functional mitral regurgitation (FMR): secondary mitral regurgitation resulting from geometrical distortion of the mitral valve supporting apparatus due to cardiomyopathy or coronary artery disease[1].

Literature search

A systematic search of the secondary literature was carried out between 15 and 23 January 2019 to identify systematic reviews, health technology assessments and other evidence-based reports. Medline, Medline in process, Embase and Web of Science databases were also searched for systematic reviews and meta-analyses.

The primary literature was systematically searched between 15 and 23 January 2019 using the following databases: Medline, Medline in process, Embase and Web of Science. Results were limited to English language randomised controlled trials (RCTs) published from 2015 onwards.

Key websites were searched for guidelines, policy documents, clinical summaries, economic studies and ongoing trials.

Concepts used in all searches included: Mitraclip, mitral valve, mitral regurgitation, mitral valve incompetence, transcatheter edge-to-edge repair. A full list of resources searched and terms used are available on request.

Introduction

Mitral regurgitation is characterised by the backward flow of blood from the left ventricle of the heart to the left atrium during the contraction phase of the cardiac cycle. Left untreated, moderate-to-severe mitral regurgitation can result in heart failure, serious cardiac arrhythmias and death[1].

Chronic mitral regurgitation can be classified into two groups: degenerative and functional. In functional mitral regurgitation the mitral valve leaflets are structurally intact and mitral regurgitation results from geometrical distortion of the mitral valve supporting apparatus as a consequence of left ventricular pathology[1]. Degenerative mitral regurgitation affects the structures of the mitral valve and their immediate supporting apparatus[1]. In degenerative mitral regurgitation the backflow of blood leads to the left ventricle becoming enlarged and weakened because of the additional workload required to maintain normal forward blood flow[2].

Symptoms of chronic mitral regurgitation and associated heart failure include palpitations, breathing difficulties, fatigue, lethargy and severe weight loss. These confer a substantial physical, emotional, and social burden on patients. Severe symptoms may prevent patients from performing everyday tasks and simple activities, such as getting out of bed. The inability to perform activities of daily living can lead to loss of independence, distress, and depression. Heart failure can impact upon all aspects of a patient's quality of life (QoL)[3-5].

Severity of mitral regurgitation is graded from mild to severe (numerically: mild 1+; severe 4+) and is usually determined by echocardiography[1]. Current therapeutic options for the treatment of severe chronic degenerative mitral regurgitation, depending on co-morbidities and whether heart failure is present, include medical management and surgical repair or replacement of the mitral valve[1]. Surgical repair, where feasible, is considered to be the gold standard treatment for severe chronic degenerative mitral regurgitation. There is less clarity on the most effective therapy for functional mitral regurgitation and uncertainty around the most appropriate surgical approach[6].

Research question

What is the clinical effectiveness, safety and cost effectiveness of the MitraClip® transcatheter mitral valve repair system in patients with moderate-to-severe or severe mitral regurgitation who are at high surgical risk or inoperable?

Health technology description

The MitraClip® System (Abbott) is a transcatheter mitral valve repair system for reconstruction of an incompetent mitral valve. The MitraClip® System consists of three major components: a guide catheter, a delivery system and a metal clip covered in polyester fabric[1]. Transoesophageal echocardiography and fluoroscopy are used to guide the implantation procedure, which is performed under general anaesthetic in a cardiac catheterisation laboratory. The steerable guide catheter is inserted into the femoral vein at the groin and threaded up to the right atrium of the heart. This use of venous access avoids the need for open heart surgery and cardiopulmonary bypass. The operator then creates a transseptal puncture to pass the catheter into the left atrium. The MitraClip® clip is passed along the guide catheter into the left atrium and through the mitral valve (into the left ventricle). The clip is then opened and gently withdrawn. If both mitral valve leaflets are captured, the clip is closed to fix the leaflets together. Implantation of the MitraClip® clip onto the valve leaflets forms a double orifice allowing greater closure and reduced leakage through the valve. Positioning of the clip is confirmed using transoesophageal echocardiography and the device can be repositioned or additional clips added if required.

The indicative cost of the MitraClip® System is £16,500 plus VAT (Dr D Northridge, Consultant Cardiologist, NHS Lothian. Personal communication, 19 Feb 2019). This is the cost of the system, regardless of the number of clips required but does not include any other consumables or staff and catheterisation laboratory time.

In 2010 there were 83 MitraClip® procedures for mitral regurgitation across nine units in NHS England[7]. This equates to approximately 9 procedures per annum per unit, with only one unit performing more than 20 procedures in one year. Five MitraClip® procedures were performed in Edinburgh in 2018 (Dr D Northridge, Consultant Cardiologist, NHS Lothian. Personal communication, 26 June 2019) with a further 12 procedures performed at the Golden Jubilee National Hospital in Glasgow over the past 3 years (Prof. K Oldroyd, Consultant Interventional Cardiologist, NHS Greater Glasgow and Clyde. Personal communication, 06 July 2019).

Epidemiology

In Europe mitral regurgitation is the second most common type of heart valve disease requiring surgery, after aortic stenosis[2]. A European prospective cohort study reported that, in a subgroup of echocardiography patients who had moderate or severe mitral regurgitation (n=3,309), 55.1% of had degenerative mitral regurgitation, 30.8% had functional mitral regurgitation, and 14.1% had mitral regurgitation of mixed aetiology[8].

No Scottish data on the size of the target population (patients with mitral regurgitation) were identified. A prospective population-based study in the UK measured prevalence of valvular heart disease (any heart valve) in 79,043 patients referred to echocardiography for suspected heart failure[9]. Mitral regurgitation (any severity) was detected in 12.5% of patients; moderate mitral regurgitation in 2,117 (2.68%) patients; and severe mitral regurgitation in 355 (0.45%) patients.

Table 1 presents estimated patient numbers in Scotland calculated by applying the findings of the population-based study by Marciniak *et al* (2017)[9] to heart failure prevalence data from the Quality Outcomes Framework (QOF) in Scotland 2015-16[10]. These results should be interpreted with caution as patients in the population-based study were referred to echocardiography due to suspected heart failure, whereas patients on the QOF heart failure register had a confirmed diagnosis. Consequently, the estimated prevalence of mitral regurgitation in table 1 may be higher or lower than actual prevalence in the Scottish population.

Table 1: estimated prevalence of heart failure and mitral regurgitation in Scotland[9, 10]

	Estimated n patients
On heart failure register	47,769
Any mitral regurgitation (12.5%)	5,971
Moderate mitral regurgitation (2.68%)	1,280
Severe mitral regurgitation (0.45%)	215

The prevalence of mitral regurgitation increases with age: clinically meaningful mitral regurgitation (moderate or greater in severity) is estimated in population-based studies to be less than 1% in people aged ≤54 years and 9.3% in people aged ≥75 years[11].

Guidelines

Three clinical guidelines were identified that contained recommendations on transcatheter mitral valve repair in patients with mitral regurgitation (table 2)[12-14]. The NICE Interventional Procedure Guidance (IPG) does not distinguish between functional and degenerative mitral regurgitation within the recommendations. The American guidance states that transcatheter mitral valve repair for functional mitral regurgitation is not approved for clinical use in the USA and that RCTs are needed to inform further recommendations in this patient group[14]. Both the American and European

guidelines were issued prior to publication of two RCTs evaluating MitraClip® in patients with functional mitral regurgitation[15, 16].

Table 2: clinical guideline recommendations relating to transcatheter mitral valve repair in patients with mitral regurgitation

Guideline	Recommendations
NICE IPG (2019)[13]	Current evidence on the safety and efficacy of transcatheter mitral valve leaflet repair [MitraClip®] for mitral regurgitation is adequate to support the use of this procedure in patients with contraindications to open surgery. Patients should be selected by a multidisciplinary structural heart team and treated in specialised centres with access to both cardiac and vascular surgical support. Transcatheter mitral valve repair should only be done by clinicians with specialist training and supervised by an experienced mentor for at least the first 20 procedures.
European Society of Cardiology (2017)[12]	When revascularisation is not indicated and surgical risk is not low, a transcatheter edge-to-edge procedure [MitraClip®] may be considered in patients with severe functional mitral regurgitation and left ventricular ejection fraction (LVEF) >30% who remain symptomatic despite optimal medical management (including cardiac resynchronisation therapy (CRT) if indicated) and who have a suitable valve morphology on echocardiography. *Evidence level C, class IIb[a].* In patients with severe functional mitral regurgitation and LVEF <30% who remain symptomatic despite optimal medical management (including CRT if indicated) and who have no option for revascularisation, the heart team may consider a transcatheter edge-to-edge procedure [MitraClip®] or valve surgery after careful evaluation for a ventricular assist device or heart transplant according to individual patient characteristics. *Evidence level C, class IIb*. A transcatheter edge-to-edge procedure [MitraClip®] may be considered in patients with symptomatic severe degenerative mitral regurgitation who fulfil the echocardiographic criteria of eligibility and are judged inoperable or at high surgical risk by the heart team. *Evidence level C, class IIb.*
American College of Cardiology (2017)[14]	Transcatheter mitral valve repair [MitraClip®] may be considered for severely symptomatic patients (New York Heart Association (NYHA) class III to IV) with chronic severe degenerative mitral regurgitation (stage D) who have favourable anatomy for the repair procedure and a reasonable life

