NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of percutaneous mitral valve leaflet repair for mitral regurgitation

Mitral regurgitation happens when the mitral valve in the heart does not close properly. This allows blood to flow back the wrong way. The heart has to work harder to pump blood around the body, which can lead to heart failure. In this procedure, a small clip is guided into the heart through a catheter (thin tube) inserted into a vein in the groin. The clip is attached to the leaflets (flaps) of the mitral valve to help it close more completely. The aim is to improve symptoms and quality of life.

Contents

Introduction

The Newcastle and York External Assessment Centre (NY-EAC) prepared this interventional procedure overview on behalf of the National Institute for Health

and Care Excellence (NICE) to help members of the interventional procedures advisory committee (IPAC) make recommendations about the safety and efficacy of this interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in August 2018.

Procedure name

- Percutaneous mitral valve leaflet repair for mitral regurgitation.

Specialist societies

- British Cardiovascular Intervention Society
- Society for Cardiothoracic Surgery in Great Britain and Ireland
- British Society of Echocardiography.

Description of the procedure

Indications and current treatment

The mitral valve allows blood to flow from the left atrium to the left ventricle. Mitral valve regurgitation (MR) happens when the valve doesn't close properly and blood flows back into the atrium from the ventricle. The heart has to work harder to pump blood from the left ventricle to the aorta, resulting in an enlarged left ventricle. If not treated, this can lead to problems including heart failure.

MR can be degenerative (primary or structural) or functional (secondary). Degenerative MR is caused by 'wear and tear' to the chords and leaflets in the valve. In functional MR the chords and leaflets are structurally normal but there is geometrical distortion of the subvalvular apparatus caused by idiopathic cardiomyopathy, or weakening of the cardiac walls caused by coronary artery disease (ischaemic MR). Degenerative MR is treated by surgery to repair or

replace the mitral valve. Functional MR can be conservatively managed using drugs for treating heart failure but this is not curative, and surgical options such as undersized annuloplasty may be an option. However, people with MR of either cause are usually older (typically over 70 years) and frail, with multiple comorbidities. This increases the perioperative risks of morbidity and mortality, making this population at high or prohibitive risk of open heart surgery. For these patients, percutaneous mitral valve leaflet repair (PMVR) may be an appropriate management option.

What the procedure involves

PMVR is a treatment option for MR if the mitral valve meets the anatomical eligibility criteria for coaption length, coaption depth, flail gap and flail width. It involves the use of a clip that mimics a surgical technique known as the 'Alfieri stitch'. The procedure is done under general anaesthesia using transoesophageal echocardiography guidance and the optional use of fluoroscopy. Access is provided through the femoral vein and an atrial trans-septal puncture is done to reach the delivery site.

The device is lowered through the mitral valve into the left ventricle. The arms of the clip grip the leaflets, bringing them closer together, and the clip is released from the delivery system. Adequate reduction of MR is assessed using echocardiography. If the reduction in MR is inadequate with 1 device it may be removed, or a second device placed alongside the first. After the procedure, patients usually have anti-platelet therapy for 6 months.

Outcome measures

MR grade

There are several classification systems of MR based on imaging. This is usually based on echocardiography, but angiography and Magnetic Resonance Imaging (MRI) are also used. Classification has 5 grades ranging from none to 1+ (mild MR), 2+, 3+, or 4+ (severe MR). A simplified 3 grade classification system is sometimes used (mild, moderate, or severe). In some cases, MR class is dichotomised to report a binary outcome (such as ≤2+ and >2+). Measurement and interpretation of MR is operator-dependant and therefore a potential source of bias.

NYHA classification

The New York Heart Association (NYHA) classification system is used to measure symptoms and loss of functionality caused by heart failure, in particular dyspnoea (breathlessness). It is a subjective outcome based on patient symptoms, as follows:

Class	Patient symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnoea.
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnoea.
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnoea.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

Generic health-related quality of life

Health-related quality of life (HR-QoL) is an important outcome in people with MR. Two systems are commonly used. The Short Form 36 (SF-36) is an indicator of overall health status composed of 10 items. It has 8 scaled scores, which are the weighted sums of the questions in each section. Scores range from 0 to 100 with lower scores meaning more disability and higher scores less disability. The sections included in the questionnaire are vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning and mental health.

The EuroQoL quality of life questionnaire (EQ-5D) is a standardised instrument for measuring generic health status. The five dimensions are mobility, self-care, usual activities, pain or discomfort, and anxiety or depression. The score is converted into an index, with 1 representing perfect health and 0 representing death. Respondents also self-rate their health on a visual analogue scale (VAS), with the endpoints labelled ‘best imaginable health state’ and ‘worst imaginable health state’.

Efficacy summary

Technical and procedural success

In a randomised controlled trial (RCT) of 614 patients, device implantation was attempted in 97% (293/302) of patients randomised to percutaneous mitral valve leaflet repair (PMVR) and 1 or more clips were implanted in 98% (287/293) of these patients (95% of the total PMVR group).[1] Technical and procedural success of PVMR was reported in 5 single-arm observational studies as 92% (n=2,952)[7], 96% (n=78)[10], 96% (n=628)[5], 97% (n=749)[6], and 100% (n=567)[4]. However, direct comparisons between these studies are limited by differing or poorly described definitions. Data from the NHS England Commissioning through Evaluation (CtE) registry were also considered (academic in confidence).[11]

Mortality

In the RCT of 614 patients, all-cause mortality was 19% and 29% in the PMVR arm at 12-month and 24-month follow-up respectively.[1] In an RCT of 304 patients, 24% died in the PMVR group during 12 months of follow up, with 22% having a cardiovascular cause.[2] In the RCT of 279 patients, mortality was 6% in the PMVR group at 1-year follow-up.[3a] This increased to 21% at 5-year follow up.[3b] In 4 of the single-arm observational studies, annual mortality was estimated using time-to-event analysis as 15%[5], 18%[4], 20%[6] and 26%[7]. Data from the NHS England CtE registry were also considered (academic in confidence).[11]

Comparative mortality

In the RCT of 614 patients, death from any cause was 19% in the PMVR group compared with 23% in the medical management group ($p<0.001$ for non-inferiority) at 12-month follow-up. At 24 months the rates were 29% and 46% respectively ($p<0.001$, hazard ratio [HR] 0.62, 95% confidence interval [CI] 0.46 to 0.82)[1]. In the RCT of 304 patients, 24% (37/152) of patients died in the PMVR group compared with 22% (34/152) in the medical management group.[2] This gives a HR of 1.11 (95% CI 0.69 to 1.77) favouring the control group. Similarly, cardiovascular-related death was 22% (33/152) in the PMVR group compared with 20% (31/152) in the control group (HR 1.09, 95% CI 0.67 to 1.78). Statistical significance was not reported, however the confidence intervals suggest that there are no statistically significant differences between groups.

In the RCT of 279 patients comparing PMVR with surgery, 1-year mortality was 6% in both groups (11/184 for PMVR and 5/95 for surgery), but this is not

statistically significant (p=1.00).[3a] After 5 years, 21% of people who had PMVR had died compared with 27% who had surgery (not statistically significant, p=0.36).[3b]

In the systematic review of 1,015 patients comparing PMVR with surgery, the survival rates were 92% and 79% in the PMVR group at 1-year and 3-year follow-up respectively.[8] This compares with 93% and 84% in the surgical groups. This difference is not statistically significant, with a pooled HR and odds ratio (OR) of 1.17 (95% CI 0.77 to 1.78, I^2=33%, p=0.46).

In a prospective observational study comparing patients with functional MR who had PMVR (n=60) with propensity-matched patients (n=60) who had optimal medical management, 'freedom from death' was reported as 90%, 71% and 61% after 1, 2, and 3 years respectively in the PMVR group.[9] This compared with 64%, 52% and 35% in the medically managed group. This difference was statistically significant after 3 years, with an HR of 2.31 (95% CI 1.30 to 4.09, p=0.007). In a prospective case series matched with historical controls (who had mainly medical management) the survival rate after 1 year was 75% in the PMVR group, compared with 55% in the control group. This difference was statistically significant in favour of PMVR (p=0.047).[10]

Readmission to hospital

In the RCT of 614 patients, the annualised rate of hospital admissions for heart failure within 24 months of the procedure was 36% in the PMVR group compared with 68% in the medical management group (p<0.001; HR 0.53, 95% CI 0.40 to 0.70).[1] In the RCT of 304 patients, 49% (74/152) of patients who had PMVR needed hospitalisation for heart failure in the 12 months after the procedure.[2] This compares with 47% (72/152) in the control group (medical management). These values were statistically equivalent (HR 1.13, 95% CI 0.81 to 1.56).

In a prospective observational study of 749 patients, the rate of rehospitalisation after 1 year was 64% (364/566).[6] In a retrospective registry of 2,952 patients, the rehospitalisation rate for heart failure was 20%.[7] In the prospective observational study of 114 patients the hospitalisation rate for congestive heart failure in patients who had PMVR was 0.65 (95% CI 0.50 to 0.86) in the year before the PMVR procedure, compared with 0.36 (95% CI 0.24 to 0.54) 12 months after the procedure (p=0.018).[10]

In the comparative observational study of 120 patients 'freedom from admission to hospital' because of heart failure was consistently higher in patients who had

PMVR compared with matched patients who had optimal medical management. After 3 years the rate was 57% in the PMVR group compared with 37% in patients who had medical management. This difference was statistically significant (HR 1.86, 95% CI 1.05 to 3.29, p=0.004).[9]

Composite outcomes

The primary outcome in the RCT of 304 patients was a composite of death by any cause and hospital readmission for heart failure at 12 months. It reported a rate of 55% (83/152) in patients who had PMVR compared with 51% (78/152) in patients who only had medical management. There was no statistically significant difference between the groups, with an OR of 1.16 in the direction of the control group (95% CI 0.73 to 1.84, p=0.53).[2]

In the RCT of 279 patients, the primary efficacy outcome was a composite end point for 'freedom from death', from surgery for mitral valve dysfunction, and from grade 3+ or 4+ mitral regurgitation at 12-month follow-up. Using intention-to-treat analysis, this was achieved in 55% of patients who had PMVR compared with 73% in the surgery group. Thus non-inferiority was not demonstrated and PMVR did not perform as well as surgery (p=0.007). The principal reason for non-equivalence between the technologies was because of the relatively high requirement for additional corrective surgery in the PMVR group (20% compared with 2%, p<0.001) in the first year. After 5 years of follow up, surgery remained superior to PMVR for the primary outcome (44% compared with 64%, p=0.01)[3b]. There were fewer episodes of repeat surgery (28% compared with 9%, p=0.003), which was largely because of the initial high rates of surgery in the PMVR group (within 6 months of randomisation). The PMVR group also had inferior freedom from grade 3+ or 4+ MR (12% compared with 2%, p=0.02). Survival rates were the same at 30 days, 1 year, and 5 years.[3a,b]

MR grade

In 8 studies that reported on MR grades, statistically significant longitudinal reductions in MR were reported at discharge and later follow-up periods (up to 1 year) compared with baseline, with moderate and severe MR (grade ≥3+) reducing to mild or absent MR (grade ≤2+) in most patients. The results are not directly comparable because of differences in reporting methods. In the RCT of 614 patients, 95% (199/210) of patients in the PMVR group had MR grade 2+ or lower at 12 months compared with 47% (82/175) of patients in the medical management group (p<0.001).[1] In the RCT of 279 patients, the reduction in MR after 1 year was statistically significantly greater in the surgery group compared

with the PMVR group (p<0.001)[3a]. This significance was lost after 5 years (p=0.01), but this later analysis was based on low patient numbers.[3b]

A systematic review of 8 studies (n=1,015) that compared PMVR with surgery reported that, after 1 year, 84% of patients who had PMVR were free of recurrent MR (defined as MR grade ≥3+) compared with 97% of patients who had surgery[8]. After 3 years, 75% of patients who had PMVR were free of recurrent MR compared with 96% of those who had surgery. This difference statistically significantly favours surgery (relative risk [RR] 4.80, 95% CI 2.58 to 8.93, p<0.00001, I^2=0%).

NYHA classification

Six studies with NYHA class as an outcome reported large shifts from higher classes at baseline (III/IV) to lower classes (none to II) at discharge and later follow-up times. The results are not directly comparable because of differences in reporting. In the RCT of 614 patients, 72% (171/237) of patients in the PMVR group had NYHA class I or II at 12-month follow-up compared with 50% (115/232) in the medical management group (p<0.001).[1] In the RCT of 279 patients, 13% of patients had NYHA class III/IV in the surgery group compared with 2% in the PMVR group (p=0.002) at 1-year follow-up.[3a] However, after 5 years, only 3% of surviving patients reported an NYHA class of III/IV in the surgery group, compared with 9% in the PMVR group (p=0.19).[3b]

Health-related quality of life

In the RCT of 614 patients, the mean change from baseline in the Kansas City Cardiomyopathy Questionnaire score (range from 0 to 100, with higher scores indicating a better quality of life) was 12.5 points in the PMVR group compared with −3.6 points in the medical management group (p<0.001) at 12-month follow-up.[1] The RCT of 279 patients reported comparative health-related quality of life (HR-QoL) data for PMVR and surgery using the SF-36 questionnaire.[3a] In the PMVR group there were statistically significant improvements in the physical component compared with baseline at 30 days (mean difference 3.1 ± 9.4 standard deviation [SD], p<0.001) and 1 year (4.4 ± 9.8, p<0.001) and in the mental component at 30 days (4.4 ± 11.3, p<0.001) and 1 year (5.7 ± 9.9, p<0.001). In the surgery group there was an initial decrease in physical HR-QoL at 30 days (−4.9 ± 13.3, p=0.004) and no significant increase in the mental component (1.8 ± 13.4, p=01.14). At 1 year, both physical (4.4 ± 10.4, p=0.002) and mental (3.8 ±10.3, p=0.006) components were significantly improved. There were no statistically significant differences between PMVR and surgery with the

exception of the physical component at 30 days, which favoured PMVR ($p<0.001$).