[a] Evidence level C = consensus of opinion of experts and/or small studies, retrospective studies, registries. Class IIb = conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure; usefulness/efficacy is less well established by evidence/opinion.

	expectancy but who have a prohibitive surgical risk because of severe comorbidities and remain severely symptomatic despite optimal guideline-directed management and therapy for heart failure. *Evidence level B, class/strength of recommendation IIb*[b]*.*

Evidence Note 58

Published in February 2016, Evidence Note 58 (EN58) addressed the same research question as is being considered in the current review[17]. No evidence was identified that directly compared MitraClip® with medical therapy in patients with moderate-to-severe or severe mitral regurgitation. All of the clinical effectiveness evidence came from studies that included patients with mitral regurgitation of either aetiology.

A systematic review of non-comparative prospective observational studies suggested that MitraClip® was a feasible option for patients with mitral regurgitation who were considered high surgical risk. A small, methodologically limited, comparative study (EVEREST II HRS) reported a 1-year survival benefit for MitraClip® in 78 patients with mitral regurgitation and high surgical risk compared with a cohort of 36 patients receiving standard medical therapy. The comparator group in this study was identified retrospectively after the outcomes of the MitraClip® group were known and included patients ineligible for the prospective part of the study; therefore this study had high risk of bias. Uncontrolled observational studies of acceptable methodological quality provided evidence that MitraClip® was associated with in-hospital mortality of around 4% (two studies), 30-day mortality ranging from 1.75% to 5.6% (four studies) and 1-year mortality ranging from 10% to 22.8% (three studies).

The cost effectiveness of MitraClip® compared with medical therapy was uncertain. One UK model based on the EVEREST II HRS study demonstrated MitraClip® was cost effective from a 5 year time horizon onwards. The robustness of the results was compromised by the absence of randomised comparative data on the survival benefits, small patient numbers and high risk of bias in the study.

EN58 concluded that use of MitraClip® for the treatment of moderate-to-severe or severe mitral regurgitation in patients at high surgical risk or inoperable should only be considered on an individual patient basis and in the context of appropriate data collection.

Clinical effectiveness

Randomised controlled trials (RCTs) in functional mitral regurgitation

Two RCTs that were identified as ongoing studies in EN58 have now been published: COAPT (n=612) and MITRA-FR (n=304)[15, 16]. Both studies were multicentre, randomised, parallel group, open-label trials that compared transcatheter mitral valve repair (MitraClip®) plus medical therapy with medical therapy alone (control) in patients with functional mitral regurgitation. Allocation of patients to

[b] Evidence level B = moderate quality evidence from one or more RCTs, or meta-analyses of moderate quality RCTs, or moderate quality evidence from one or more well-designed, well-executed non-randomised studies, observational studies, or registries, or meta-analyses of such studies. Class IIb = weak, benefit ≥ risk.

intervention and control groups in each trial used 1:1 stratified, block randomisation with centralised computer-based allocation sequences that were only revealed to study investigators after patients had been verified as eligible for enrolment. Both studies were open-label due to the obvious differences between treatments. Intention-to-treat analyses were reported in the main results for both RCTs, with per-protocol analyses available in online supplementary materials. The trials both reported power calculations for the primary outcome and recruited sufficient patient numbers at baseline to achieve 80% power for their primary efficacy outcome. As shown in table 3, inclusion and exclusion criteria in the two trials were similar in many respects. Both studies received at least partial funding from the MitraClip® manufacturer (Abbott). In the case of the COAPT trial the manufacturer was involved in the trial design, management and data analysis.

Table 3: selected inclusion and exclusion criteria from the COAPT and MITRA-FR trials[15, 16]

	COAPT	MITRA-FR
Inclusion criteria	LVEF 20-50% Grade 3+ or 4+ functional mitral regurgitation confirmed by echocardiography Symptomatic despite maximum-dose medical therapy and cardiac resynchronisation (if appropriate) NYHA class II, III or ambulatory IV At least one hospitalisation for heart failure in past 12 months Ischaemic or non-ischaemic cardiomyopathy Not eligible for mitral valve surgery Left ventricular end systolic dimension ≤70mm	LVEF 15-40% Severe functional mitral regurgitation (based on European guideline criteria) Optimal standard of care therapy for heart failure Chronic heart failure symptoms (NYHA class II, III, IV) Minimum of one hospitalisation for heart failure in past 12 months Regurgitant volume >30ml per beat Effective regurgitant orifice area (EROA) >0.2cm^2 as assessed by echocardiography
Exclusion criteria	Cardiovascular surgery in prior 30 days Anatomy that may preclude MitraClip® implantation Life expectancy <12 months Prior surgery on mitral valve Mitral valve orifice area <4.0cm^2 Contraindication or high risk for transoesophageal echocardiography	Cardiovascular surgery in past 3 months Deemed not suitable for MitraClip® by expert proctor from Abbott Life expectancy <12 months Previous mitral valve repair Candidates for mitral valve surgery

Baseline characteristics of patients included in the COAPT and MITRA-FR studies are described in table 4. The COAPT trial recruited patients with severe (grade 4+) or moderate-to-severe (grade 3+)

functional mitral regurgitation. The COAPT trial limited patient enrolment to those who remained symptomatic despite receiving the maximum recommended dose of medical therapy and cardiac resynchronisation therapy if appropriate. In the MITRA-FR trial patients were recruited if they had severe (grade 4+) functional mitral regurgitation. However, the MITRA-FR trial supplementary data suggest that approximately 40% of patients in the MitraClip® group had moderate-to-severe (grade 3+) mitral regurgitation at baseline. Surgical risk for patients enrolled in the two trials was estimated using different validated scores: the Society of Thoracic Surgeons (STS) Predicted Risk of Mortality Score and the Logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE). In both studies the mean or median risk score indicated that participants were at moderate-to-high surgical risk. The authors of the COAPT study reported no statistically significant differences in baseline patient characteristics between the treatment and control group. In the MITRA-FR trial, prior myocardial infarction was more common in the MitraClip® group at baseline.

Table 4: baseline characteristics of patients enrolled in the COAPT and MITRA-FR trials[15, 16]

	COAPT		MITRA-FR	
	MitraClip®	Control	MitraClip®	Control
N	302	312	152	152
Age (years) Mean ± SD	71.7±11.8	72.8±10.5	70.1±10.1	70.6±9.9
Male (%)	66.6	61.5	78.9	70.4
Moderate-to-severe mitral regurgitation, grade 3+ (%)	49.0	55.3	–	–
Severe mitral regurgitation, grade 4+ (%)	51.0	44.7	–	–
NYHA class (%)	I = 0.3 II = 42.7 III = 51.0 IVa = 6.0	I = 0 II = 35.4 III = 54.0 IVa = 10.6	II = 36.8 III = 53.9 IV = 9.2	II = 28.9 III = 63.2 IV = 7.9
High risk of surgery-related complications or death (%)	68.6%	69.9%	–	–
STS risk score (%) Mean ± SD	7.8±5.5	8.5±6.2	–	–
Median EuroSCORE II risk score (%)	–	–	6.6 (IQR 3.5 to 11.9)	5.9 (IQR 3.4 to 10.4)

IQR=inter-quartile range; SD = standard deviation

The largest RCT, COAPT (n=612), was conducted across 78 centres in the USA and Canada[16]. The primary efficacy outcome in this trial was all hospitalisations for heart failure within 24 months follow-up. By 12 months follow-up, 11 patients (3.6%) had been lost from the MitraClip® group and 21 patients (6.7%) from the control group. Although these levels of loss to follow-up are low, it is of slight concern that almost twice as many withdrew or were otherwise lost to follow-up in the control group compared with the MitraClip® group. The median length of follow-up was also shorter in the control group compared with the intervention group: 16.5 months (inter-quartile range (IQR) 10.1 to 24.0) versus 22.7 months (IQR 12.4 to 24.0).