In the prospective registry of 114 high-risk patients (78 PMVR and 36 controls), PMVR was associated with a significant improvement in the physical component of SF-36 at 12 months ($p=0.01$) compared with baseline.[10] There was also a non-significant trend towards improved mental QoL ($p=0.06$). In a prospective European registry of 749 patients there were significant improvements in self-care and anxiety domains of the EQ-5D.[6] There was also a significant improvement in VAS, from a median of 50 mm (IQR 40 mm to 60 mm) at baseline to 60 mm (IQR 50 mm to 70 mm) at follow up ($p<0.00001$).

Data from the NHS England CtE registry were also considered (academic in confidence).[11]

Additional interventions

In the RCT of 279 patients, 20% (37/184) of patients who were randomised to PMVR had surgery for mitral valve dysfunction within 1 year of the procedure.[3a] This rose to 27% (43/154) after 5 years.[3b] A prospective observational study of 567 patients reported that, after 12 months, 6% of patients had surgery and 3% had repeat PMVR.[4] Similar results were observed in a retrospective observational study of 2,952 patients who had PMVR, with 2% of patients having surgery and 6% having repeat PMVR after 1 year.[7] A prospective observational study of 628 patients reported that 4% of patients who had PMVR needed reintervention after 1 year; most (3%) were repeat PMVR procedures.[5]

Safety summary

Overall in-hospital and 30-day adverse events

Freedom from death from any cause, stroke, myocardial infarction, and non-elective cardiovascular surgery for a device-related complication at 30 days was 97% in an RCT of 614 patients.[1] The overall peri-procedural complication rate was 15% (21/144) in an RCT of 304 patients.[2] The primary safety outcome of an RCT of 273 patients was a composite of adverse events 30 days post-procedure.[3a] During this time PMVR was statistically significantly safer than open surgery, with 15% of patients having at least 1 adverse event with PMVR compared with 48% for surgery ($p<0.001$). However, this was mainly because of the increased requirement for blood transfusion associated with open surgery.

There was no significant difference in the complication rate when transfusions were excluded from the analysis.

The rate of major adverse cardiac and cerebral events at 30 days was 3% in a prospective observational study of 749 patients.[6] The rate of major adverse events (including death, myocardial infarction, and stroke) in patients who had PMVR was 27% in a prospective observational study of 114 patients.[10] Data from the NHS England Commissioning through Evaluation (CtE) registry were also considered (academic in confidence).[11]

Overall longer-term adverse events

The rate of freedom from device-related complications at 12-month follow-up was 97% in the RCT of 614 patients.[1] The RCT of 304 patients reported a high rate of serious adverse events in both groups over 12 months.[2] In patients who had PMVR this was 82% (125/152) compared with 80% (121/152) in the control group (p value not reported). Major cardiovascular events (death, stroke, myocardial infarction, and heart failure requiring hospitalisation) were reported in 57% (86/152) of patients in the PMVR group compared with 51% (78/152) in the control group (hazard ratio [HR] 1.22, 95% confidence interval [CI] 0.89 to 1.66).

The prospective observational study of 114 patients reported that the overall major adverse event rate in PMVR patients after 12 months was 42%.[10] Data from the NHS England CtE registry were also considered (academic in confidence).[11]

In-hospital and 30-day deaths

The rate of procedural deaths was less than 1%, but this was not reported in all studies. Mortality at 30 days was reported in 6 prospective studies and ranged from 0% to 8%, with a median value of 3%. An in-hospital death rate of 2% (18/749) was reported in the observational study of 749 patients.[6] Data from the NHS England CtE registry were also considered (academic in confidence).[11]

Mortality at 30 days was 1% (2/184) in patients who had PMVR compared with 2% (2/95) in patients who had surgery in the RCT of 279 patients (p=0.89).[3a] The early death rate (in-hospital or 30 days) was 2% for PMVR compared with 3% for surgery in the systematic review of 1,015 patients.[8] This difference was not statistically significant (relative risk [RR] 0.54, 95% CI 0.27 to 1.08, p=0.008, I^2=7%).

Device detachment and/or embolisation

Clip embolisation was reported in less than 1% of patients in 2 prospective observational studies (4/628[5] and 5/749[6] of patients). Single leaflet detachment occurred in 2% of patients in a retrospective registry, but fewer than 1% resulted in embolism.[7] In a prospective observational study of 567 patients, partial detachment (defined as the loss of insertion of a single leaflet from the implant device with ongoing insertion of the opposing leaflet) was reported in 5% (27/567) of patients, but complete detachment with embolisation was not reported.[4]

Device thrombus

No studies reported the occurrence of device thrombus formation.

Cardiac perforation and tamponade

Cardiac perforation, with or without tamponade, was reported in 2% (12/710) and 1% (actual numbers not reported) of patients after PMVR in 2 studies of 749 and 2,952 patients respectively[6,7]. Tamponade was reported in 1% (2/144) of patients in the RCT of 304 patients and in 1% of patients in 2 studies (6/567; 7/268).[4,5]

Cardiovascular and cerebrovascular complications

Short-term cardiovascular complications (that is, peri-procedural, in-hospital, and within 30 days), such as myocardial infarction and new onset atrial fibrillation, were reported at a rate of 1% or fewer in most studies. An exception to this was the prospective observational study of high-risk patients (n=78 who had PMVR), which reported a rate of 3% for both myocardial infarction and stroke; however, this was based on only 2 events each.[10] One prospective observational study reported a rate of new onset atrial fibrillation of 12% (73/628).[5] However, the definition of atrial fibrillation was not described, and may have included transient arrhythmia.

Cardiogenic shock resulting in intravenous inotropic support and cardiac embolism were each reported in 3% (4/144) of patients in the RCT of 304 patients.[2] In the longer term (12 months of follow up) the study reported a stroke rate of 5% (7/152), with 6 being ischaemic. This compared with 1 ischaemic stroke in the control group (0.7%). Significance was not tested. Stroke within 24 months of the procedure was reported in 4% (11/302) of patients in the PMVR group and 5% (11/312) of patients in the control group in the RCT of 614 patients (p=0.93).[1] Myocardial infarction within 24 months was reported in 5% (12/302) and 7% (14/312) of patients respectively (p=0.62).[1]

Atrial septum lesion or atrial septal defect was reported in 3% (4/144) of patients who had PMVR in the RCT of 304 patients.[2]

Infection

Sepsis was reported in 3% (2/60) of patients who had PMVR in a comparative study of 120 patients.[9] In the RCT of 304 patients, infections were reported in 18% (28/152) of patients who had PMVR and 18% (27/152) of patients in the control group.[2]

Anecdotal and theoretical adverse events

In addition to safety outcomes reported in the literature, specialist advisers are asked about anecdotal adverse events (events which they have heard about) and about theoretical adverse events (events which they think might possibly occur, even if they have never happened). For this procedure, specialist advisers listed the following anecdotal adverse events: oesophageal perforation, arteriovenous fistula, device embolisation, partial clip detachment. They considered that the following were theoretical adverse events: allergic reaction, development of mitral stenosis, chordal entanglement/rupture, air emboli, endocarditis, oesophageal stricture, pulmonary thromboembolism, renal failure, respiratory failure/atelectasis/pneumonia, septicaemia and skin injury or tissue changes because of exposure to ionising radiation.

The evidence assessed

Rapid review of literature

NICE search strategies, which were used to inform the October 2008 overview for IPG309, were re-run to identify new studies published since the searches conducted by NICE in 2009 (see the literature search strategy).

The NICE strategies for replication were sourced through documents supplied by NICE and through communication with the Senior Information Manager at NICE Guidance Information Services. The EAC team and NICE agreed that no quality assessment would be made of the NICE strategies and the intention was to use the NICE-designed strategies as supplied. While no quality assessment was made, some search structure and syntax errors in the NICE strategies (as

reported) were noticed as the searches were being run, and these were corrected. Apart from these minor edits, the terms used in the updated strategies reflect those used in the original NICE strategies (reported in table 1).

Given the timelines of the project and the purpose of the update search, the EAC team and NICE agreed that only the bibliographic databases listed in table 1 would be searched. In addition, it was agreed that strategies would be limited to results published in English language only, and that conference-related publication types would be excluded from the Embase search.

Where database functionality allowed, results were limited to records added to the database since the date of the last search, using appropriate fields such as the entry date field in MEDLINE. Where database functionality did not allow this, results were limited by publication date, reflecting the pragmatic context of the search. The EAC team agreed that use of the Entry Week field was not effective for date restriction in Embase; this field was therefore not used.

In addition to the literature search, 2 important new studies were published during the preparation of the draft overview. Due to the pivotal nature of these studies, they were also included (studies 1 and 2).

The following selection criteria (table 1) were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients with mitral valve regurgitation
Intervention/test	Percutaneous mitral valve repair
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the IP overview

This IP overview is based on approximately 6,000 patients. The studies consist of 3 randomised controlled trials (RCTs) [1, 2, 3a,3b], 4 single-arm observational studies [4-7]; 1 systematic review and meta-analysis [8]; 2 comparative observational studies [9, 10]; and 1 unpublished registry study[11] that reported on patients having PMVR through the NHS England Commissioning through Evaluation (CtE) programme.

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2) are listed in the appendix.

Table 2 Summary of key efficacy and safety findings on percutaneous mitral valve leaflet repair for mitral regurgitation

Study 1 (Stone GW, 2018)

Details

Study type	**Randomised controlled trial (COAPT)**
Country	US and Canada (78 centres)
Recruitment period	2012 to 2017
Study population and number	**n=614 (302 transcatheter mitral valve repair plus medical therapy [device group] versus 312 medical therapy alone [control group])** Patients with heart failure and moderate to severe secondary mitral regurgitation
Age and sex	Mean age 72 years; 64% male
Patient selection criteria	Patients with ischaemic or nonischaemic cardiomyopathy with a left ventricular ejection fraction of 20 to 50%; moderate to severe (grade 3+) or severe (grade 4+) secondary mitral regurgitation confirmed by echocardiography before enrolment; symptomatic (New York Heart Association [NYHA] functional class II, III, or IVa [ambulatory]) despite using stable maximal doses of guideline-directed medical therapy and cardiac resynchronisation therapy (if appropriate), which were administered in accordance with guidelines of professional societies; mitral valve surgery was deemed not to be appropriate. Each patient was assessed by a team that consisted of a heart-failure specialist, an interventional cardiologist, and a cardiothoracic surgeon with expertise in mitral valve disease.
Technique	Mitral valve repair was done using the Mitraclip device (Abbott).
Follow-up	**Median follow-up in device group was 22.7 months (16.5 months in control group)**
Conflict of interest/source of funding	The trial was sponsored by Abbott.

Analysis

Follow-up issues: 97.7% of patients in the device group and 94.2% of patients in the control group had 1 year follow-up data. Clinical follow-up, which is ongoing, was done at 1 week and 1, 6, 12, 18 and 24 months after the valve repair in the device group and after a visit with the heart failure specialist in the control group, and then annually through 5 years.

Study design issues: Multicentre, randomised, controlled, open-label trial. The primary effectiveness endpoint was all hospitalisations for heart failure within 24 months of follow-up, including recurrent events in patients with more than 1 event. The primary safety endpoint was freedom from device-related complications at 12 months (a prespecified objective performance goal was set at 88%). Analysis of the primary effectiveness endpoint was done with a joint frailty model to account for correlated events and the competing risk of death. A sample size of 610 patients was calculated to give 80% power to show the superiority of device-based treatment over medical therapy alone with regard to the primary effectiveness endpoint (assuming an annualised rate of all hospitalisations for heart failure of 42% per patient year in the device group and 60% in the control group, a 12-month mortality of 22% and 27% respectively and a 12-month attrition rate of 7.5%). All effectiveness analyses were done in the intention to treat population.

Study population issues: The baseline characteristics in the 2 groups were well matched. 36.5% of patients had received previous cardiac resynchronisation therapy. The cause of cardiomyopathy was ischaemic in 61% of patients. The mean Society of Thoracic Surgeons (STS) score for the risk of death within 30 days after mitral valve replacement was 8.2±5.9%. The central eligibility committee determined that 69.2% of patients were at high risk for surgery-related complications or death.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **614 (302 versus 312)**

Device implantation was attempted in 97.0% (293/302) of patients in the device group and 1 or more clips were implanted in 98.0% (287/293) of patients in whom implantation was attempted (95.0% of all patients in the device group). A mean of 1.7±0.7 clips were implanted per patient (range 1 to 4).

Primary and secondary end points - efficacy

	Device group (n=302)	Control group (n=312)	Hazard ratio (95% CI)	p value
Hospitalisations for heart failure within 24 months – events/patient years (annualised rate)	160/446.5 (35.8)	283/416.8 (67.9)	0.53 (0.40 to 0.70)	<0.001
Mitral regurgitation grade 2+ or lower at 12 months	199/210 (94.8%)	82/175 (46.9%)	-	<0.001
Death from any cause at 12 months - no. of events (Kaplan Meier [KM] estimate of rate)	57 (19.1)	70 (23.2)	0.81 (0.57 to 1.15)	<0.001*
Death from any cause at 24 months - no. of events (KM estimate of rate)	80 (29.1)	121 (46.1)	0.62 (0.46 to 0.82)	<0.001
Change in Kansas City Cardiomyopathy Questionnaire (KCCQ) score from baseline to 12 months – points**	12.5±1.8	-3.6±1.9	16.1 (11.0 to 21.2)	<0.001
Change in distance on 6-min walk test from baseline to 12 months - metres	-2.2±9.1	-60.2±9.0	57.9 (32.7 to 83.1)	<0.001
Hospitalisation for any cause within 24 months – events/patient years (annualised rate)	474/446.5 (106.2)	610/416.8 (146.4)	0.76 (0.60 to 0.96)	0.02
New York Heart Association (NYHA) functional class I or II at 12 months	171/237 (72.2%)	115/232 (49.6%)	-	<0.001
Change in left ventricular end-diastolic volume from baseline to 12 months - ml	-3.7±5.1	17.1±5.1	-20.8 (-34.9 to -6.6)	0.004

* for non-inferiority

**KCCQ scores range from 0 to 100, with higher scores indicating better quality of life and a difference of 5 points indicating a minimally significant difference.