Results from the COAPT trial are presented in table 5. The MitraClip® procedure was successful in 95% of patients randomised to the intervention group. Mitral valve repair with MitraClip® plus medical therapy was associated with statistically significant reductions in the risk of all-cause mortality, heart failure related mortality and hospitalisation for heart failure compared with the control group at 24 months follow-up. Improvements in quality of life scores and distance on the 6 minute walk test were significantly greater following treatment with MitraClip® plus medical therapy compared with medical therapy alone at 12 months follow-up. The trial authors estimated that the number needed to treat in order to prevent one hospitalisation for heart failure was 3.1 (95% confidence interval (CI) 1.9 to 7.9) patients. To save one life at 24 months follow-up the number needed to treat was 5.9 (95% CI 3.9 to 11.7).

The MITRA-FR trial (n=304) was conducted across 37 centres in France[15]. The primary outcome in this trial was a composite of all-cause mortality and hospitalisation for heart failure at 12 months follow-up. Outcomes were assessed by an adjudication committee that was blinded to treatment allocation. No statistical adjustments were made for multiple testing due to the large number of patients lost to follow-up (approximately 19%). Many secondary outcomes are not reported in the published study due to this substantial loss to follow-up which the study authors felt increased the risk of selection bias. Results from the MITRA-FR study are reported in table 5. The device was successfully implanted in 90.7% of patients randomised to the MitraClip® group. Unlike the COAPT trial, there were no statistically significant differences for any of the outcomes reported in the MITRA-FR RCT at 12 months follow-up.

A number of potential explanations are offered by the MITRA-FR study authors for the lack of statistically significant results in this trial:

- Underlying cardiomyopathy may be the principal driver of patient outcomes in the study sample.
- Mitral regurgitation was not completely corrected for many patients in the MitraClip® arm of the trial.
- The severity of mitral regurgitation at baseline may indicate that the intervention was applied too late in the disease progression.

Table 5: clinical effectiveness results from the COAPT and MITRA-FR trials[15, 16]

	COAPT			MITRA-FR*		
	MitraClip® (n=302)	Control (n=312)	Relative findings	MitraClip® (n=152)	Control (n=152)	Relative findings
Successful device implantation	287	–	95.0%	138	–	90.8%
All-cause mortality at 12 months	57 (19.1%)	70 (23.2%)	HR 0.81 (95% CI 0.57 to 1.15) p<0.001 for non-inferiority	37 (24.3%)	34 (22.4%)	HR 1.11 (95% CI 0.69 to 1.77)
All-cause mortality within 24 months	80 (29.1%)	121 (46.1%)	HR 0.62 (95% CI 0.46 to 0.82) p<0.001	–	–	–
Heart failure related mortality within 24 months	28 (12.0%)	61 (25.9%)	HR 0.43 (95% CI 0.27 to 0.67) p<0.001	–	–	–
All hospitalisations for heart failure within 12 months	–	–	–	74 (48.7%)	72 (47.4%)	HR 1.13 (95% CI 0.81 to 1.56)
All hospitalisations for heart failure within 24 months	160 events (35.8%)	283 events (67.9%)	HR 0.53 (95% CI 0.40 to 0.70) p<0.001	–	–	–
Change in Kansas City Cardiomyopathy Questionnaire (KCCQ) quality of	12.5±1.8 points	−3.6±1.9 points	MD 16.1 (95% CI 11.0 to 21.2) p<0.001	–	–	–

life score from baseline to 12 months× Mean ± SE						
EQ5D global quality of life score at baseline versus 12 months×	–	–	–	–	–	MitraClip®: 51.5±19.2 vs. 60.8±20.3 Control: 53.2±16.6 vs. 58.6±18.2
Change in distance on 6 minute walk test from baseline to 12 months (metres)	Mean ± SE −2.2±9.1	Mean ± SE −60.2±9.0	MD 57.9 (95% CI 32.7 to 83.1) p<0.001	–	–	MitraClip®: Median 25 (IQR -40 to 71) Control: Median 19 (IQR -27 to 75)
Composite of death from any cause or hospitalisation for heart failure at 12 months	–	–	–	83 (54.6%)	78 (51.3%)	OR 1.16 (95% CI 0.73 to 1.84) p=0.53
Mitral regurgitation grade ≤2+ at 12 months	199/210	82/175	MitraClip® 94.8% Control 46.9%	–	–	–

HR = hazard ratio; MD = mean difference; SD = standard deviation; IQR = inter-quartile range; SE = standard error; OR = odds ratio

*No p-values were reported for any of the secondary outcomes in MITRA-FR as no statistical adjustment had been made for multiple testing.

×Higher scores indicate better quality of life

Reconciling results from RCTs on functional regurgitation

As noted in the previous section, the authors of the MITRA-FR trial have suggested a number of possible explanations for the lack of statistically significant results in their study[15]. Other potential explanations for the differing results reported in the COAPT and MITRA-FR trials include variation in patient selection, differences in study design and guideline definitions of severe functional mitral regurgitation in American versus European guidelines.

RCT participants

Although both RCTs recruited patients with functional mitral regurgitation, it is possible that there were underlying differences in the patients recruited into each trial. For example, the COAPT trial enrolled patients with severe or moderate-to-severe mitral regurgitation that had failed to resolve despite maximal dose medical therapy. Selecting this patient group may have resulted in patients in the COAPT trial having, on average, more severe mitral regurgitation at baseline. This was not a restriction on patient enrolment in the MITRA-FR trial. Participants in the COAPT trial also had a higher mean effective regurgitant orifice area (EROA) at baseline which is a clinically significant indicator of regurgitation severity (table 6). Finally, the COAPT trial only included NYHA class IV patients if they remained ambulatory, while the MITRA-FR trial does not appear to have limited class IV patients by ambulatory status.

Table 6: patient cardiac function data from the COAPT and MITRA-FR trials[15, 16]

	COAPT		MITRA-FR	
	MitraClip®	Control	MitraClip®	Control
EROA (cm^2) Mean ± SD	0.4±0.2	0.4±0.2	0.3±0.1	0.3±0.1
LVEF (%) Mean ± SD	31.3±9.1	31.3±9.6	33.3±6.5	32.9±6.7
Left ventricular end diastolic volume (LVEDV) (ml) Mean ± SD	135.5±56.1	191.0±72.9	136.2±37.4	134.5±33.1

SD = standard deviation

A further explanation for the discrepant trial findings is offered in a paper published by one of the authors of the COAPT trial[18]. The authors of the paper posit that the effectiveness of MitraClip® for treating functional mitral regurgitation is determined by whether the degree of mitral regurgitation is proportionate or disproportionate to the degree of left ventricular enlargement in the individual patient. If this theory is correct then the COAPT and MITRA-FR trials may have enrolled very different patients, even though both were recruiting patients with functional mitral regurgitation. Based on cardiac function data reported in the COAPT and MITRA-FR trials (table 6) the COAPT trial may have enrolled patients with functional mitral regurgitation that was disproportionate to the left ventricular enlargement present (left ventricular end diastolic volume (LVEDV), while the MITRA-FR study enrolled patients with functional mitral regurgitation proportionate to left ventricular enlargement:

- In the COAPT study 14% of patients had an EROA <0.3cm^2 and 41% had an EROA ≥0.4cm^2. Patients with substantial left ventricular enlargement (LVEDV >70mm) were excluded from the trial.
- In the MITRA-FR trial, 52% of patients had an EROA <0.3cm^2 and 70% of participants had substantial left ventricular enlargement (LVEDV >65mm).

Patients with proportionate functional mitral regurgitation may respond well to medical therapy targeted at left ventricular changes. If this is the case, the COAPT trial may have excluded patients with proportionate mitral regurgitation due to the criterion that participants should remain symptomatic despite maximal medical therapy. At the same time, if the MITRA-FR trial enrolled patients with proportionate functional mitral regurgitation, the mitral regurgitation in this group may have been driven by left ventricle dilatation rather than mitral valve deformities and therefore the MitraClip® System would not be as effective. The paper authors conclude that patients with proportionate mitral regurgitation could respond well to medical therapy, while patients with disproportionate mitral regurgitation may respond better to MitraClip® valve repair.

Study design differences

Although many of the inclusion and exclusion criteria were similar in the COAPT and MITRA-FR trials, there were some differences (table 3). Most of these differences arise from criteria only applied in one trial, for example left ventricular end systolic dimension, mitral valve orifice area and regurgitant volume. One exclusion criterion used in both trials, but where rates differ between them, is the time since prior cardiovascular surgery (30 days versus 3 months).

A further potential difference, which is difficult to measure, involves the 'standard medical therapy' given to participants in each trial. Specific details of the drugs and doses used in medical therapy for trial participants is not described in the studies. Supplementary material for the trials indicates many similarities in medical therapy regimens, as well as differences that may have been clinically relevant.

Differences in standard practice for treating functional mitral regurgitation between countries in which the COAPT and MITRA-FR trials were conducted may also account for the contrasting results. In the USA, MitraClip® had only been approved for use in patients with degenerative mitral regurgitation and would not have been available as standard care for patients with functional mitral regurgitation. However, in Europe MitraClip® is more commonly offered to patients with functional mitral regurgitation.