Mitral regurgitation grade at discharge (n=260 patients who had echocardiography)

- 1+ or lower = 82.3% (214/260)
- 2+ = 12.7% (33/260)
- 3+ = 3.5% (9/260)
- 4+ = 1.5% (4/260)

Safety

Rate of freedom from device-related complications at 12 months=96.6% (lower confidence limit 94.8%), p<0.001 for comparison with goal of 88%

Freedom from death from any cause, stroke, myocardial infarction, and nonelective cardiovascular surgery for a device-related complication at 30 days (lower 95% confidence limit)=96.9% (94.7%), p<0.001 for comparison with goal of 80%

Adverse events within 24 months in the intention to treat population - number of patients with event (KM estimate of event rate)

	Device group (n=302)	Control group (n=312)	Hazard ratio (95% CI)	p value
Death from any cause	80 (29.1)	121 (46.1)	0.62 (0.46 to 0.82)	<0.001
Cardiovascular cause	61 (23.5)	97 (38.2)	0.59 (0.43 to 0.81)	0.001
Related to heart failure	28 (12.0)	61 (25.9)	0.43 (0.27 to 0.67)	<0.001
Not related to heart failure	33 (13.1)	36 (16.6)	0.86 (0.54 to 1.38)	0.53
Noncardiovascular cause	19 (7.3)	24 (12.7)	0.73 (0.40 to 1.34)	0.31
Hospitalisation for any cause	194 (69.6)	228 (81.8)	0.77 (0.64 to 0.93)	0.01
Cardiovascular cause	138 (51.9)	180 (66.5)	0.68 (0.54 to 0.85)	<0.001
Related to heart failure	92 (35.7)	151 (56.7)	0.52 (0.40 to 0.67)	<0.001
Not related to heart failure	72 (29.4)	72 (31.0)	0.98 (0.71 to 1.36)	0.92
Noncardiovascular cause	124 (48.2)	128 (52.9)	0.91 (0.71 to 1.17)	0.47
Death or hospitalisation for heart failure	129 (45.7)	191 (67.9)	0.57 (0.45 to 0.71)	<0.001
Death from cardiovascular cause or hospitalisation for heart failure	117 (42.7)	177 (63.6)	0.56 (0.44 to 0.70)	<0.001
Unplanned mitral valve intervention	10 (4.0)	15 (9.0)	0.61 (0.27 to 1.36)	0.23
MitraClip implantation	9 (3.7)	8 (6.6)	0.99 (0.38 to 2.58)	0.99
Mitral valve surgery	1 (0.4)	7 (2.5)	0.14 (0.02 to 1.17)	0.07
PCI or CABG	7 (2.8)	13 (4.3)	0.62 (0.24 to 1.60)	0.32
PCI	7 (2.8)	11 (3.6)	0.75 (0.28 to 2.02)	0.57
CABG	0	2 (0.7)	-	-
Stroke	11 (4.4)	11 (5.1)	0.96 (0.42 to 2.22)	0.93
Myocardial infarction	12 (4.7)	14 (6.5)	0.82 (0.38 to 1.78)	0.62
New cardiac resynchronisation therapy	7 (2.9)	8 (3.3)	0.85 (0.31 to 2.34)	0.75
LVAD implantation or heart transplantation	9 (4.4)	22 (9.5)	0.37 (0.17 to 0.81)	0.01
LVAD implantation	6 (3.0)	16 (7.1)	0.34 (0.13 to 0.87)	0.02
Heart transplantation	3 (1.4)	8 (3.6)	0.35 (0.09 to 1.32)	0.12

In the device group, the 30-day rates of death and stroke were 2.3% and 0.7% respectively.

Abbreviations used: CABG, coronary artery bypass grafting; CI, confidence interval; KCCQ, Kansas City Cardiomyopathy Questionnaire; KM, Kaplan Meier; LVAD, left ventricular assist device; PCI, percutaneous coronary intervention

Study 2 Obadia, J-F. (2018)

Details

Study type	**Prospective parallel randomised controlled trial**
Country	France (37 centres)
Recruitment period	2013 to 217
Study population and number	**n=304** Randomised in 1-to-1 ratio (open label). PMVR: n=152 Control (optimal medical management): n=152 Patients had chronic mitral regurgitation (MR) of functional (secondary) aetiology. Patients were considered to be unsuitable candidates for mitral valve surgery, with a EuroSCORE II value of 6.6 (IQR 3.5 to 11.9) in PMVR group compared with 5.9 (IQR 3.4 to 10.4) in control group.
Age and sex	PMVR group: mean 70.1 years (78.9% male) Control group: 70.6 years (70.4% male)
Patient selection criteria	Patients were eligible if they had severe secondary MR with a regurgitant volume of >30 ml per beat or an effective regurgitant orifice area of >20 mm^2 as assessed by echocardiography, in accordance with the 2012 guidelines of the European Society of Cardiology and the European Association for Cardio-Thoracic Surgery. Patients were also required to have a LVEF between 15% and 40% and to have chronic heart failure symptoms (assessed as NYHA functional class ≥II).
Technique	Intervention: percutaneous mitral valve leaflet repair using the MitraClip system and medical management. Details of post-procedural medical management not reported. Implantation carried out within 21 days of randomisation. Comparator: medical management alone.
Follow-up	**12 months**. All patients had 12 months for primary outcome (composite of death and readmission for heart failure). Follow up was incomplete for secondary outcomes (echocardiographic parameters, MR grade, NYHA class, quality of life).
Conflict of interest/source of funding	Funded by the French Ministry of Health and Research National Program and Abbott Vascular(the manufacturer of MitraClip). Abbott supplied most the devices but had no part in the design, implementation, analysis, or reporting of the study.

Analysis

Follow-up issues: This was a prospective RCT that aimed to actively follow up all enrolled patients at 12 months. Out of 452 patients enrolled, 145 were excluded, mainly because echocardiography indicated they were unsuitable for the procedure. 307 patients were randomised, with 3 patients excluded from the control arm for reasons related to informed consent, leaving 152 in each arm for intention to treat (ITT) analysis. Following randomisation, 43 patients were excluded from the PMVR arm because of cross over (n=8), protocol deviation (n=13), device failure (n=6), or underwent implantation ≥21days after randomisation. In the control group15 were excluded for reasons of crossover (n=2) or protocol deviation (n=13). This left 109 PMVR patients and 137 control patients eligible for *per protocol* analysis. A specific weakness of the study was that a number of secondary outcomes, including MR grade, NYHA class, and quality of life data were not reported due to "missing data" on follow up.

Study design issues: This was a multicenter, randomized, open-label, controlled phase 3 trial conducted in 37 centres in France. This was an independent study designed and implemented by the French Health Service. The control group, optimal medical management, was relevant to NHS practice in this patient group. Randomisation was conducted using permuted blocks and concealment of allocation maintained. Blinding of patients and treating personnel was not possible. Assessors were not blinded but primary outcomes were objective. A power calculation was performed to determine sample size (based on superiority of the primary outcome), and a protocol was published (NCT01920698). The primary outcome was a composite of death and readmission for heart failure which was analysed after one year using time-to-event analysis (Kaplan-Meier). These were objective outcomes which would lower the risk of detection bias. However, a number of secondary outcomes were not reported.

Study population issues: No statistically significant differences in baseline characteristics were reported with the exception of prior myocardial infarction (MI), which was higher in the intervention group (p=0.01, likely a chance finding). The patients were considered to

be at prohibitive risk for open surgery and therefore the population was generalisable to the UK NHS. All patients had NYHA class ≥2, but baseline MR grades were not reported.

Other issues: There was significant loss to follow up in the PMVR arm (28%), with 8 patients crossing over to medical management, and 6 device failures. These patients were accounted for in ITT (primary) analysis. Only patients with successful PMVR procedures were included in *per protocol* analysis.

Key efficacy and safety findings

Efficacy

Number of patient analysed (ITT): **304** (152 PMVR versus 152 control)

Primary and secondary efficacy outcomes (at 1 year ITT)

Outcome	PMVR group % (n/N)	Control group % (n/N)	HR or OR (95% CI)*
Primary outcome**	54.6 (83/152)	51.3 (78/152)	1.16 (0.73 to 1.84)
Secondary outcomes***			
Death from any cause	24.3 (37/152)	22.4 (34/152)	1.11 (0.69 to 1.77)
Cardiovascular death	21.7 (33/152)	20.4 (31/152)	1.09 (0.67 to 1.78)
Unplanned hospitalisation for heart failure	48.7 (74/152)	47.4 (72/152)	1.13 (0.81 to 1.56)
Major adverse cardiovascular events†	56.6 (86/152)	51.3 (78/152)	1.22 (0.89 to 1.66)

* HR were calculated with the use of stratified Cox proportional-hazards models. The 95% CI were not corrected for multiple testing; therefore, these intervals should not be used to infer definitive treatment effects.

** Composite primary outcome was death from any cause or unplanned hospitalization for heart failure at 12 months. The primary outcome was calculated with the use of a logistic-regression model and corresponds to an OR. No statistical difference was observed between arms (p=0.53).

*** The rates of the components of the composite primary outcome do not total the rates of the composite because patients could have more than one event.

† Composite of death, stroke, myocardial infarction, or unplanned hospitalisation for heart failure.

Per protocol analysis reported no statistically significant difference between PMVR or control in primary or secondary outcomes.

Safety

Peri-procedural complications (*per protocol*)

Complication	Proportion % (n/N)*
Peri-procedural complications during device implantation	14.6 (21/144)
Device-implantation failure**	4.2 (6/144)
Haemorrhage resulting in transfusion or vascular complication resulting in surgical intervention	3.5 (5/144)
Atrial septum lesion or atrial septal defect	2.8 (4/144)
Cardiogenic shock resulting in intravenous inotropic support	2.8 (4/144)
Cardiac embolism, including gas embolism and stroke	1.4 (2/144)
Tamponade	1.4 (2/144)
Urgent conversion to heart surgery	0 (0/144)

* The denominator of 144 represents the number of patients in whom device implantation was attempted.

** Among the 6 patients, the device was not implanted in 3 patients owing to the inability of the operator to grasp the mitral-valve leaflets during implantation, 2 patients had cardiac tamponade that occurred during trans-septal puncture, and 1 patient had cardiogenic shock during the procedure, which resulted in the procedure being aborted.

Pre-specified SAE at 12 months (ITT)

	PMVR % (n/N)	Control % (n/N)*
All SAE	82.2 (125/152)	79.6 (121/152)
Heart transplantation or mechanical cardiac assistance	3.9 (6/152)	5.9 (9/152)
Stroke**	4.6 (7/152)	0.7 (1/152)
Myocardial infarction	0 (0/152)	1.3 (2/152)
Need for renal-replacement therapy	3.3 (5/152)	0.7 (1/152)
Severe haemorrhage***	7.2 (11/152)	3.9 (6/152)
Infections	18.4 (28/152)	17.8 (27/152)

* No p values are reported because no adjustment was made for multiple testing.

** 1 patient in the intervention group had a haemorrhagic stroke; the remaining patients had an ischemic stroke.

*** Severe haemorrhage was defined as bleeding that was categorized as type 2 or higher, according to the modified BARC bleeding scale.

Abbreviations used: BARC, Bleeding Academic Research Consortium; CI, confidence interval; HR, hazard ratio; LVEF, left ventricular ejection faction; ITT, intention to treat; IQR, interquartile range; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; NYHA, New York Heart Association; OR, odds ratio; SAE, serious adverse events.

Study 3a and b Feldman, T (2011) and Feldman, T (2015) – also included in meta-analysis by Takagi, H (2017)

Details

Study type	**Prospective parallel randomised controlled trial**
Country	USA and Canada (37 centres)
Recruitment period	2005 to 2008
Study population and number	**n=279** Randomised in 2-to-1 ratio. PMVR: n=184 Surgery: n=95 Patients had grade 3+ or 4+ chronic mitral regurgitation (MR) and were eligible for mitral-valve repair or replacement. 73% had degenerative MR and 27% had functional MR.
Age and sex	PMVR group: mean 67.3 years (62% male) Surgery group: 65.7 years (66% male)
Patient selection criteria	All eligible patients had grade 3+ or 4+ chronic mitral regurgitation. Patients who were symptomatic were required to have a left ventricular ejection fraction (LVEF) of more than 25% and a left ventricular end-systolic diameter of 55 mm or less. Those who were asymptomatic were required to have at least one of the following: an LVEF of 25 to 60%, a left ventricular end-systolic diameter of 40 mm to 55 mm, new atrial fibrillation, or pulmonary hypertension. Eligible patients were candidates for mitral-valve repair or replacement surgery. According to the anatomical inclusion criteria, the primary regurgitant jet originated from malcoaptation of the middle scallops of the anterior and posterior leaflets.
Technique	Intervention: Percutaneous mitral valve leaflet repair using the MitraClip system. Patients were treated with heparin during the procedure, with aspirin (at a dose of 325 mg daily) for 6 months and with clopidogrel (at a dose of 75 mg daily) for 30 days after the procedure. Comparator: surgical repair or replacement of the mitral valve.
Follow-up	**5 years**. Follow up reported at 1 year [1] and 5 years in selected outcomes [2].
Conflict of interest/source of funding	The study was sponsored by Abbot Vascular (the manufacturer of MitraClip).