Two other differences relating to study design are the length of follow-up and the level of experience required for cardiologists participating in the trials. As noted previously, the MITRA-FR trial measured outcomes after 12 months follow-up, whereas COAPT assessed primary outcomes at 24 months follow-up. As can be seen in table 5, all-cause mortality results only became statistically significant at 24 months follow-up and may not therefore have been detectable at 12 months follow-up in the MITRA-FR trial. The level of prior experience for cardiologists performing the MitraClip® procedures in the two trials also differed. In COAPT, cardiologists had to have performed at least 100 previous cardiac procedures and have experience with transseptal puncture. The MITRA-FR trial cardiologists required cardiology surgical experience (volume unspecified) and to have performed a minimum of 5 MitraClip® procedures prior to the study. This could indicate that cardiologists involved in the two RCTs had different levels of experience and therefore the learning curve may have affected trial results.

Guideline definitions

As noted in the Guidelines section, the current European and American guidelines on treatment of mitral regurgitation provide different recommendations on the use of MitraClip®[12, 14]. In the most recent iterations of these guidelines, the definition of severe functional mitral regurgitation is also different and could influence patient selection for trials. However, the previous iteration of these two guidelines, which were in circulation during recruitment to the COAPT and MITRA-FR trials, had very similar definitions of severe mitral regurgitation and therefore this is unlikely to explain the discrepant findings[2, 6].

Systematic reviews of observational studies in functional mitral regurgitation

In addition to the COAPT and MITRA-FR trials, four meta-analyses were identified that incorporated observational studies on the use of MitraClip® in patients with functional mitral regurgitation[19-22]. Three of these meta-analyses included only single-arm studies and therefore do not add to the evidence base beyond the findings from the comparative evidence available at this time[19, 20, 22]. The fourth meta-analysis incorporated observational studies that had a comparator arm of patients who received medical therapy alone[21]. The six studies in this analysis mainly used retrospective or historical cohorts to form the comparator arm (one study had a concurrent prospective comparator arm). Key patient characteristics and results from this meta-analysis are reported in table 7. These results appear to be consistent with findings from the COAPT trial rather than the MITRA-FR trial.

Table 7: baseline patient characteristics and results from a study-level meta-analysis of six comparative observational studies[21]

	Findings	p-value	I^2
Patient characteristics			
N	MitraClip® = 833 Medical therapy = 1,288	–	–
Median age (years)	71 (IQR 65 to 82)	–	–
Male (%)	78 (IQR 72 to 81)	–	–
Median STS risk score (%)	11 (IQR 8 to 12)	–	–
Median EuroSCORE risk score (%)	21 (IQR 18 to 23)	–	–
Patients with functional mitral regurgitation (%)	93 (IQR 91 to 97)	–	–
NYHA class III or IV (%)	95 (IQR 90 to 97)	–	–
Median LVEF (%)	24 (IQR 23 to 36)	–	–
Results			
Mitral regurgitation grade 1+ or 2+ at discharge (%)	median 80 (IQR 78 to 82)	–	–

Median follow-up (years)	1.1 (IQR 1.1 to 1.4)	–	–
All-cause mortality at median follow-up	OR 0.79 (95% CI 0.68 to 0.92)	0.002	96%
Hospitalisations for heart failure at median follow-up	OR 0.73 (95% CI 0.59 to 0.91)	0.005	89%

Degenerative versus functional mitral regurgitation

Two systematic reviews with meta-analyses compared outcomes following MitraClip® implantation in patients with functional mitral regurgitation versus MitraClip® in patients with degenerative mitral regurgitation[23, 24]. These reviews were based on observational studies that did not have comparator groups, but reported outcomes separately for each mitral regurgitation aetiology. Heterogeneity was high in analyses in some analyses (table 8). Both reviews concluded that outcomes at 12 months follow-up were similar for patients with functional and degenerative mitral regurgitation treated with MitraClip®. However, in one review, patients with functional mitral regurgitation were significantly more likely to have a re-intervention procedure or be hospitalised for heart failure within 12 months follow-up compared with patients with degenerative mitral regurgitation[23].

Table 8: results from two meta-analyses comparing outcomes following MitraClip® in patients with different mitral valve aetiology

	Chiarito (2018)[23]		Liu (2018)[24]	
	Degenerative	Functional	Degenerative	Functional
N patients	833	1,782	758	1,593
N studies	9		13	
Age (years) Mean ± SD	78.1±10	73.1±10	77±11	73±10
Male (%)	57	66	55	69
Mean EuroSCORE (%) ± SD	–	–	16±15	22±17
Regurgitation grade ≥3 at baseline (%)	95	89	99	99
Procedural success (%)	94	95	91.2	95.2
Outcomes at 1 year follow-up (functional versus degenerative mitral regurgitation)				
Regurgitation grade ≤2	RR 0.91 95% CI 0.76 to 1.09 p=0.30, I^2=80%		RR 0.92 95% CI 0.84 to 1.02 p=0.11, I^2=32%	
Re-intervention	RR 0.60		–	–

	95% CI 0.38 to 0.97 p=0.04, I^2=33%		
All-cause mortality	RR 1.26 95% CI 0.90 to 1.77 p=0.18, I^2=55%	RR 0.86 95% CI 0.67 to 1.12 p=0.27, I^2=0%	
Re-hospitalisation for heart failure	RR 1.74 95% CI 1.05 to 2.85 p=0.03, I^2=46%	–	–

RR = relative risk/risk ratio; SD = standard deviation

Degenerative mitral regurgitation

No new RCTs have been published since EN58 that evaluate the use of MitraClip® in patients with degenerative mitral regurgitation who are at high surgical risk. No systematic reviews were identified that incorporated observational studies limited to degenerative mitral regurgitation populations, therefore a decision was made to extract data (on degenerative mitral regurgitation patients) from relevant primary studies included in the recent NHS England and NICE IPG evidence reviews[13, 25].

Four single-arm studies where patients with degenerative mitral regurgitation made up ≥75% of the study sample were extracted from the NHS England and NICE reviews[26-29]. One study retrospectively analysed data from the TVT registry, two studies were retrospective cohort studies and one study was a *post hoc* analysis of patients within the EVEREST II HRS study and the REALISM continued access registry. The EVEREST II HRS study was subject to the same high risk of bias noted in EN58. In the TVT registry study, retrospective database linkage limited the analysis to routinely collected data. There was no reporting of loss to follow-up or central adjudication of outcomes in this study. In the small, single-centre cohort study by Geis *et al* (2018) participants all had degenerative mitral regurgitation due to chordal rupture, which may mean results do not generalise to the wider degenerative mitral regurgitation population. This study was described in the NHS England review as having poor methodology and reporting.

Patients in these studies had a mean age of approximately 80 years, were at high surgical risk, and had grade 3+ or 4+ degenerative mitral regurgitation. Two studies reported change in mitral regurgitation severity as their primary clinical outcome (table 9)[26, 29]. In both studies, severity of mitral regurgitation was significantly reduced at 1-year follow-up compared with baseline. The two studies that assessing mortality both reported approximately 24% mortality at 1 year follow-up[27, 28]. In the TVT registry this mortality rate was compared with 31% mortality in patients with functional mitral regurgitation at 1 year follow-up[28]. The *post hoc* analysis considered health related quality of life (HRQoL) and rehospitalisation for heart failure as outcomes of interest. Quality of life significantly improved and hospitalisation for heart failure declined by 1 year follow-up.

Table 9: patient characteristics and results from four primary studies recruiting patients with degenerative mitral regurgitation

Study	Patient characteristics	Results
TVT registry (2017)[28] Retrospective data analysis 1 year follow-up	N=2,952 Mitral regurgitation: 85.9% degenerative, 8.6% functional, 8.9% mixed Median age 82 years (IQR 74 to 86) 55.8% male Symptomatic grade 3+ (16.6%) or 4+ (76.4%) mitral regurgitation Prohibitive surgical risk: median STS score for MitraClip® 6.1 (IQR 3.7 to 9.9)	<u>1 year follow-up</u> Degenerative mitral regurgitation: Mortality 24.7% Readmission for heart failure 20.5% Combined outcomes 35.7% Functional mitral regurgitation: Mortality 31.2% Readmission for heart failure 32.6% Combined outcomes 49.0% Median length of hospital stay = 2.0 days (IQR 1.0 to 5.0) <u>Adverse events</u> Cardiac perforation 1.0%; transseptal complications 0.9%; major/life-threatening bleeding 3.9%; device embolisation 0.1%; single leaflet device detachment 1.5%; conversion to open heart surgery 0.1%
Estevez-Loureiro (2013)[26] Retrospective cohort 30 days follow-up	N=79 All had degenerative mitral regurgitation Mean (±SD) age 79.2±7.9 years 58.2% male Mean (±SD) EuroSCORE 14.3±10.3 92.4% had grade 3+ or 4+ mitral regurgitation	% patients with grade 3+ or 4+ regurgitation: Baseline 92.4% 1 month follow-up 3.8% <u>Adverse events</u> All complications = 12.6% Peri-procedure adverse events: Partial clip detachment 2.5%; cardiac tamponade 1.2%; mitral valve surgery 1.2%; death 1.2%
Geis (2018)[29] Retrospective cohort	N=90 All had degenerative mitral regurgitation	Mitral regurgitation grade (mean ±SD): Baseline 3.5±0.2 1-year follow-up 1.2±0.3 p<0.001

Single-centre 1 year follow-up	All patients aged >80 years: median age 84 years (range 80 to 92) 52% male Mean (±SD) mitral regurgitation grade 3.5±0.2 Ineligible for surgical mitral valve reconstruction or repair	<u>30-day adverse events</u> Mortality 2%; major bleeding 2%; minor bleeding 5%; partial clip detachment 1%; unsuccessful procedure 9%; additional surgery 4%
Lim (2014)[27] *Post hoc* analysis of EVEREST II HRS and the REALISM continued access registry 1 year follow-up	N=127 All had degenerative mitral regurgitation Prohibitive risk of surgery Mean (±SD) age 82.4±8.7 years 55.1% male Mitral regurgitation grade 4+ (29.9%) or grade 3+ (56.7%)	Mortality: 30-day mortality 6.3% 1-year mortality 23.6% SF-36 quality of life score (baseline to 1 year): Difference in mean physical HRQoL 6.0 (p<0.001) Difference in mean mental HRQoL 5.6 (p<0.0011) Mean (±SD) length of stay: ICU 1.4±1.8 days Hospital 2.9±3.1 days 73% reduction in rate of hospitalisation for heart failure <u>30 day adverse events</u> Major bleeding 12.6%; major vascular complications 5.5%; atrial septal defect 1.6%; non-elective surgery 0.8% <u>1 year adverse events</u> Major bleeding 15.7%; major vascular complications 7.1%; atrial septal defect 2.3%; mitral valve stenosis 2.4%

IQR = inter-quartile range; SD = standard deviation; SF-36 = short form 36 item health survey; HRQoL = health-related quality of life; ICU = intensive care unit

UK registry data: functional and degenerative mitral regurgitation

In England, the Commissioning through Evaluation (CtE) programme gathered data on percutaneous mitral valve leaflet repair (MitraClip®) in a multicentre observational registry[30]. Patients were accepted for MitraClip® intervention if they had moderate-to-severe (grade 3+) or severe (grade 4+) mitral regurgitation of any aetiology and were deemed by a multidisciplinary team to be too high risk for conventional surgery. A total of 199 MitraClip® procedures from the registry were analysed and described in a report to NHS England Commissioning. Patients had a mean age of 76.2 years, a mean EuroSCORE II score of 6.4 (SD 5.7), 68.8% were male and 60% had functional mitral regurgitation. Results were not reported separately for functional and degenerative mitral regurgitation.

The procedural success rate was somewhat lower than reported in the RCTs (85.9%, 95% CI 80.3% to 90.4%)[30]. Patients remained in hospital for a median of five nights (IQR 3.3 to 8.0) after a MitraClip® procedure and in-hospital mortality was 5% (95% CI 2.4% to 9.0%). Mortality at 1-year follow-up was 11.6% (95% CI 7.5% to 16.8%). Major in-hospital complications were reported for 8.2% of patients and minor in-hospital complications for 7.6% of patients. Mitral regurgitation severity ≥3+ was reduced from 99.5% of patients prior to MitraClip® intervention, to 6.7% post-procedure. By 12 months follow-up the proportion of patients with mitral regurgitation grade ≥3+ had increased to 24.4%. The proportion of patients in NYHA class III or IV decreased from 92.4% at baseline to 17.9% at 1 year follow-up indicating a substantial improvement in patient symptoms.

Ongoing studies

Four relevant ongoing studies with randomised comparisons were identified (table 10). Two studies focus on degenerative mitral regurgitation and two on functional mitral regurgitation. One study compares the MitraClip® System with a new competitor technology – the Edwards PASCAL System. Two studies compare MitraClip® with surgical mitral valve repair or replacement in patients at high surgical risk.

Table 10: ongoing comparative randomised studies on transcatheter mitral valve repair in patients with mitral regurgitation who are at high surgical risk or who are non-surgical candidates

Study	Comparison	Patient group	Estimated completion date
MATTERHORN NCT02371512	MitraClip® vs. surgical mitral valve repair or replacement	Moderate-to-severe functional mitral regurgitation Reduced left ventricular function Considered high surgical risk	December 2019
RESHAPE-HF2 NCT02444338	MitraClip® plus optimal standard of care vs. optimal standard of care alone	Moderate-to-severe or severe functional mitral regurgitation Symptomatic despite optimal standard of care	March 2021

MITRA-HR NCT03271762	MitraClip® NT vs. surgical mitral valve repair (or replacement if not feasible)	Grade 3+ or 4+ degenerative mitral regurgitation with high surgical risk	June 2023
CLASP IID NCT03706833	Transcatheter mitral valve repair with the Edwards PASCAL System vs. MitraClip®	Degenerative mitral regurgitation (grade 3+ or 4+) Prohibitive surgical risk	July 2026

Safety

Functional mitral regurgitation

Device-related safety outcomes associated with the MitraClip® System in patients with functional mitral regurgitation were assessed in the two RCTs described in the clinical effectiveness section: COAPT and MITRA-FR[15, 16]. In the COAPT trial the primary safety outcome (freedom from device-related complications at 12 months follow-up) was measured against a pre-specified level of 88% based on an acceptable device-related complication rate of 12% developed in collaboration with the American Food and Drugs Administration (FDA). The MITRA-FR study did not have a pre-specified acceptable complication rate.

Adverse events relating to the MitraClip® device or procedure tended only to be reported in one or the other of the RCTs (table 11). The most common adverse events were failure of the device implantation procedure (4.2% in MITRA-FR) and unplanned mitral valve surgery or MitraClip® implantation (3.3% in COAPT).

Table 11: safety outcomes reported in the COAPT and MITRA-FR trials[15, 16]

	COAPT	MITRA-FR
Peri-procedure		
All complications during device implantation (%)	–	14.6
Device implantation failure[×] (%)	~2.0	4.2
Cardiac tamponade (%)	0.3	1.4
Cardiac embolism, including gas embolism and stroke (%)	–	1.4
Haemorrhage requiring transfusion or vascular complications requiring surgery (%)	–	3.5
Atrial septum lesion or defect (%)	–	2.8
Cardiogenic shock (%)	–	2.8

Urgent conversion to heart surgery (%)	–	0
12 months follow-up		
Freedom from device-related complications (%)	96.6	–
All serious adverse events (%)	–	82.2*
Any device-related complications requiring non-elective surgery (%)	0.3	–
Single leaflet attachment (%)	0.7	–
Device embolisation (%)	0.3	–
Unplanned mitral valve surgery or MitraClip® implantation (%)	3.3%	–

×In the COAPT trial this was defined as "the rate of successful delivery and deployment of the MitraClip device(s) with echocardiographic evidence of leaflet approximation and retrieval of the delivery catheter". The MITRA-FR trial defined device implantation failure as absence of procedural mortality, successful access, delivery and retrieval of the device delivery system and successful deployment and positioning of the device.

*The high proportion of 'serious adverse events' in the MITRA-FR study was queried with the study author. Following a response from the author, and review of table S5 in the study appendix, it appears that serious adverse events in this study included a wide range of often poorly defined outcomes, which may have been over-reported by some participating centres.

Degenerative mitral regurgitation

Adverse events relating to MitraClip® in patients with degenerative mitral regurgitation were reported in the four single-arm observational studies described in the clinical effectiveness section[26-29]. The TVT registry study reported in-hospital adverse events[28]. The highest adverse event rate in this study was for major or life-threatening bleeding which was recorded in 3.9% of patients (table 9). Two studies reported adverse events occurring within 30 days of the MitraClip® procedure[27, 29]. Minor bleeding (5%) and major bleeding (12.6%) were the most commonly reported adverse events in these studies, respectively. It is unclear why the rate of major bleeding is so high in the study by Lim *et al* (2014) compared with other studies. The final study did not define 'peri-procedure'[26]. In this study 12.6% of patients experienced a complication and the most common peri-procedural adverse event was partial clip detachment (2.5%).