Analysis

Follow-up issues: This was a prospective RCT that aimed to actively follow up all enrolled patients at 1 year [3a] and 5 years [3b]. 279 patients were randomised in a 2-to-1ratio to undergo either percutaneous repair (184 patients) or mitral-valve surgery (95 patients). A total of 21/279 patients who underwent randomization withdrew consent for treatment (3% in the PMVR group and 16% in the surgery group). Of 258 treated patients, 243 (94%) complied with the protocol for the 12-month follow-up. 210 patients reported 5-year follow up data (154/178 in the PMVR group [87%] and 56/80 in the surgery group [70%]). Results from this time point (5 years) were reported using *per protocol* analysis rather than intention-to-treat analysis.

Study design issues: The study was designed by the sponsor, Abbott Vascular, in collaboration with the investigators. Patients were recruited at 37 study centres in the United States and Canada. Randomisation was conducted using permuted blocks and concealment of allocation maintained. Blinding of patients and treating personnel was not possible. Assessors were not blinded but primary outcomes were objective. Intention-to-treat analysis was reported. There were 2 primary outcomes which informed sample size through a power calculation. A non-inferiority design was implemented based on the expectation that surgery would be more effective in reducing the grade of MR and that PMVR would have a lower risk of adverse events. The primary efficacy outcome was a composite of freedom from death, from further surgery for mitral-valve dysfunction, and from grade 3+ or 4+ mitral regurgitation at 12 months. The primary safety outcome was the composite rate of adverse effects at 30 days post procedure.

Study population issues: No differences in baseline characteristics were reported. EuroSCORE and Society of Thoracic Surgeons (STS) scores were not reported. However, the patient population enrolled into the EVEREST II were by definition physically well enough to have open heart surgery. This may not be applicable to the population typically treated in the UK NHS (typically who cannot receive open heart surgery due to excessive surgical risk).

Other issues: There was significant cross-over reported, including patients with persistent MR grade ≥3+ being referred for surgery. After 1 year, 37/178 (21%) patients allocated to PMVR went on to receive surgical intervention.

Key efficacy and safety findings

Efficacy

Number of patient analysed: **279** (184 PMVR versus 95 surgery)

Primary efficacy outcome (at 1 year and 5 years)

Event*	PMVR % (number)	Surgery % (number)	Statistical comparison (p value)
Primary outcome at 1 year (ITT)			
Composite	55 (100/181)	73 (65/89)	0.007
Death	6 (11/181)	6 (5/89)	1.00
Surgery for MR dysfunction	20 (37/181)	2 (2/89)	<0.001
Grade 3+ or 4+ MR	21 (38/141)	20 (18/89)	1.00
Primary outcome at 5 years ("all treated")			
Composite	44 (68/154)	64 (36/56)	0.01
Death	21 (32/154)	27 (15/56)	0.36
Surgery for MR dysfunction	28 (43/154)	9 (5/56)	0.003
Grade 3+ or 4+ MR	12 (19/154)	2 (1/56)	0.02
Primary outcome at 5 years (if event-free at 1 year)			
Composite	69 (60/87)	75 (36/48)	0.55
Death	16 (14/87)	17 (8/48)	>0.99
Surgery for MR dysfunction	6 (5/87)	6 (3/48)	>0.99
Grade 3+ or 4+ MR	12 (10/87)	2 (1/48)	0.10

Secondary outcomes (change in ventricular measurements at 12 months)

Change from baseline Measurement	PMVR		Surgery	
	Value (patient number)	P Value*	Value (number of patients)	P value*
End-diastolic volume (ml)	−25.3±28.3 (144)	<0.001	−40.2±35.9 (66)	<0.001
End-diastolic diameter (cm)	−0.4±0.5 (148)	<0.001	−0.6±0.6 (67)	<0.001**
End-systolic volume (ml)	−5.5±14.5 (144)	<0.001	−5.6±21.0 (66)	0.04
End-systolic	−0.1±0.6 (146)	0.06	−0.0±0.6 (67)	0.8

Safety

Primary safety outcome at 30 days

Event*	PMVR % (number)	Surgery % (number)	Statistical comparison (p value)
Composite (any event)	15 (27/180)	48 (45/94)	<0.001**
Any excluding transfusion	5 (9/180)	10 (9/94)	0.23
Death	1 (2/180)	2 (2/94)	0.89
Myocardial infarction	0	0	N/A
Reoperation for failed surgical repair or replacement	0	1 (1/94)	0.74
Urgent or emergency CV surgery	2(4/180)	4 (4/94)	0.57
Major stroke	1 (2/180)	2 (2/94)	0.89
Renal failure	<1 (1/180)	0	1.00
Deep wound infection	0	0	N/A
Mechanical ventilation >48 hours	0	4 (4/94)	0.02
GI complication requiring surgery	1 (2/180)	0	0.78
New onset of permanent AF	1 (2/180)	0	0.78
Septicaemia	0	0	N/A
Transfusion of ≥2 units blood	13 (24/180)	45 (42/94)	<0.001

*Patients could have more than one adverse event at 30 days.
**P value of primary composite safety outcomes was calculated to test for the increased superiority of PMVR, as compared with surgery, by a pre-specified safety margin of -2%.

diameter (cm)				
Ejection fraction (%)	−2.8±7.2 (144)	<0.001	−6.8±10.1 (66)	<0.001

Values are reported as mean ± SD

* P value reports difference between baseline and 12 month data.

** End-diastolic diameter was statistically significantly less in surgery group compared with PMVR (p=0.04)

Secondary outcomes (change in quality of life as measured by SF-36)

Change from baseline Measurement	PMVR		Surgery	
	SF-36 value (patient number)	P Value*	SF-36 value (patient number)	P value*
30 days SF-36 scores**				
Physical component summary	3.1±9.4 (147)	<0.001	−4.9±13.3 (64)	<0.004***
Mental component summary	4.4±11.3 (148)	<0.001	1.8±13.4 (64)	0.29
12 months SF-36 scores**				
Physical component summary	4.4±9.8 (132)	<0.001	4.4±10.4 (60)	0.002
Mental component summary	5.7±9.9 (133)	<0.001	3.8±10.3 (60)	0.006

Values are reported as means ± standard deviation (SD).

* P value reports difference between baseline and follow up data.

** Quality of life was measured with the use of the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36), with scores ranging from 0 to 100, with higher scores indicating better quality of life.

*** Physical component summary was statistically significantly less in surgery group at 30 days compared with PMVR group (p<0.001)

Secondary outcomes (severity of mitral regurgitation at 12 months)

Severity of mitral regurgitation	PMVR % (n/N)	Surgery % (n/N)
0+ (none)	6 (9/153)	19 (13/69)
1+ (mild)	37 (57/153)	57 (39/69)
1+ to 2+ (mild to moderate)	12 (18/153)	7 (5/69)

2+ (moderate)	27 (41/153)	13 (9/69)
3+ (moderate to severe)	14 (21/153)	4 (3/69)
4+ (severe)	5 (7/153)	0 (0/69)
Reduction in severity of MR at 12 months was statistically superior in the surgery group (p<0.001)		

Subgroup analysis of primary efficacy outcome

Subgroup	PMVR Number of events (%)	Surgery Number of events (%)	P value of interaction
All patients	100/181 (55)	65/89 (73)	
Gender			
Male	63/114 (55)	43/59 (73)	0.97
Female	37/67 (55)	22/30 (73)	
Age			
≥70 years	52/86 (60)	23/38 (61)	0.00
<70 years	48/95 (51)	42/51 (82)	
MR aetiology			
Functional	26/48 (54)	12/24 (50)	0.02
Degenerative	74/133 (56)	53/65 (82)	
LVEF			
<60%	35/68 (51)	15/28 (54)	0.06
≥60%	64/111 (58)	50/61 (82)	

New York Heart Association (NYHA) class

12 months (ITT analysis)

Proportion of patients with functional NYHA class III or IV (signifying moderate to severe heart failure) using ITT analysis:

PMVR group: 2% (n=not stated)

Surgery group: 13% (n=not stated)

p=0.002

5 years ("all patients analysed)

Proportion of patients with functional NYHA class III or IV (signifying moderate to severe heart failure) using "all treated" analysis (Feldman 2015):

PMVR group (n=105): 9%

Surgery group (n=40): 3%

p=0.19

Abbreviations used: CV, cardiovascular; EVEREST, Endovascular Valve Edge-to-Edge Repair Study; GI, gastrointestinal; LVEF; ITT, intention to treat); LVEF, left ventricular ejection fraction; MR, mitral regurgitation; SD, standard deviation; SF-36, short form 36 items.

Study 4 Maisano, F. (2013)

Details

Study type	**Case series**
Country	Denmark, Germany, Italy, Switzerland
Recruitment period	2009 to 2012
Study population and number	**n=567** patients with significant mitral valve regurgitation (MR).
Age and sex	Mean 73.7 years; 63.8% male (362/567).
Patient selection criteria	Indication for treatment with PMVR therapy was given according to local institutional practice in consideration of CE Mark approved labelling and the MitraClip System "Instructions for Use". Eligible patients included those with symptomatic MR or asymptomatic moderate-to-severe (3+) or severe (4+) MR. Patients were at high risk from surgery (mean logistic EuroSCORE 23.0±18.3 [SD]) which would have made them ineligible for conventional surgery.
Technique	Percutaneous mitral valve leaflet repair using the MitraClip system. Details of post-procedural medical management not reported.
Follow-up	**12 months**
Conflict of interest/source of funding	The study was sponsored by Abbot Vascular Inc., with the principal investigator receiving consultancy fees from the sponsor.

Analysis

Follow-up issues: This was an observational study with passive follow up. 540/567 (95%) followed up at discharge; 450/567 (79%) followed up at 6 months; and 389/567 (69%) followed up at 12 months. There were 58 patient withdrawals and 98 deaths. Reasons for study withdrawal not fully reported.

Study design issues: The ACCESS-EU study (ACCESS-Europe A Two-Phase Observational Study of the MitraClip System in Europe), was a European prospective, multicentre, nonrandomized post-approval study of MitraClip therapy. The primary objective of the first phase of the ACCESS-EU study (reported) was to gain information with regard to the use of the MitraClip system in Europe with respect to health economics and clinical care, to define demographic data of patients, and to provide further evidence of the safety and effectiveness of the MitraClip System in a real-world setting. The study was single armed and reported intention-to-treat analysis. A primary outcome was not specified.

Study population issues: The study population was stratified by aetiology (23% had degenerative MR, 77% had functional MR), and comparisons were made between aetiologies. The study population were at high risk of surgery which matches the population eligible for the procedure in the UK NHS.

Other issues: Phase 2 of the ACCESS-EU study has been reported as being closed by the sponsor (NCT01288976).

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: **567** **Successful implant rate** 99.6% (565/567) **Mortality** KM derived freedom from mortality: 6 months: 88.2% (95% CI: 85.1% to 90.6%) 12 months: 81.8% (95% CI: 78.1% to 84.8%) **Haemodynamic measurements** Mean cardiac output for an undefined subset of patients increased from 3.7±1.5 l/min to 4.4±1.9 l/min at least 10 minutes after (0.7 l/min increase). Pulmonary Capillary Wedge Pressure V-wave decreased from 23.0±10.8 mmHg to 19.5±9.1 mmHg (3.5 mmHg reduction). All other hemodynamic parameters remained stable post-implant. **MR reduction** At discharge: • 91.2% achieved reduction to ≤MR2+ • 50.9% achieved reduction to ≤MR1+ At follow up: • 313/392 (79.8%) of patients free from >MR2+ at 6 months. • 258/327 (78.9%) of patients free from >MR2+ at 12 months (p<0.0001 compared with baseline). Improvements at 12 months: • 289/327 (88%) had ≥1 grade improvement. • 173/327 (53%) had ≥2 grades improvement. • 16% had ≥3 grade improvement. **NYHA class** 245/343 (71.4%) had NYHA class of II or I at 12 months. **6MWT** Improvement at 6 months (n=261): 56.4 ± 120.1 m (95% CI: 41.8 to 71.0, p=0.0006). Improvement at 12 months (n=216): 59.5 ± 112.4 m (95% CI: 44.5 to 74.6, p<0.0001). No significant improvement in the distance walked during the 6MWT between 6 and 12 months. **MLHFQ** Improvement at 6 months (n=311): 12.3 ± 20.9 points (95% CI: 14.6 to 10.0, p<0.0001). Improvement at 12 months (n=264): 13.5 ± 20.5 points (95% CI: 11.0 to 16.0, p<0.0001). Improvement between 6 months and 12 months (n=264): 0.4 ± 16.2 p=0.0002)	**Major peri-procedural complications** There were no deaths, strokes, or respiratory failure intra-procedurally and in the immediate post-operative period after the PMVR procedure. MI was reported acutely in 1/567 (0.2%); cardiac tamponade in 5/567 (0.9%) and the need for resuscitation in 6/567 (1.1%). **Safety outcomes after 30 days and 12 months** 30-day safety outcome / All patients at 30 days Proportion (%) / All patients at 12 months Proportion (%) Death: 19/567 (3.4)* / 98/567 (17.3) Stroke: 4/567 (0.7) / 6/567 (1.1) MI: 4/567 (0.7) / 8/567 (1.4) Renal failure: 27/567 (4.8) / 49/567 (8.6) Respiratory failure: 4/567 (0.7) / 5/567 (0.9) Need for resuscitation: 4/567 (1.8) / 12/567 (2.1) Cardiac tamponade: 6/567 (1.1) / 7/569 (1.2) Bleeding complication: 22/567 (3.9) / 27/567 (4.8) *Site-reported causes of death (30 days) were: cardiac (8/19); multi-organ failure (3/19); sepsis (2/19); pneumonia (1/19); respiratory failure (1/19); pulmonary embolism (1/19); cerebral (1/19); and unknown causes (2/19) **Device detachment** 27/567 patients (4.8%) had single leaflet device attachment (defined as the loss of insertion of a single leaflet from the MitraClip device with on-going insertion of the opposing leaflet). 26 of these were diagnosed within 6 months of the procedure. No device embolisation was reported. **Repeat intervention** 36/567 (6.3%) underwent mitral valve surgery within 12 months of the procedure. 19/567 (3.4%) underwent a second PMVR procedure to reduce MR; 14/19 (74%) of the second procedures were described as successful.
Abbreviations used: 6MWT, six minute walk test; CI, confidence interval; KM, Kaplan Meier; MI, myocardial infarction; MLHFQ, Minnesota Living with Heart Failure quality of life questionnaire; MR, mitral valve regurgitation; NYHA, New York Heart Association	

Study 5 Nickenig, G. (2014)

Details

Study type	**Case series**
Country	Belgium, Denmark, Germany, Italy, Sweden, Switzerland, UK (25 centres).
Recruitment period	2011 to 2012
Study population and number	**n=628** 72.0% (452/628) had functional MR. 22.8% (143/628) had degenerative MR. 2.7% (17/628) had mixed aetiology. Mean EuroSCORE 20.4 ± 16.7 (SD)
Age and sex	Mean 74.2 years, 63.1% (396/628) male.
Patient selection criteria	All consecutive patients receiving transcatheter mitral edge-to-edge repair with MitraClip were recruited.
Technique	Percutaneous mitral valve leaflet repair using the MitraClip system. Details of post-procedural medical management not reported.
Follow-up	**12 months** Median follow up 346 days (IQR 211 to 385 days)
Conflict of interest/source of funding	No direct industry funding was involved in this study.