Cost effectiveness: functional and degenerative

UK cost data from the CtE registry

In the CtE report on MitraClip®, the costs of the MitraClip® procedure were estimated from national datasets and commercial in confidence manufacturer quotes[30]. The report authors used these data to estimate a central cost, along with high and low cost estimates, for the MitraClip® procedure (table 12). In each estimate the procedure itself accounted for 85% of the total costs, followed by post-operative management (13%) and pre-operative care (2%) costs. Based on these calculations

and four published economic evaluations, the CtE report authors concluded that the incremental costs for MitraClip® were unlikely to be offset by savings from fewer hospitalisations or surgeries avoided.

Table 12: central, low and high cost estimates for the MitraClip® procedure based on UK data[30]

Pathway stage	Central cost	Low cost	High cost
Pre-operative assessment	£790	£412	£998
Peri-operative procedure	£27,707	£26,681	£28,714
Post-operative management	£4,062	£1,697	£4,407
Total	**£32,560**	**£28,790**	**£34,119**

Published economic evaluations

No economic evaluations that were conducted in the UK and published since EN58 were identified in the literature search. The three non-UK economic evaluations that were identified assessed cost effectiveness of MitraClip® in the French[31], Italian[32] and Canadian[33] context. All three evaluations were based on observational data from patients receiving MitraClip® who were retrospectively matched to patients receiving standard medical therapy.

The Italian analysis compared MitraClip® plus medical therapy with medical therapy alone in a retrospective registry-based study[32]. Patients with functional mitral regurgitation were randomly selected from a registry of patients treated with medical therapy in 2007-2009 (n=151). Consecutive patients treated with MitraClip® at two major Italian hospitals between 2008 and 2012 (n=232) comprised the second group of patients. Patients were propensity score matched using multiple variables including age, comorbidities, prior hospitalisations and NYHA classification. The analysis used a lifetime horizon with 1-year cycles of the model starting at age 70. There were only two states in the model – alive or dead. A third party payer perspective was taken and only direct medical costs were considered (medication, hospitalisation and device implantation costs). Costs and benefits were both discounted at 3.5% per annum. Utility values for each NYHA class were extracted from the published literature and applied in the economic model. Disease-free age-related utility decrements were applied equally to each patient group.

In the base case analysis, MitraClip® was associated with an incremental cost of €23,342 (£20,196) and 3.01 additional quality adjusted life years (QALYs). The incremental cost effectiveness ratio (ICER) was €7,908/£6,842 (95% CI €7,878/£6,817 to €7,938/£6,868) indicating MitraClip® was cost effective at commonly accepted willingness-to-pay thresholds. In probabilistic sensitivity analyses MitraClip® was cost effective in 95% of cases at a willingness-to-pay threshold of €10,000 (£8,649)/QALY. The promising results of this analysis should be treated with caution due to methodological limitations. Despite attempts at propensity score matching, there were significant differences between patient groups at baseline, particularly in NYHA class, number of hospitalisations in the previous year and history of revascularisation[32].

The Canadian economic evaluation compared MitraClip® with medical therapy in patients with moderate-to-severe or severe functional mitral regurgitation and high surgical risk[33]. The model employed parameters derived from an observational study in which 50 patients were prospectively enrolled in the MitraClip® cohort, while patients in the medical therapy cohort (n=42) were retrospectively identified. Patients were propensity score matched using 16 different variables and pairs were linked based on the smallest absolute difference between scores. The model adopted the perspective of the Canadian healthcare system and was based on a 10-year time horizon. The decision analytic model simulated disease progression and each monthly cycle included the possibility of death, mitral valve surgery, emergency department visits or hospitalisation, and re-intervention or complications in the MitraClip® group. Cohort specific probabilities for each state were calculated from actual event rates in the observational study. Utilities were derived from the published literature. Procedural costs, inpatient treatment costs, and patient follow-up costs were included. Costs for hospitalisation and emergency department visits were provided by the Montreal Heart Institute and the Heart Failure Clinic database provided costs for the medical therapy cohort. All costs were reported as 2013 Canadian dollars and discounted at 5% per annum.

MitraClip® was associated with an incremental cost of CAD$52,600 (£29,856) and 1.63 additional QALYs, giving an ICER of CAD$32,300 (£18,335). The higher costs of the MitraClip® device and procedure were only partially offset by savings in hospitalisations, emergency room visits and mitral valve surgeries[33]. The main cost drivers were initial device implantation costs and disease management costs. The model was sensitive to changes in mortality risk, time horizon or absence of MitraClip®-associated improvements in quality of life. In probabilistic sensitivity analyses MitraClip® was cost effective in 67% of simulations with a threshold of CAD$50,000 (£28,655) and 95% of cases with a threshold of CAD$100,000 (£57,309). Key limitations of this study include the small cohort size, extrapolation of survival and mortality rates, and patients not being matched according to NYHA classification which resulted in the medical therapy cohort being less symptomatic at baseline. This may have led to underestimation of the benefits of MitraClip® in terms of reduced hospitalisations.

The final study compared MitraClip® with standard medical therapy in patients with degenerative or functional mitral regurgitation who were ineligible for surgery[31]. The Markov model used in the analysis comprised of four states based on grade of mitral regurgitation severity: grade 0, grades 1+ and 2+, grades 3+ and 4+, or deceased. A French payer perspective was taken which considered only direct medical costs incurred in each treatment group. These costs included initial hospitalisation for MitraClip® implantation, the MitraClip® System, mean annual cost of rehospitalisation, care and rehabilitation costs, transport costs, and mean annual cost of outpatient follow-up. Efficacy data used in the economic model were derived from the single-arm EVEREST II HRS study, matched to control arm patients from the REALISM continued access registry. Cost data were provided by a French hospital participating in the MITRA-FR trial (n=17). Costs were discounted at 4% per annum over a 5 year time horizon. In each 1-month cycle patients could be hospitalised for heart failure or not, and deceased or alive. Transition probabilities were derived from the EVEREST II HRS trial.

In the first year, the MitraClip® strategy cost €29,984 (£25,929) compared with €8,557 (£7,400) for standard medical therapy[31]. In subsequent years the MitraClip® strategy incurred an annual cost of €3,122 (£2,700) while the medical therapy cost remained €8,557 (£7,400) per annum. The ICER after 5 years was €15,741 (£13,615) per life year gained and €79,792 (£69,017) per death avoided. In probabilistic sensitivity analyses, MitraClip® had a 90% chance of being cost effective at a threshold of €60,000 (£51,890) per life year gained and >80% at a threshold of €30,000 (£25,945) per life year

gained. These ICERs were sensitive to changes in the initial cost of device implantation. Results were also sensitive to the probabilities of transitioning to death from different grades of mitral regurgitation severity, stemming from the reliance on aggregate data from a modestly sized non-randomized study with a short-term follow-up period. The authors only presented results based on life years gained, not QALY gains. This was justified in the paper as being due to a lack of utility data specific to French patients. However, utility values for cardiac symptoms and mortality are likely to be generalisable and not using QALYs may have underestimated the ICER values.

Patient and social aspects

Patient aspects from the CtE registry

The CtE registry in England used the EQ5D tool to collect quality of life data from patients undergoing a MitraClip® procedure[30]. EQ5D data were available for 163 patients prior to the MitraClip® procedure (61.1% functional mitral regurgitation). At 6 weeks follow-up, paired data were available for 136 patients and at 6 months, paired data for 113 patients were available. Statistically significant improvements in HRQoL were reported for mobility, self-care, usual activities, pain/discomfort and anxiety/depression at 6 weeks and 6 months follow-up (table 13).

At 6 weeks follow-up, 83.1% of patients reported improved quality of life, 10.3% a deterioration and 9.0% no change. After 6 months, HRQoL was reported to have improved for 79.6% of patients, deteriorated for 13.3% and remained unchanged for 7.1% of patients. The mean increase in utility score from baseline to 6 weeks follow-up was 0.18 (SD 0.23). Similar increases in utility score were reported at 6 months (0.20, SD 0.24) and 12 months (0.15, SD 0.22) follow-up. All increases in utility scores from baseline to 6 weeks, 6 months and 12 months were statistically significant (p<0.0001).

Table 13: statistical significance of change in baseline HRQoL domains by 6 weeks, 6 months and 12 months follow-up[30]

	Mobility	Self-care	Usual activities	Pain/ discomfort	Anxiety/ depression
6 weeks	p<0.0001	p<0.0001	p<0.0001	p=0.0001	p<0.0001
6 months	p<0.0001	p=0.0001	p<0.0001	p<0.0001	p=0.0001
12 months	p=0.016	p=0.391	p=0.0001	p=0.0009	p=0.0061

Responses to the NICE survey

As part of the NICE IPG update on percutaneous mitral valve repair, questionnaire responses from a convenience sample of 20 patients who had undergone MitraClip® at two centres in NHS England were collated[34]. The mitral regurgitation aetiology for respondents is not clear from the survey responses. Respondents had a mean age of 80 (range 65 to 94 years) and had undergone percutaneous mitral valve repair between 1 month and 4 years prior to the survey (mean 2.3 years). Fifteen respondents (75%) reported they had recovered from the procedure in less than one month. For the remainder of respondents recovery took between 2 and 6 months.

Ninety percent (n=18) of survey respondents reported having a successful procedure[34]. The remaining two respondents stated they had 'somewhat' successful procedures. Only one patient reported experiencing a side-effect following their procedure and this was not directly related to the device or procedure (new arrhythmia followed by a cardiac arrest).

All survey respondents reported positive effects of the MitraClip® procedure on their symptoms or quality of life; particularly improvements in confidence and levels of breathlessness. Quotes from the NICE patient commentary document which summarised the survey results include[34]:

- "I can walk more, breathe better and do more about the house without breaks. My life is much easier. I was in good spirits before and so wellbeing remains good. I remain able to look after myself and meet my needs with minimal help from others."
- "Although still suffering from angina, the procedure definitely left me stronger than before and has probably given me a longer lifespan without major surgery."
- "Allowed me a more normal and relaxed lifestyle. Ability to sleep in a normal position without the need to be propped up in an almost sitting position."
- "My breathing at rest is much improved. I still get breathless on moderate exercise. My walking distance is improved and in general I have an improved quality of life."
- "I have been given a new lease of life. I can't believe how poorly I was before the procedure. I am enjoying life again because I no longer have to worry. I can go upstairs without stopping and angina has gone. I am feeling stronger and stamina has returned, as has my confidence."

No negative effects of the MitraClip® procedure were reported by any of the survey respondents and 95% (n=19) would recommend the procedure to another patient with mitral regurgitation. One patient wished they could have had the procedure sooner and one patient did not know if they would recommend the procedure to another person with mitral regurgitation or not.

Other comments from respondents to the NICE survey include[34]:

- "No stress, very quick in hospital and recovery."
- "….Well worth it. Felt somewhat better straight away. No negative thoughts at all."
- "It has improved my heart conditions and has improved my way of life and made my family much more relaxed and happy."
- "At my age and after previous bypass surgery it is the safest and hopefully successful alternative."
- "I would encourage more patients to have this procedure. I am convinced it has improved my lifestyle."
- "Painless and positive."

Volume-outcome

Two retrospective analyses from the USA assessed the effects of annual MitraClip® procedure volume on patient outcomes[35, 36]. Since MitraClip® has only been approved in the USA for use in

patients with degenerative mitral regurgitation, it is likely that a large proportion of the patients in these studies had degenerative mitral regurgitation as the indication for mitral valve repair.

The most recent study used data from the National Readmission Database 2013-2014 which contains data on approximately 49.3% of all hospitalisations in the USA[35]. Relevant patients were identified using ICD-9-CM codes for percutaneous mitral valve repair (MitraClip®) which was listed as the primary or secondary procedure in the database record. The primary outcome was a composite of in-hospital mortality and complications. The secondary outcome was readmission to hospital within 30 days. Hospital volume was divided into hospitals performing <10 MitraClip® procedures per year (n=55) and hospitals conducting ≥10 procedures/year (n=157). Approximately 76% of patients undergoing the MitraClip® procedure were 65 years or older and 54% were male. For 71% of patients the MitraClip® procedure was elective. In multivariate regression analysis, higher hospital volume (≥10 procedures per annum) was significantly associated with a lower risk of the composite outcome of in-hospital mortality and complications: odds ratio (OR) 0.46, 95% CI 0.12 to 0.89, p=0.02. This result was likely driven largely by a reduction in complication rates as the effect of hospital volume on mortality alone was not statistically significant: OR 0.74, 95% CI 0.21 to 2.66, p=0.65. There was no statistically significant association between hospital procedure volume and 30-day readmissions to hospital: OR 0.92, 95% CI 0.48 to 1.78, p=0.81.

The second study used data from the National Inpatient Sample Database 2012, which is a stratified 20% sample of all patients discharged from community hospitals in the USA[36]. As with the study described above, the authors identified relevant records using the ICD-9-CM codes for percutaneous mitral valve repair listed as the primary or secondary procedure. The primary outcome was a composite of in-hospital mortality and procedural complications. A sample of 55 hospitals was divided into tertiles: 39 hospitals in tertile 1 performed <1 MitraClip® procedure per annum; 10 hospitals in tertile 2 performed 2-3 procedures per year; 6 hospitals in tertile 3 performed ≥4 procedures per annum. Patients had a mean age of 70 and 56.8% were male. Statistically significant differences between tertiles were identified for the composite primary outcome and for procedure complications alone (table 14). There were no statistically significant differences in crude mortality rate, therefore significant differences between hospitals with different procedure volume are likely driven by a reduction in complication rates. After adjusting for confounding factors the statistical significance of the association between hospital volume and the primary composite outcome remained only for comparisons between tertile 1 (<1 MitraClip® per annum) and tertile 3 (≥4 MitraClip® per annum).

Table 14: relationship between annual hospital MitraClip® procedure volume and patient outcomes in a retrospective analysis from the USA[36]

	Tertile 1 (<1 per year)	Tertile 2 (2-3 per year)	Tertile 3 (≥4 per year)	p-value
Composite of in-hospital mortality and complications (%)	48.7	17.4	9.1	<0.001
In-hospital mortality (%)	2.6	4.4	3.0	0.68

Any procedural complication (%)	48.7	17.4	9.1	<0.001
Composite mortality and complications	Referent	OR 0.23 95% CI 0.12 to 0.41 p=0.18	OR 0.12 95 % CI 0.06 to 0.23 p<0.001	–

Learning curve

Transcatheter implantation of MitraClip® for the treatment of mitral regurgitation is a complex procedure involving a device with multiple control knobs, a multi-stage intervention, a requirement for transseptal puncture for left atrium access and use of transoesophageal echocardiography to guide the procedure[37]. Therefore MitraClip® implantation may involve a significant learning curve for interventional cardiologists and echocardiographers who are new to this procedure or to cardiac procedures requiring transseptal left atrium access. Four studies explored the learning curve for MitraClip®: three from Europe and one from the USA[37-40]. Three of these studies incorporated both degenerative and functional mitral regurgitation patients.

One retrospective study explored the learning curve for MitraClip® in 53 patients with functional mitral regurgitation treated at a single centre in Poland[38]. Three interventional cardiologists, with unknown levels of prior experience, performed the procedures. Patients treated between 2012 and 2016 formed the first group (n=26); the second group was formed of patients treated in 2017 (n=27). The study cohort had a mean age of 67.8 (SD 7.2) years, 81% were male and 87% were in NYHA class III or IV at baseline. Procedure success rates increased from 77% in group 1 to 96% in group 2, p=0.039. Total device time, defined as the time from transseptal puncture to removal of the guiding catheter from the femoral artery, was significantly shorter in the second group of patients: 166 (SD 62.5) minutes versus 106.3 (SD 44.9) minutes, p=0.0002. There were no statistically significant differences in complication rates or number of patients with NYHA class >2 at 30 days follow-up.

The other two European studies were conducted in Germany[39, 40]. The most recent of these studies used data from the multicentre, prospective, German Mitral Valve Registry[39]. Centres performing at least 50 MitraClip® procedures were selected from the registry (10 hospitals). A total of 496 patients were identified from these hospitals; the first 25 procedures from each centre formed group 1 and the second 25 procedures from each centre formed group 2. Patients had a median age of 75 years (IQR 70 to 81 years) and 67% were male. Patients in the first group had slightly higher NYHA class at baseline and a higher frequency of impaired left ventricular function. There was a trend towards more patients in the second group having functional mitral regurgitation: 56.9% versus 65.7%, p=0.05. No statistically significant differences between groups were found for procedure success, post-procedure mitral regurgitation grade, median time in intensive care, length of hospital stay, major adverse cardiovascular or cerebrovascular events, in-hospital mortality, severe complications, mild adverse events, 30-day mortality or 30-day rehospitalisation for cardiac causes.