Analysis

Follow-up issues: Clinical and echocardiographic follow-up was performed at discharge and at 1 and 12 months after implantation. For echocardiographic data, only patients with paired observations were included (n=368, 61% of total cohort). Follow up was not 100% because this was a voluntary, pragmatic, observational study.

Study design issues: This was a report on the Pilot European Sentinel registry. All consecutive patients receiving PMVR in the included centres (N=25) were included. The primary objective of the registry was to present a real-world overview of percutaneous leaflet-to-leaflet repair use in Europe. The study informed a range of important procedural and clinical outcomes at 1 year follow up. This study also presented comparative analysis of patients with MR of a degenerative or functional aetiology.

Study population issues: This was a multi-centre study including a UK centre; however, there were substantial differences in the characteristics of patients between participating centres. The patients had a high EuroSCORE indicating they were at high or prohibitive risk of open surgery.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **628**

Acute procedural success

95.4% (599/628)

Echocardiographic measurements

Measurement	Baseline	Discharge	Δ	p value
LVEDV (ml)	159.4 ± 86.1	154.8 ± 86.3	4.6	0.119
LVESV (ml)	103.0 ± 69.0	102.4 ± 74.6	0.6	0.797
LA volume (ml)	120.8 ± 66.3	110.4 ± 58.1	10.4	0.004
LVEF (%)	42.6 ±15.9	41.6 ± 15.0	1.0	0.020
SPAP (mmHg)	46.0 ± 14.5	40.2 ± 11.7	5.8	<0.001
TMG (mmHg)	2.0 ± 1.2	3.4 ± 2.0	-1.4	<0.001
Values are reported as mean ± SD				

Degree of MR pre- and post-procedure, and 12 months FU

Degree of MR	Pre-Clip	Post-Clip	1 year FU
None/mild	0.7 (3/368)	72.8 (268/368)	58.6 (216/368)
Moderate	13.2 (49/368)	25.4 (93/368)	35.4 (130/368)
Severe	86.1 (317/368)	1.8 (7/368)	6.0 (22/368)
Results reported as % (n/N). Significant improvement in MR post-procedure and at 1 year FU (p<0.001).			

NYHA class pre- and post-procedure, and 12 months FU

NYHA class	Pre-Clip	Post-Clip	1 year FU
I	2.2 (8/357)	28.9 (103/357)	26.9 (96/357)
II	13.7 (49/357)	50.4 (180/357)	47.3 (169/357)
III	67.8 (242/357)	19.1 (68/357)	21.0 (75/357)
IV	16.3 (58/357)	1.7 (6/357)	4.8 (17/357)
Results reported as % (n/N). Significant improvement in NYHA class post-procedure and at 1 year FU (p<0.001).			

1 year clinical outcomes

Mortality rate: 15.3% (KM analysis)

Survival free from death or readmission for heart failure: 69.0% ± 2.3% SD)

Re-intervention rate: 3.8% (n=17 of “overall population”)

PMVR re-intervention: 2.9% (n=13)

Mitral valve repair: 0.7% (n=3)

Mitral valve replacement: 0.2% (n=1)

Safety

Procedural and in-hospital outcomes

Outcome	Overall (%, n/N)
Death	2.9 (18/628)
Tamponade	1.1 (7/628)
Stroke	0.2 (1/628)
Severe bleeding	1.1 (7/628)
Transfusion	10.1 (63/628)
Vascular complication requiring intervention	0.7 (4/628)
New onset AF	11.7 (73/628)
Clip embolised	0.7(4/628)
Inability to reduce MR	3.5 (22/628)
Implant ≥2 clip	37.
Procedure duration (minutes)	138.3±67.9
Median hospital stay (IQR, days)	5 (3 to 7)
Results reported as percentages unless otherwise stated. Number of patients not reported. Overall cohort includes patients with FMR (n=452), DMR (n=143) and patients with mixed/other aetiologies (n=17). There were no significant differences detected between aetiologies.	

Multivariate subgroup analysis The following were independently associated with the primary composite outcome (freedom from mortality and re-admission for heart failure): • EuroSCORE: OR 1.44 (95% CI 1.11 to 1.86) • LVEF <30%: OR 2.69 (95% CI 1.64 to 4.42) • Successful clip deployment: OR 0.12 (95% CI 0.03 to 0.53)	
Abbreviations used: CI, confidence interval; DMR, degenerative mitral valve regurgitation; FMR, functional mitral valve regurgitation; IQR, interquartile range; KM, Kaplan Meier; LA, left atrium; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; MR, mitral valve regurgitation; OR, odds ratio; PMVR, percutaneous mitral valve repair; SD, standard deviation, SPAP, systolic pulmonary artery pressure; TMG, transmitral pressure gradient.	

Study 6 Puls, M. (2016)

Details

Study type	**Case series**
Country	Germany (21 centres)
Recruitment period	Prospective recruitment 2010 to 2013.
Study population and number	**n=749** (n=828 for Cox regression analysis) Patients who had percutaneous mitral valve leaflet repair (PMVR) in Germany.
Age and sex	Mean 76.0 years, 61.4% male.
Patient selection criteria	Patients who had percutaneous mitral valve leaflet repair were recruited non-consecutively. The decision for patient allocation to PMVR was left to the discretion of the participating centres and was made by a heart team (60.9%), by a cardiologist alone (37.8%), or by a cardiac surgeon (1.3% of patients). Reason for denying surgery was estimated surgical high-risk status (58.0%), age (48.3%), patient preference (25.0%), poor prognosis due to non-cardiac (mostly malignant) comorbidity (22.3%) and inoperability (11.4%). More than one reason was permitted.
Technique	Percutaneous mitral valve leaflet repair using the MitraClip system. Details of post-procedural medical management not reported.
Follow-up	**12 months** Median 386 days following PMVR implantation.
Conflict of interest/source of funding	Majority of funding was provided by Stiftung Institut fur Herzinfarktforschung (IHF)/Ludwigshafen. Independent of industry.

Analysis

Follow-up issues: Patients were included in this study if they were prospectively enrolled and were expected to have 12 months follow up data; 90.5% of patients reported this follow up period. Only patients with 12 months follow up were considered for the analyses with the exception of the Cox regression model study. Of the 79 “missing” patients 16/79 withdrew consent and 63/79 were lost to follow up.

Study design issues: The data reported in this study was from the prospective arm of the German TRAMI registry (Transcatheter Mitral Valve Interventions). Data from the TRAMI registry has been reported in several publications. This particular publication was selected as it reported prospective patients and had relatively complete 1 year follow up on all these patients. The study was pragmatic and should reflect practice of percutaneous mitral valve leaflet repair in Germany. However, the study did not adopt consecutive enrolment leaving it particularly prone to selection bias.

Study population issues: No specific eligibility criteria were described. 71.3% (478/570) patients had FMR, 27.8% (172/618) had DMR (sum not 100% because of indeterminate aetiology). The median logistic EuroSCORE was 20.0 (IQR 12.0 to 31.0). The median STS score was 6.0 (IQR 4.0 to 11.0). Logistic EuroSCORE was ≥20 in 50% of patients. This indicates the patients were at high or prohibitive risk of cardiac surgery

Key efficacy and safety findings

Efficacy

Number of patients analysed: **749**

Procedural success (clip implanted and MR "not severe")

97.0% (719/741)

MR grade at baseline and discharge

Grade	Baseline % (n/N)	Discharge % (n/N)
Mild	NR	85.2(631/741)
Moderate	NR	12.6 (93/741)
Severe	93.8 (660/704)	2.3 (17/741)

Note: 12 months MR grade not reported.

NYHA class after 12 months

Class I/II: 63.3% (305/482)

Class III/IV: 36.7% (177/482)

Quality of life at 12 months

Component of EQ-5D-3L	p value compared with baseline*
Mobility	0.58
Self-care	<0.001
Usual activities	0.89
Pain/discomfort	0.21
Anxiety	<0.0001
* Actual values not reported.	

EQ-VAS

Baseline: median 60 mm (IQR 50 to 70 mm)

12 months: 50 mm (IQR 40 to 60 mm, p<0.0001)

Rehospitalisation at 12 months

Rehospitalisation (all) 64.3% (364/566):

- Cardiac decompensation: 14.1% (80/566)
- Other cardiac reason: 17.8% (101/566)
- Non-cardiac reason: 25.8% (146/566)

Predictors of 1 year mortality (n=828)

NYHA class IV: HR 1.62 (p=0.02)

Anaemia: HR 2.44 (p=0.02)

Previous aortic valve intervention: HR 2.12 (p=0.002)

Serum creatinine ≥1.5mg/dL: HR 1.77 (p=0.002)

Peripheral artery disease: HR 2.12 (p=0.0003)

Left ventricular ejection fraction <30%: HR 1.58 (p=0.01)

Severe tricuspid regurgitation: HR 1.84 (p=0.003)

Procedural failure: HR 4.36 (p<0.0001)

Safety

In-hospital and 30-day outcomes

Adverse events*		Proportion % (n/N)
MACCE		3.1 (22/712)
	In-hospital mortality	2.4 (18/749)
	30-day mortality	4.5 (34/749)
	MI	0 (0/711)
	Stroke	0.8 (6/712)
Non-MACCE		
	TIA	0.8 (6/712)
	Respiratory failure	2.3 (16/711)
	Severe bleeding	7.0 (50/711)
	Low cardiac output	1.3 (9/710)
	Pericardial tamponade	1.7 (12/710)
	Clip embolisation	0 (0/710)
	Partial clip detachment	0.7 (5/749)
Additional MV procedure		1.5 (11/710)
	Surgical	0.8 (6/710)
	Percutaneous	0.7 (5/710)
* In-hospital unless otherwise stated.		

Intra-procedural death: 0.1% (1/749)

Procedural failure (defined as severe residual MR, abortion of PMVR procedure, conversion to open heart surgery, or failure as assessed by the interventional team): 3.2% (24/749).

Severe MR at discharge: 2.3% (17/741).

12 month outcomes

Adverse events*		Proportion % (n/N)
MACCE		
	Death	20.3 (152/749)
	MI	0.9 (4/425)
	Stroke	2.1 (9/423)
Non-MACCE		
	TIA	3.8 (16/426)
	Bleeding complications	12.6 (56/443)
	Need for resuscitation	2.1 (9/426)
Additional MV procedure		8.5 (37/436)
	Surgical	2.3 (10/436)

		Percutaneous	5.2 (23/436)
	* Cause of death: sudden unexpected death in 15.1% (23/152); other cardiovascular causes 36.8% (56/152); non-cardiovascular reasons 12.5% (19/152); unknown/ unreported 35.5% (54/152).		

Abbreviations used: DMR, degenerative mitral valve regurgitation; EQ-5D-3L, Euroqol 5 dimension 3 levels; FMR, functional mitral valve regurgitation; HR; hazard ratio; IQR, interquartile range; MACCE, major adverse cardiac and cerebrovascular events; MI, myocardial infarction; MR, mitral valve regurgitation; MV, mitral valve; NR, not reported; NYHA, New York Heart Association; SCS, Society of Thoracic Surgeons; SD, standard deviation, TIA, transient ischaemic attack.

Study 7 Sorraja, P (2017)

Details

Study type	**Registry**
Country	USA (>250 centres)
Recruitment period	2013 to 2015
Study population and number	**n=2,952** (baseline) All patients who had commercial therapy with the MitraClip system since initial U.S. Food and Drug Administration approval and who were enrolled in the TVT registry through the recruitment period were included in the study. Median STS-PROM for: • MV repair: 6.1 (IQR 3.7 to 9.9) • MV replacement: 9.2 (IQR 6.0 to 14.1) Aetiology: degenerative only: 85.9%; functional only: 8.6%; mixed degenerative and functional MR: 8.9%; post-inflammatory MR: 0.7%; other/indeterminate: 2.8%
Age and sex	Median 82 years, 55.8% male (1647/2952).
Patient selection criteria	Determination for transcatheter MV repair with MitraClip required: • The presence of symptomatic, severe (grade 3+ or 4+) primary MR (although most had DMR, patients with FMR were also included). • The patient to be at prohibitive surgical risk. • An evaluation of the patient by a cardiac surgeon, and participation of the clinical centre in a national registry. Prohibitive surgical risk was considered to be an STS predicted risk of operative mortality of either ≥6% for isolated MV repair or ≥8% for isolated MV replacement, or the presence of clinical features not captured in the risk calculator algorithm that portend such heightened risk (e.g. severe liver disease, radiation injury, dementia, porcelain aorta, frailty).
Technique	Percutaneous mitral valve leaflet repair using the MitraClip system. Details of post-procedural medical management not reported.
Follow-up	**1 year**
Conflict of interest/source of funding	No funding reported. Data analysis of the TVT (Transcatheter Valve Therapy) registry; this registry was implemented by the national Society of Thoracic Surgery (SCS) and American College of Cardiology (ACC).