The second German study was a prospective observational study based on the first 75 patients treated with MitraClip® at a single centre[40]. One interventional cardiologist performed all procedures in this study; no information is provided about their prior experience. Patients were divided into three groups: group 1 for patients 1-25, group 2 for patients 26 to 50 and group 3 for patients 51 to 75. Study participants had a mean age of 73 (SD 2.0) years, 70% were male, 65% had functional

mitral regurgitation, and median grade of mitral regurgitation at baseline was 4+ (IQR 2+ to 4+). Patients treated in the second group (patients 26 to 50) were slightly younger and had lower LVEF at baseline compared with groups 1 and 3. There were no statistically significant differences between groups in acute procedure success: 80% versus 80% versus 92%, p=0.46. Median total procedure time was significantly reduced with increasing experience: 180 minutes versus 123 minutes versus 95 minutes, p=0.0001. There was also a statistically significant reduction in adverse events between groups: 16 versus 6 versus 3, p=0.0003. No statistically significant association was found between treatment group and mortality or hospitalisation for heart failure. At 6 months follow-up (n=59) a greater proportion of patients treated in group 3 had residual mitral regurgitation ≤2+ compared with group 1: 89.4% versus 65.0%, p=0.03. In the discussion section of this paper the authors note that systemic changes had been introduced during the study period to try and reduce MitraClip® procedure time which may have affected estimates of the learning curve.

The study from the USA was a retrospective analysis of the first 75 patients with mitral regurgitation treated with MitraClip® at a single centre[37]. Patients were divided into three groups of 25 each. All procedures were performed by three operators with considerable prior experience of transseptal puncture (559 procedures, 229 procedures and 213 procedures). Patients had a mean age of 80 (SD 9.0) years, 77% were male and 11% had functional mitral regurgitation. Patients in the third group were significantly older than those in groups 1 and 2 (p=0.03). Procedure time, time from transseptal puncture to device release, and fluoroscopy time all reduced significantly with increasing experience:

- Procedure time: 123 (SD 42) minutes versus 93 (SD 34) minutes versus 103 (SD 37) minutes, p=0.04
- Transseptal puncture to device release: 81 (SD 34) minutes versus 55 (SD 19) minutes versus 56 (SD 19) minutes, p<0.001
- Fluoroscopy time: 66 (SD 28) minutes versus 48 (SD 19) minutes versus 51 (SD 27) minutes, p<0.001

Improvements in procedure time and time from transseptal puncture to device release plateaued after the first 50 patients. Mean length of hospital stay decreased significantly between group 1 and group 2 (3.7 (SD 4.0) days versus 1.8 (SD 1.5) days, p=0.03). There were no statistically significant differences between groups for major adverse event rates or NYHA class at 30 days follow-up.

Organisational issues/context

NHS England has included MitraClip® for mitral valve regurgitation in their CtE programme. A national commissioning policy is expected to publish in the near future based on data collected at three hospital Trusts in England involved in the CtE programme.

Based on estimates of the number of patients eligible for MitraClip® in NHS England, the number of Scottish patients – with degenerative or functional mitral regurgitation – projected to be suitable for MitraClip® in the future ranges from 37 to 106 per annum (appendix 2).

Conclusion

The only two currently available randomised studies on MitraClip® transcatheter mitral valve repair were conducted in patients with functional mitral regurgitation and reported contrasting results. While one trial found significant improvements in patient mortality and hospitalisation for heart failure, the other found no statistically significant differences. Given the similarities in design and conduct of these RCTs the contrasting results are unexpected. Potential explanations for the different findings centre on the possibility that the RCTs recruited patients from different sub-groups within the functional mitral regurgitation population and variations in study design.

Evidence for MitraClip® in patients with degenerative mitral regurgitation was limited to four single-arm, observational studies reporting a limited range of outcomes. Improvements in mitral regurgitation severity, rate of hospitalisations for heart failure and quality of life patient were reported in one or more of these studies. However, a lack of comparator group limits the conclusions that can be drawn from these data.

Adverse event rates for each complication type were reported for <5% of patients in the two RCTs and were not considered major by the trial investigators. In the primary studies incorporating patients with degenerative mitral regurgitation, the most common adverse events related to peri-operative bleeding.

Feedback from MitraClip® patients in NHS England indicate that patients that that MitraClip® had a positive impact on their symptoms, quality of life, and ability to carry out everyday activities such as walking up stairs.

Owing to a lack of new UK-focused economic evaluations the cost effectiveness of MitraClip® transcatheter mitral valve repair remains uncertain. Evidence from European and Canadian studies suggest it is cost-effective at commonly used willingness-to-pay thresholds (£20,000-£30,000), however these analyses were mainly based on observational studies that used retrospectively identified comparator groups and required extrapolation of long-term survival which could have biased results.

Although there is likely a steep initial learning curve for MitraClip®, the studies identified in this review did not detect any significant effects of operator experience on patient outcomes. It is possible this was due to interventional cardiologists in these studies having prior experience with transcatheter cardiac procedures involving transseptal puncture. Two retrospective studies indicated that higher annual hospital procedure volume was associated with significant reductions in patient mortality and adverse events.

Identified research gaps

Additional RCTs comparing MitraClip® plus medical therapy with medical therapy alone in patients with functional or degenerative mitral regurgitation who are at high surgical risk are desirable to clarify the effectiveness of MitraClip® for reducing mitral regurgitation. RCTs that explore potential patient sub-groups and functional versus degenerative mitral regurgitation separately would be useful.

Economic evaluations that take a UK perspective and are based on randomised evidence are required to establish the cost effectiveness of MitraClip® for patients with moderate-to-severe or severe mitral regurgitation who are at high surgical risk or inoperable.

Equality and diversity

Healthcare Improvement Scotland is committed to equality and diversity in respect of the nine equality groups defined by age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion, sex, and sexual orientation.

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A glossary of commonly used terms in Health Technology Assessment is available from htaglossary.net.

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Appendix 1: abbreviations

CAD	Canadian dollars
CI	confidence interval
CRT	cardiac resynchronisation therapy
CtE	Commissioning through Evaluation
DMR	degenerative mitral regurgitation
EROA	effective regurgitant orifice area
EuroSCORE	Logistic European System for Cardiac Operative Risk Evaluation
FDA	Food and Drug Administration (USA)
FMR	functional mitral regurgitation
GDMT	guideline-directed management and therapy
HR	hazard ratio
HRQoL	health-related quality of life
ICD-9-CM	international classification of diseases, 9th edition, clinical modification
ICER	incremental cost effectiveness ratio
IQR	inter-quartile range
KCCQ	Kansas City Cardiomyopathy Questionnaire
LVEDV	left ventricular end diastolic volume
LVEF	left ventricular ejection fraction
MD	mean difference
NICE	National Institute for Health and Care Excellence

NYHA	New York Heart Association
OR	odds ratio
QALY	quality adjusted life year
QOF	quality outcomes framework
QoL	quality of life
RCT	randomised controlled trial
RR	relative risk or risk ratio
SD	standard deviation
SE	standard error
SF36	short-form 36-item health survey
STS	Society of Thoracic Surgeons
VAT	value added tax

Appendix 2: estimated patient volume in Scotland

In the draft commissioning policy for MitraClip® in NHS England, the number of patients with degenerative mitral regurgitation who would be referred for MitraClip® is estimated as initially 400 patients per year. This estimate is based on the following calculation:

- Population of England — 53 million
- 7.8% of the population are aged over 75 years — 4 million
- Approximately 8% have moderate-severe mitral regurgitation — 320,000
- 50% have significant leaflet prolapse effectively treated with MitraClip® — 160,000*
- 25% have suitable anatomy for MitraClip® — 40,000
- 10% would be considered for treatment due to comorbidities etc. — 4,000
- 10% of those eligible will be referred — 400 p.a.

Based on the calculation used in NHS England, published studies from the UK, and clinician input, the following future projections of patient numbers for MitraClip® – functional or degenerative mitral regurgitation – were calculated for Scotland using three different prevalence values for mitral regurgitation. In all three scenarios it is assumed that MitraClip® would only be offered to patients aged 75 or older.

In all three scenarios the following values were held constant:

- Population of Scotland (mid-2018) — 5.44 million
- 8% of the population are aged 75 or older — 454,736

Scenario 1

2.68% have moderate mitral regurgitation and 0.45% have severe mitral regurgitation[9]	14,233
25% have suitable anatomy for MitraClip®	3,558
10% would be considered for treatment due to comorbidities etc.	356
10% of those eligible will be referred	**37 per annum**

Scenario 2

8% have moderate or severe mitral regurgitation (NHS England prevalence estimate)	36,379

25% have suitable anatomy for MitraClip®	9,095
10% would be considered for treatment due to comorbidities etc.	910
10% of those eligible will be referred	**91 per annum**

Scenario 3

9.3% have moderate or severe mitral regurgitation[11]	42,290
25% have suitable anatomy for MitraClip®	10,573
10% would be considered for treatment due to comorbidities etc.	1,057
10% of those eligible will be referred	**106 per annum**

*This criterion applies mainly to patients with degenerative mitral regurgitation. Since the Scottish estimates are for either type of mitral regurgitation, this criterion is not included in the calculations reported in scenarios 1-3.

**Population and proportion of population aged 75 and over in Scotland could in reality be expected to increase in future, in line with current population trends.