Analysis

Follow-up issues: Details of attrition and reasons for loss to follow up not reported. However, consideration of KM analysis shows data was heavily censored at 1 year. Follow up outcomes (30 days and 1 year) were obtained through data linkage with CMS (Center for Medicare and Medicaid Services) database using patient identifiers. Centre participation with linkage was voluntary and excluded patients with private third party insurance.

Study design issues: Retrospective analysis of data from TVT registry and linkage to CMS database. As a retrospective analysis, reporting of outcomes were restricted to routine data. Specific limitations included issues with a lack of central adjudication of patient characteristics and outcomes, and bias associated with follow up using linked data.

Study population issues: All patients receiving PMVR during the recruitment period were included in the analysis, eliminating selection bias at baseline. This population was predominantly degenerative in aetiology, in line with FDA premarket approval; this population therefore differs from those treated in Europe, including the UK. Most patient receiving PMVR in the TVT registry were at prohibitive risk of surgery. EUROSCORE and STS score systems are not automatically interchangeable.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **2,952**

Successful procedure

Post-implant MR grade ≤ 2, no in-hospital mortality, and no cardiac surgery – 91.8%

Post-implant MR grade 1, no in-hospital mortality, and no cardiac surgery – 60.9%

MR at baseline and discharge

MR grade	Proportion patients in grade at baseline (%)	Proportion patients in grade at discharge
None/trace/trivial	NR	15.0
Mild (grade 1)	NR	46.8
Moderate (grade 2)	4.9	31.2
Moderate severe (grade 2 to 3)	16.6	2.9
Severe (grade 4)	76.4	4.1
Reported from full dataset (n=2952)		

30 day and 1 year clinical outcomes

	Events	30 days (%)	Events	1 year (%)
Death	96	5.2	336	25.8
MI	3	0.2	27	2.5
Stroke (any)	17	1.0	36	2.7
Haemorrhagic stroke	6	0.4	8	0.6
Heart failure hospitalisation (see below)	80	4.7	254	20.2
Mitral valve surgery	9	0.4	10	2.1
Repeat PMVR	23	1.3	80	6.2
Percentage of events based on number of linked patients (n=1867). However, not all linked patients reported all outcomes.				

1 year mortality and readmission to hospital for HF

DMR patients only (1 year FU, KM analysis):

- Mortality: 24.7%
- Readmission for HF: 20.5%
- Combined outcomes:35.7%

FMR patients only (1 year FU, KM analysis):

- Mortality: 31.2%
- Readmission for HF: 32.6%
- Combined: 49.0%

1-year

Predictors of 1 year mortality

The following factors were associated a with 1 year mortality:

- Severe tricuspid regurgitation: (HR: 1.91, 95% CI: 1.42 to 2.55)

Safety

Procedural and in-hospital outcomes

Complication type	Specific complication	Complication rate (%)
Cardiac perforation		1.0
Trans-septal complication		0.9
Bleeding		
	Access site	1.1
	Haematoma	1.6
	Major/life-threatening (VARC)	3.9
MI		0.1
Stroke		0.4
	TIA	0.1
	Ischaemic	0.4
	Haemorrhagic	0.03
Device related adverse events		
	Single leaflet device detachment	1.5
	Device embolisation	0.1
	Delivery system component embolisation	0.0
	Device thrombus	0.0
	Other	0.7
Open heart surgery		0.7
In hospital mortality		2.7
Outcomes based on full dataset (n=2952)		

• Increased age (HR 1.13, 95% CI 1.04 to 1.24, p=0.005) • LVEF (HR 0.93, 95% CI 0.89 to 0.96, p<0.0001) • Renal dialysis (HR 2.19; 95% CI 1.28 to 3.74, p=0.004) • Moderate or severe lung disease (HR 1.36, 95% CI 1.06 to 1.74, p<0.02). • Residual MR (HR not reported) **Combined 1 year mortality and readmission to hospital for HF** The following factors were associated a with the combined outcome of 1-year mortality and readmission for HF: • Age: HR per 5 years 1.08 (95% CI 1.01 to 1.15; p=0.02) • Renal dialysis: HR 2.09 (95% CI 1.37 to 3.28, p=0.001) • LVEF: HR per 5% 0.92 (95% CI 0.88 to 0.95, p<0.001) • Moderate or severe lung disease: HR 1.28 (95% CI 1.05 to 1.58, p<0.02) • Severe tricuspid regurgitation: HR 1.89 (95% CI: 1.49 to 2.39, p<0.001) • Post-procedural residual MR (HR not reported)	
Abbreviations used: CI, confidence interval; DMR, degenerative mitral valve regurgitation; FMR, functional mitral valve regurgitation; HF, heart failure; HR, hazard ratio; KM, Kaplan Meier; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MR, mitral valve regurgitation; MV, mitral valve; NR, not reported; STS-PROM, Society of Thoracic Surgery predicted risk of mortality; VARC, Valve Academic Research Consortium.	

Study 8 Takagi, H (2017)

Details

Study type	**Systematic review and meta-analyses**
Country	Constituent studies from Germany, Italy, Netherlands, Spain, and USA.
Recruitment period	Search date: June 2016. Studies published between 2012 and 2016.
Study population and number	**n=1,015** (574 patients who had percutaneous mitral valve leaflet repair versus 441 who had open surgical repair or valve replacement)**.** 1 RCT, 7 observational studies. Patients with MR (aetiology and severity undefined).
Age and sex	PMVR group: mean 68.4 years. Surgery group: mean 64.9 years. Mean difference between groups: 5.6 years, 95% CI 2.8 to 8.4 years, p<0.0001). Proportion of male patients not reported. However, no significant difference in proportion of sexes in the studies was reported (female risk (rate) difference = -1.5% [95% CI -13.4% to 10.4%])
Patient selection criteria	Study selection criteria: the design was an RCT or observational comparative study: the study population was patients with MR; patients were assigned to PMVR versus surgical repair; and main outcomes included early (30-day or in-hospital) or late (≥6-month including early all-cause mortality).
Technique	Percutaneous mitral valve leaflet repair using the MitraClip system. Further details of intervention not defined.
Follow-up	**Late follow up in studies ranged from 180 days to 5 years.**
Conflict of interest/source of funding	"There is no conflict of interest" was reported.

Analysis

Follow-up issues: "Early" follow up outcomes were defined as being in-hospital or within 30 days. "Late" follow up was between 180 days and 5 years. Only 1 RCT was included which reported on the primary outcome in 94% of the initial cohort at 1 year and 77% at 5 years. The observational studies collected data prospectively in the case of the intervention (PMVR), but sometimes used historical controls for the comparator group. In these studies, data collection was passive.

Study design issues: All studies comparing PMVR with surgical alternatives were included in this systematic review. The methodological quality and limitations of the individual studies were not assessed. The contributing observational studies were methodologically limited and subject to confounding. Cochrane and GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodology was not used. The reporting of outcomes was limited to early and late mortality and recurrent or residual MR.

Study population issues: No exclusion criteria were placed on the studies. Participants in the included RCT were at relatively low risk of surgery. In contrast, participants in the observational studies were considered to be at high risk of surgery (as measured by EuroSCORE or STS score). 3 observational studies were in patients with exclusively functional MR aetiology, whilst 1 observational study reported in patients with exclusively degenerative MR. The RCT and remaining 3 observational studies reported on an aetiological case mix of functional, degenerative, or mixed MR. The heterogeneous population reported in this study may limit its generalisability to the intended use in the NHS.

Other issues: This systematic review included surgery only as a comparator. In practice, medical management may be preferred in patients at high risk of surgery. One of the studies included was the RCT by Feldman (2011)[3a] and Feldman (2015)[3b], which have been described separately.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **1015** (574 PMVR versus 441, N=8)

"Late" survival

Freedom from death	PMVR	Surgery
1 year	91.5	92.7
3 years	79.2	84.0
RR estimate*	1.17 (95% CI 0.77 to 1.78, p=0.46) I^2=33%	
* Pooled HR/OR.		

Recurrent MR

Freedom from MR*	PMVR	Surgery
1 year	84.0	97.3
3 years	75.0	96.0
RR estimate**	4.80 (95% CI 2.58 to 8.93, p<0.00001) I^2=0%	
* Defined as MR grade ≥3+ ** Pooled HR/OR.		

Safety

"Early" mortality

	PMVR	Surgery
Mean of early mortality (%)*	1.6	3.1
RR estimate	0.54 (95% CI 0.54 0.27 to 1.08, p=0.08) I^2=7%	
* Early mortality refers to in hospital mortality or 30-day mortality.		

Abbreviations used: CI, Confidence interval; HR, hazard ratio, MR, mitral valve regurgitation; OR, odds ratio; RR, relative risk: STS, Society of Thoracic Surgeons.

Study 9 Giannini, C. (2016)

Details

Study type	**Comparative observational study**
Country	Italy
Recruitment period	2009 to 2015
Study population and number	**n=120** (60 who had PMVR versus 60 who had optimal medical therapy [OMT]) Patients had symptomatic, severe functional mitral valve regurgitation (FMR) and were at high surgical risk, estimated by means of the logistic EuroSCORE or by the presence of relevant risk factors associated with excessive morbidity and mortality as judged by the heart team.
Age and sex	Mean age 75 years, 67% male (80/120).
Patient selection criteria	160 patients were recruited consecutively. Patients were assessed for suitability for PMVR using trans-thoracic echocardiography (TTE) or trans-oesophageal echocardiography (TOE). Patients with suitable anatomy were offered the device (n=70), patients with unsuitable anatomy were maintained on OMT (n=90). 60 patients in each arm were recruited for analysis following propensity matching.
Technique	Percutaneous mitral valve leaflet repair using the MitraClip system.
Follow-up	**Median follow up 515 days (IQR 248 to 828 days)** 3 year follow up reporting using time-to-event analysis.
Conflict of interest/source of funding	"The authors have no conflicts of interest to disclose".

Analysis

Follow-up issues: This was a prospective observational study with passive follow up. Outcomes were reported using Kaplan-Meier (KM) analysis. There was extensive censorship at 3 years indicating significant patient attrition in both groups (e.g. mortality outcome 17% of original cohort at 3 years). Reasons for loss to follow up were not described.

Study design issues: The study was non-randomised. Patients with severe MR were selected for treatment with PMVR or OMT based on anatomical suitability which inevitably is a source of confounding. Overall, the study was well reported and transparent in its aims and methodology. The outcomes reported were limited to procedural events (PMVR group only) and comparative analysis of patient mortality and hospital readmission.

Study population issues: All patients had FMR, so generalisability to the broader population including patients with degenerative disease is limited. The enrolled population was at prohibitive risk from open heart surgery (median logistic EuroSCORE 17 [IQR 11 to 28]). Following propensity matching, no statistically significant difference was observed between the groups in terms of baseline characteristics and echocardiographic characteristics, other than more patients receiving PMVR had severe MR (grade 4+, 55% vs. 37%, p=0.05) and previous stroke (p=0.05).

Other issues: This study reported a comparison with medical management, which practically may be the only other management option in this high-risk cohort.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **120** (60 PMVR versus 60 OMT)

Clinical outcomes at 30 days, and 1, 2, and 3 years

Outcome*		PMVR (% ± SD)	OMT (% ± SD)
Freedom from death	30 days	100	98.3 ± 1.7
	1 year	89.7 ± 4.4	64.3 ± 6.4
	2 years	71.2 7.8	51.7 ± 7.0
	3 years	61.4 ± 9.4	34.9 ± 7.9
Comparison after 3 years: HR 2.31, 95% CI 1.30 to 4.09 (Log-rank test p=0.007)			
Freedom from cardiac death	30 days	100	96.5 ± 2.4
	1 year	93.6 ± 3.6	68.3 ± 6.4
	2 years	80.8 ± 6.8	58.6 ± 7.1
	3 years	76.6 ± 7.9	41.8 ± 8.8
Comparison after 3 years: HR 3.31, 95% CI 1.71 to 6.45 (Log-rank test p=0.002)			
Freedom from readmission due to HF	30 days	98.2 ± 1.7	96.4 ± 2.5
	1 year	76.5 ± 6.2	66.9 ± 7.4
	2 years	71.5 ± 6.8	48.2 ± 7.4
	3 years	57.2 ± 10.6	36.5 ± 8.4
Comparison after 3 years: HR 1.86, 95% CI 1.05 to 3.29 (Log-rank test p=0.04)			
* Calculated using time-to-event (KM) analysis.			

Deaths

47 patients (40%) died during the follow up period (at a median of 351 days, IQR 182 to 682 days). 36/47 deaths were cardiac related and 11 were non-cardiac. 9 cardiac deaths were reported in the PMVR group, classified as follows:

- Refractory heart failure (n=5)
- Acute cardiogenic shock (n=1)
- Electrical storm and storm and incessant ventricular tachycardia (n=2)
- Multi-organ failure (n=1).

A total of 43 patients (41%) underwent rehospitalisation due to heart failure in the follow-up period.

Safety

Procedural results (n=60)

Outcome	n/N (%)
Freedom from death (30 days)	60/60 (100%)
Implant≥2clips	19/60 (32%)
Sepsis	2/60 (3.3%)
Acute renal failure	1/60 (1.7%)
New onset AF	2/60 (3.3%)
Bleeding requiring transfusion	4/60 (6.6%)
Partial clip detachment before discharge	3/60 (5%)
Other*	0/60 (0%)

* Pericardial tamponade; urgent cardiovascular surgery for adverse event; vascular complication requiring intervention; stroke, mechanical ventilation >48h; Myocardial infarction.

Abbreviations used: CI, confidence interval; DME, degenerative mitral valve regurgitation; FMR, functional mitral valve regurgitation; HF, heart failure; HR, hazard ratio; KM, Kaplan Meier; IQR, inter-quartile range; OMT, optimal medical therapy; TOE, trans-oesophageal echocardiography; TTE, trans-thoracic echocardiography.

Study 10 Whitlow (2012)

Study type	**Prospective case series with retrospective control**
Country	USA
Recruitment period	Recruitment dates not reported.
Study population and number	**n=114** (78 received PMVR versus 36 in comparator group). Patients were symptomatic with grade 3+ to 4+ MR and a predicted surgical mortality risk of ≥12%. 41% of PMVR group and 36% of control group had DMR.
Age and sex	PMVR group: mean 76.7 years, 62.8% male Comparator group: mean 77.2 years, 50% male.
Patient selection criteria	Selection for PMVR was based on the presence of severe MR following echocardiography with TOE or TTE. Prohibitive surgical risk based on either the STS risk calculator, or surgeon co-investigator estimated mortality risk following pre-specified protocol criteria. Patients were excluded if they had had evidence of an acute myocardial infarction within 2 weeks; if they had an LVEF<20% and/or a LV end-systolic dimension >60 mm; an MV area >4.0 cm^2; leaflet anatomy that might preclude successful device implantation; a history of MV leaflet surgery; echocardiographic evidence of an intra-cardiac mass, thrombus, or vegetation; or active endocarditis.
Technique	Percutaneous mitral valve leaflet repair using the MitraClip system. Following the procedure, patients were treated with aspirin 325 mg/day for 6 months and clopidogrel 75 mg for 30 days. In the comparator group, 86% were managed using optimal medical management, and 14% underwent MV surgery.
Follow-up	**12 months.**
Conflict of interest/source of funding	Study sponsored by Abbot Vascular (manufacturer of MitraClip).

Analysis

Follow-up issues: This was a prospective observational study with 12 months planned follow up. Of the 78 patients enrolled, 96% (75/78) had the device implanted, and of these, 84% (62/75) reported satisfactory reduction in MR. At 12 months, 56/78 (72%) of patients reported clinical outcomes. In the control group, patients were selected retrospectively with all having reported 12 months data.

Study design issues: This was the EVEREST II HR study which analysed the use of PMVR using EVEREST II RCT[1] methodology but, in contrast to that study, recruited a population at prohibitive risk of surgery. Methods of recruitment were not described but may have not been consecutive, meaning there was potential selection bias. Both the intervention group (n=78) and comparator group (n=36) were small; and 5 patients in the comparator group had surgery, introducing confounding. Procedural and longitudinal outcomes were reported for the PMVR group only. Actual comparison between the two groups was limited to freedom from death using time-to-event (Kaplan Meier) analysis.

Study population issues: The study population was patients with severe MR of degenerative or functional aetiology who were at high or prohibitive risk of surgery. This may reflect the most likely eligible population for the procedure in the UK. With the exception of history of congestive heart failure (higher in PMVR group, p<0.001) and presence of pacemaker or implantable cardioverter-defibrillator device (higher in PMVR group, p=0.02), there were no statistically significant differences between the PMVR group and the control group reported at baseline.

Other issues: This cohort was one of the EVEREST II family of studies. Other cohorts included the EVEREST II RCT and EVEREST II REALISM continued access protocol.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **78** (receiving PMVR)

Successful implantation

96% (75/78)

Reasons for lack of success: MR could not be reduced (n=1); trans-septal complication and observation of an intra-cardiac thrombus after induction of general anaesthesia and before initiating the PMVR (exclusion criteria) (n=2)

Comparative freedom from death (at 12 months)

PMVR group: 76.4%

Control group: 55.3%

Survival was statistically significantly superior in PMVR group (p=0.047).

13/78 patients died in PMVR group between 30 days and 12 months, 6/13 were adjudicated as cardiac. Overall 19 patients died in the PMVR group:

- 12/19 were cardiac causes
- 6/19 were non-cardiac causes
- 1/19 was unknown cause

Longitudinal MR and NYHA outcomes in PMVR group

Clinical parameter	Baseline (n=78) n/N (%)	30 days (n=72) n/N (%)	6 months (n=63) n/N (%)	12 months (n=56) n/N (%)†
MR grade ≤2+*	1/78 (1.3)	51/70 (72.9)	44/60 (73.3)	42/54 (77.8) p<0.0001
NYHA class I/II**	8/78 (10.2)	52/71 (73.2)	49/61 (80.3)	40/54 (74.1) p<0.0001
NYHA class III/IV**	70/78 (89.8)	19/71 (26.8)	12/61 (19.7)	14/54 (25.9) p<0.0001

* Denominator indicates number of patients with echocardiographic follow-up.

** Denominator indicates number of patients with NYHA functional class assessment in the follow-up period.

† p value based on data for surviving patients with baseline and 12-month follow-up.

Longitudinal QoL outcomes in PMVR group

SF-36 score	Baseline (n=78) Mean ± SD (number)	30 days (n=72) Mean ± SD (number)	12 months (n=56) Mean ± SD (number)*
Physical component	31.6 ± 9.1 (73)	37.0 ± 9.7 (64)	36.5 ± 10.6 (51) p=0.01

Safety

Major adverse events at 30 days and 12 months (PMVR group)

Major adverse events*	Proportion of patients at 30 days** n/N (%)	Proportion of patients at 12 months** n/N (%)
Death	6/78 (7.7)	19/78 (24.4)
MI	2/78 (2.6)	4/78 (5.1) [5]
Major stroke	2/78 (2.6)	2/78 (2.6)
Renal failure	3/78 (3.8)	5/78 (6.4)
Deep wound infection	0/78 (0)	0/78 (0)
Mechanical ventilation >48 hours	2/78 (2.6)	2/78 (2.6)
GI complication requiring surgery	1/78 (1.3)	3/78 (3.8)
New onset of permanent AF	0/78 (0)	0/78 (0)
Septicaemia	0/78 (0)	3/78 (3.8)
Transfusion of ≥2 units blood	14/78 (17.9) [22]	19/78 (24.4) [31]
Total	21/78 (26.9) [38]	33/78 (42.3) [69]

* Adverse events are non-hierarchal (that is, an individual may experience more than one adverse event). Events adjudicated by a central events committee.

** When an event has occurred in an individual more than once, the total number of events is reported in square parentheses.

Mental component	44.2 ± 12.6 (73)	47.1 ± 12.4 (64)	49.2 ± 12.0 (51) P=0.06

* p value based on data for surviving patients with baseline and 12-month follow-up.

Physiological measurements in PMVR group

Clinical parameter	Baseline (n=78) Mean ± SD (number)	30 days (n=72) Mean ± SD (number)	6 months (n=63) Mean ± SD (number)	12 months (n=56) Mean ± SD* (number)
LV end-diastolic volume (ml)	166 ± 51 (78)	146 ± 48 (70)	141 ± 46 (60)	140 ± 43 (54) p<0.001
LV end-systolic volume (ml)	80 ± 43 (78)	74 ± 41 (70)	71 ± 35 (60)	72 ± 36 (54) p=0.001
Septal-lateral annular diastolic dimension (mm)	3.8 ± 0.4 (74)	3.8 ± 0.5 (64)	3.7 ± 0.4 (57)	3.6 ± 0.3 (52) p<0.0001
Septal-lateral annular diastolic dimension (mm)	3.2 ± 0.4 (74)	3.2 ± 0.4 (64)	3.1 ± 0.4 (57)	3.0 ± 0.4 (52) p=0.0008

* p value based on data for surviving patients with baseline and 12-month follow-up.

Rate of hospitalisation for congestive heart failure

Baseline: 0.65 (95% CI 0.50 to 0.86)

12 months: 0.36 (95%CI 0.24 to 0.54)

Difference p=0.018. Data analysis using Poisson regression model.

Abbreviations used: AF, atrial fibrillation; DMT, degenerative mitral valve regurgitation; EVEREST, Endovascular Valve Edge-to-Edge Repair Study; FMR, functional mitral valve regurgitation; GI, gastrointestinal; HR, high risk; KM, Kaplan Meier; LV, left ventricular; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MR, mitral regurgitation; MV, mitral valve; NYHA, New York Heart Association; QoL, quality of life; SF-36, short form 36 items; STS, Society of Thoracic Surgeons; TOE, trans-oesophageal echocardiography; TTE, trans-thoracic echocardiography.

Study 11 NHS England CtE registry (unpublished data at 28th February 2018)

[Academic in confidence]

Data have been redacted.

Validity and generalisability of the studies

- There were 2 RCTs (1 from the US and Canada and 1 from France) that compared PMVR with optimal medical management in people with functional mitral regurgitation for whom surgery was unsuitable.[1,2]
- One RCT from the US compared PMVR with surgery in a relatively healthy population which may not be representative of the indicated population in the UK NHS.[3a]
- Most studies (n=8) enrolled a mixed population of people with functional or degenerative MR. The efficacy and safety of PMVR may be partly dependent on MR aetiology.
- Most (n=5) of the observational studies were single-armed, so comparative data were not reported.
- The definition of what constitutes an adverse effect, complication, or procedural success varied between studies. Most studies did not summarise adverse events as a composite or summary outcome.
- The largest study (n=2,952) was a retrospective registry set in the US with limited reporting of outcomes (particularly procedural outcomes).
- Comparison with surgery was restricted to 1 RCT and 1 systematic review (n=8 including the RCT). Comparator groups in these studies were mainly from propensity-matched historical controls.
- The NHS England CtE registry was the only study that enrolled patients from centres based solely in the UK.
- The maximum follow-up in the included studies was 5 years (in the RCT).[3a,b]
- All the studies reported on the use of the MitraClip system in PMVR groups (now manufactured by Abbott).

Existing assessments of this procedure

There were no published assessments from other organisations identified at the time of the literature search.

Related NICE guidance

Interventional procedures

- Transapical transcatheter mitral valve-in-valve implantation for a failed surgically implanted mitral valve bioprosthesis. NICE interventional procedures guidance 541 (2015). Available from https://www.nice.org.uk/guidance/IPG541.

- Percutaneous pulmonary valve implantation for right ventricular outflow tract dysfunction. NICE interventional procedures guidance 436 (2013). Available from http://www.nice.org.uk/guidance/IPG436

- Percutaneous mitral valve annuloplasty (July 2010). NICE interventional procedures guidance 352 (2010) Available from http://www.nice.org.uk/guidance/IPG352

- Thoracoscopically-assisted mitral valve surgery (December 2007). NICE interventional procedures guidance 245 (2007). Available from http://www.nice.org.uk/guidance/IPG245

Additional information considered by IPAC

Specialist advisers' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College. The advice received is their individual opinion and is not intended to represent the view of the society. The advice provided by specialist advisers, in the form of the completed questionnaires, is normally published in full on the NICE website during public consultation, except in circumstances but not limited to, where comments are considered voluminous, or publication would be unlawful or inappropriate. Five Specialist Adviser Questionnaires for percutaneous mitral valve leaflet repair for mitral regurgitation were submitted and can be found on the NICE website.

Patient commentators' opinions

NICE's Public Involvement Programme sent 50 questionnaires to 2 NHS trusts for distribution to patients who had the procedure (or their carers). NICE received 20 completed questionnaires.

The patient commentators' views on the procedure were consistent with the published evidence and the opinions of the specialist advisers. See the patient commentary summary for more information.

Company engagement

A structured information request was sent to 1 company who manufactures a potentially relevant device for use in this procedure. NICE received 1 completed submission. This was considered by the IP team and any relevant points have been taken into consideration when preparing this overview.

Issues for consideration by IPAC

- The use of PMVR in patients with severe MR has been assessed by NHS England through CtE and is the subject of a prospective registry (study 11). The patient selection criteria for the CtE registry was restricted to patients with severe MR (grade 3+ or 4+) who were at high or prohibitive risk of conventional surgery.
- Most the studies included in the overview were largely representative of the CtE population. However, a noticeable exception is the EVEREST II RCT [3], which enrolled operable patients.
- There are 2 ongoing RCTs, 1 of which will compare PMVR (with MitraClip) with medical management (ReShape-HF2 trial NCT02444338) and 1 will compare it with surgery (MATTERHORN trial NCT02371512). These studies are restricted to populations with functional MR.

References

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3b. Feldman T, Kar S, Elmariah S, et al. Randomized Comparison of Percutaneous Repair and Surgery for Mitral Regurgitation: 5-Year Results of EVEREST II. *Journal of the American College of Cardiology*. 2015; 66: 2844-54
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5. Nickenig G, Estevez-Loureiro R, Franzen O, et al. Percutaneous mitral valve edge-to-edge repair: in-hospital results and 1-year follow-up of 628 patients of the 2011-2012 Pilot European Sentinel Registry. *Journal of the American College of Cardiology*. 2014; 64: 875-84
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9. Giannini C, Fiorelli F, De Carlo M, et al. Comparison of Percutaneous Mitral Valve Repair Versus Conservative Treatment in Severe Functional Mitral Regurgitation. *American Journal of Cardiology*. 2016; 117: 271-7
10. Whitlow PL, Feldman T, Pedersen WR, et al. Acute and 12-month results with catheter-based mitral valve leaflet repair: the EVEREST II (Endovascular Valve Edge-to-Edge Repair) High Risk Study. *Journal of the American College of Cardiology*. 2012; 59: 130-9
11. Unpublished data from the NHS England Commissioning through Evaluation (CtE) MitraClip registry: https://www.england.nhs.uk/commissioning/spec-services/npc-crg/comm-eval/

Literature search strategy

Resource	Date searched	Records identified
Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present	06/06/18	1144
EMBASE	06/06/18	1400
Cochrane Database of Systematic Reviews (CDSR)	07/06/18	10
Cochrane Central Register of Controlled Trials (CENTRAL)	07/06/18	105
Database of Abstracts of Reviews of Effects (DARE)	07/06/18	5
Health Technology Assessment Database (HTA)	07/06/18	15
NHS Economic Evaluation Database (EED)	07/06/18	2
TOTAL		**2681**

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

1 Surgical Procedures, Minimally Invasive/
2 percutan$.tw.
3 endovascular$.tw.
4 or/1-3
5 Mitral Valve/
6 Heart Valves/
7 (mitral adj3 valve$).tw.
8 (heart adj3 valve$).tw.
9 (bicuspid adj3 valve$).tw.
10 (cardiac adj3 valve$).tw.
11 or/5-10
12 (repair$ or reconstruc$ or clos$).tw.
13 11 and 12
14 Mitral Valve Insufficiency/
15 (Mitral adj3 insufficien$).tw
16 (Mitral adj3 regurgitat$).tw.
17 (mitral adj3 incompet$).tw.
18 or/14-17
19 4 and 13 and 18
20 Mitraclip.tw.
21 19 or 20
22 (mitral$ adj3 annuloplast$).tw.
23 4 and 22 and 18
24 21 or 23
25 (2009$ or 2010$ or 2011$ or 2012$ or 2013$ or 2014$ or 2015$ or 2016$ or 2017$ or 2018$).ed,dc,dp,ep,vd,yr.
26 24 and 25
27 limit 26 to english language
28 remove duplicates from 27

Appendix

The following table outlines the studies that are considered potentially relevant to the IP overview but were not included in the main data extraction table (table 2). It is by no means an exhaustive list of potentially relevant studies. In particular, due to the high volume of literature recovered, non-comparative studies with less than 100 participants were excluded, as were most prognostic studies (studies which focussed on the relationship between patient characteristics and outcomes).

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Alozie A, Paranskaya L, Westphal B, et al. (2017) Clinical outcomes of conventional surgery versus MitraClip therapy for moderate to severe symptomatic mitral valve regurgitation in the elderly population: an institutional experience. BMC Cardiovascular Disorders.17(1):85.	Retrospective cohort study (surgery vs. MitraClip) n=136 [n=84 after matching] Surgery FU=2.08 years MitraClip FU=0.75 years	Procedural success was 100% in surgery cohort compared with 96% in MitraClip patients. 30-day mortality was 7.1% vs. 4.8% (p=1.000) in surgery and PMVR cohorts respectively. At 1 year mortality was 9.5% vs. 21.4%. in surgery and PMVR cohorts respectively. Surgery was associated with improved MR (post-operative MR≥2 at discharge 100% vs. 23.8%).	Comparator group included additional surgical procedures to mitral valve repair or replacement.
Attizzani GF, Ohno Y, Capodanno D, et al.(2015) Extended use of percutaneous edge-to-edge mitral valve repair beyond EVEREST (Endovascular Valve Edge-to-Edge Repair) criteria: 30-day and 12-month clinical and echocardiographic outcomes from the GRASP (Getting Reduction of Mitral Insufficiency by Percutaneous Clip Implantation) registry. Jacc: Cardiovascular Interventions;8(1 Pt A):74-82.	Analysis of prospective registry n=120 FU=12 months	Re-analysis of GRASP registry data, dividing patients into echocardiographic characteristics of EVEREST I and II trials (with and without). No important difference in outcomes were reported between theses subgroups.	Re-analysis of GRASP registry data. GRASP registry was not included because larger prospective registries exist.
Bail DH and Doebler K. The MitraClip System: a systematic review of indications, procedural requirements, and guidelines. Thoracic &	Systematic review N=42 studies identified	Aimed to identify indication criteria for PMVR and assess efficacy of procedure.	Narrative review with no meta-analysis. No usable data reported.

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Cardiovascular Surgeon. 2014; 62: 18-25.			
Bozdag-Turan I, Paranskaya L, Birkemeyer R, et al. (2014) Percutaneous mitral repair with the MitraClip system in patients with mild-to-moderate and severe heart failure: a single-centre experience. Cardiovasc Ther.32(2):66-73.	Case series n=121 Comparison of patients with LVEF ≤30% (n=39) and LVEF>30 (n=82) 12 months FU	No significant difference in procedural success, number of clips used, or in hospital mortality. No significant difference in MR grade, NYHA class, or MACCE at 12 months. Multivariate analysis reported post-procedural MR grade was most associated with mortality (OR 2.121, 95% CI 1.1 to 4.1).	Smaller observational study that did not compare alternative management strategies. Only larger observational studies included in table 2 (n>500).
Braun D, Lesevic H, Orban, et al. Percutaneous edge-to-edge repair of the mitral valve in patients with degenerative versus functional mitral regurgitation. Catheterization & Cardiovascular Interventions. 2014 Jul 1;84(1):137-46.	Prospective observational study n=119, DMR (n=72), FMR (n=47) 12 months FU	Procedural success was 83.3% for DMR vs. 89.4% for FMR. Composite endpoint (freedom from MR 3+ or 4+, mitral valve reintervention and death) after 12 months FU was 59.7% for DMR vs. 63.8% FMR. Significant reductions in NYHA class and MR grade.	Smaller observational study that did not compare alternative management strategies. Only larger observational studies included in table 2 (n>500).
Buccheri S, Capodanno D, Barbanti M, et al. A Risk Model for Prediction of 1-Year Mortality in Patients Undergoing MitraClip Implantation. American Journal of Cardiology. 2017 May 01;119(9):1443-9.	Prospective case series n=311 1 year FU	Validation of GRASP nomogram. GRASP nomogram had superior discriminative ability than EuroSCORE II or STS-PROM at determining cardiovascular mortality risk.	Study did not report clinical outcomes and probably enrolled patients included in other studies.
Buzzatti N, De Bonis M, Denti P, Barili F, et al. What is a "good" result after transcatheter mitral repair? Impact of 2+ residual mitral regurgitation. Journal of Thoracic & Cardiovascular Surgery. 2016 Jan;151(1):88-96.	Retrospective observational study n=223 Median FU 20.5 months	Residual MR grade 2+ in 64 patients (n=64). These patients exhibited greater levels of cardiac death (HR 5.3, 95% CI interval, 2.41 to 11.56, p<.001). MR grade 2+ also associated with NYHA class (p=0.07)	Smaller observational study that did not compare alternative management strategies. Only larger observational studies included in table 2 (n>500).
Cheng R, Tat E, Siegel RJ, Arsanjani R, et al. Mitral annular calcification is not associated with decreased procedural success, durability of repair, or left ventricular remodelling in percutaneous edge-to-edge repair of mitral regurgitation. EuroIntervention. 2016 Oct 20;12(9):1176-84.	Observational study n=173 Comparison of patients with MAC (n=28) and without (n=145) 1 year FU	No difference between patients with post-procedural MAC in terms of post-procedural MR severity. No difference in NYHA class.	Smaller observational study that did not compare alternative management strategies. Only larger observational studies included in table 2 (n>500). Comparison of

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
			MAC less relevant in determining
Chiarito M, Pagnesi M, Martino EA, et al. Outcome after percutaneous edge-to-edge mitral repair for functional and degenerative mitral regurgitation: a systematic review and meta-analysis. Heart. 2017 Jun 29;29:29.	Systematic review and meta-analysis Comparison of outcomes in patients receiving PMVR with FMR and DMR. N=9 studies	FMR vs. DMR *Risk of ≥ 2 MR:* RR 1.12 (95% CI 0.86 to 1.47) *Risk of re-intervention:* RR 0.60 (95% CI 0.37 to 0.97) *Risk of mortality:* RR 1.28 (95% CI 0.90 to 1.77) *Risk of primary safety endpoint:* RR 0.76 (95% CI 0.08 to 7.27)	The review focussed on the comparison between FMR and DMR rather than alternative management interventions.
Conradi L, Seiffert M, Treede H, et al. Towards an integrated approach to mitral valve disease: implementation of an interventional mitral valve programme and its impact on surgical activity. European Journal of Cardio-Thoracic Surgery. 2013 Aug;44(2):324-8; discussion 8-9.	Evaluation of interventional programme of PMVR n=1112 patients receiving mitral surgery n=270 receiving PMVR	Following introduction of PMVR, the overall 30-day mortality decreased from 7.2 to 4.4% (p=0.22). Mean logistic EuroSCORE I of PMVR patients was significantly higher compared with surgical patients (28.8 ± 18.8 vs. 9.5 ± 10.5%; p=0.01).	Study on surgical activity using "before and after" analysis subject to confounding. A larger, more robust study has been included (Study 5, Sorraja, P (2017)).
Conradi L, Treede H, Rudolph V, et al. Surgical or percutaneous mitral valve repair for secondary mitral regurgitation: comparison of patient characteristics and clinical outcomes. European Journal of Cardio-Thoracic Surgery. 2013 Sep;44(3):490-6; discussion 6.	Retrospective observational analysis n=171 n=95 PMVR n=76 surgical repair 190 days FU	Patients receiving PMVR were significantly older, had lower LVEF, and had higher logistic EuroSCORE I compared with surgical patients. Procedural success was 95.8% in PMVR patients compared with 98.7% in patients receiving PMVR. Thirty-day mortality was 4.2 and 2.6% (p=0.557), and the mean grade of residual MR was 1.4 ± 0.8 and 0.2 ± 0.4 (P < 0.001) after MitraClip treatment and surgical MVR, respectively. There was no significant difference in 6 month mortality.	Smaller observational study that did not compare alternative management strategies. Only larger observational studies included (n>500) in table 2.
Capodanno D, Adamo M, Barbanti M, Giannini C, et al. Predictors of clinical outcomes after edge-to-edge percutaneous mitral valve repair. American Heart Journal. 2015 Jul;170(1):187-95.	Retrospective case series (GRASP-IT registry) n=304 2 years (median 366 days) FU	Acute procedural success was obtained in 92% of cases, with no intraprocedural death. The cumulative incidences of all-cause death were 3.4%, 10.8%, and 18.6% at 30 days, 1 year, and 2 years, respectively. NYHAl class IV and ischemic MR etiology at baseline were found to significantly and independently predict both all cause death and a composite of all cause death or rehospitalisation for heart failure. Acute procedural	Smaller observational study (GRASP registry) that did not compare alternative management strategies. Only larger observational studies included in table 2 (n>500).

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
		success was independently associated with a lower risk of all-cause death and the composite secondary outcome.	
De Bonis M, Lapenna E, Buzzatti N, et al. Optimal results immediately after MitraClip therapy or surgical edge-to-edge repair for functional mitral regurgitation: are they really stable at 4 years? European Journal of Cardio-Thoracic Surgery. 2016 Sep;50(3):488-94.	Retrospective comparative study (PMVR vs. surgery) n=143 Median 3.2 years FU	Freedom from cardiac death at 4 years was similar in the surgical and PMVR group (81 ± 5.2 vs 84 ± 4.6%, p=0.5). However, the initial PMVR results did not remain stable in terms of MR grade, with significant severity of MR compared at 4 years compared with earlier time periods. with the corresponding 1 year grades. Compared with surgery, PMVR was a predictor of recurrence of MR grade ≥ 2+ (HR 5.2, 95% CI) 2.5 to 10.8,p=0.000).	Study not selected because it was retrospective and characteristics of patients were different at baseline.
De Bonis M, Taramasso M, Lapenna E, et al. MitraClip therapy and surgical edge-to-edge repair in patients with severe left ventricular dysfunction and secondary mitral regurgitation: mid-term results of a single-centre experience+. European Journal of Cardio-Thoracic Surgery. 2016 Jan;49(1):255-62.	Retrospective observational study n=120 n=65 surgical repair n=55 PMVR (secondary MR) Median 4 years FU	No significant difference in groups in terms of in-hospital mortality or 4 year mortality (81% for surgery vs. 79% for PMVR, p=0.9). MR ≥ 2+ at hospital discharge was 7.6% for surgery and 29% for MitraClip (p=0.002). At 4 years, freedom from MR grade ≥ 2+ significantly benefitted surgery (74.9% vs 51.4%, p=0.01). Use of PMVR was identified as a predictor for MR grade ≥2+ as well as ≥3+; no predictors were identified for surgery.	Study not selected because patient characteristics were different at baseline.
Di Prima AL, Covello DR, Franco A, et al. Do patients undergoing MitraClip implantation require routine ICU admission? Journal of Cardiothoracic & Vascular Anesthesia. 2014 Dec;28(6):1479-83.	Retrospective case series n=130 All patients admitted to ICU	Median ICU stay was 0.98 days (95% CI 0.82 days to 1.87 days). Median mechanical ventilation time was 9.5 (6.8-14.1) hours. Predictors of "complicated post-operative course" were serum creatinine, cardiogenic shock, ventricular tachycardia and use of intra-procedural inotropes. It was difficult to predict the postoperative course based on preoperative characteristics.	Smaller retrospective study with focus on ICU requirement.
Downs E, Lim S, Ragosta M, Yount K, et al. The influence of a percutaneous mitral repair program on surgical mitral valve volume. Journal of Thoracic & Cardiovascular Surgery. 2015 Nov;150(5):1093-7.	Retrospective observational study Cohort of n=468 eligible for PMVR analysed n=156 PMVR n=82 surgery.	During the timeframe studied, the volume of patients eligible for mitral valve surgery increased. Operative mortality for all patients undergoing isolated mitral surgery from 2008 to 2014 was 2.6%. The availability of PMVR resulted in	Smaller retrospective study with limited reporting of outcomes.

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
		an increase in mitral valve referrals.	
Downs EA, Lim DS, Saji M, and Ailawadi G. Current state of transcatheter mitral valve repair with the MitraClip. Annals of Cardiothoracic Surgery. 2015 Jul;4(4):335-40.	Retrospective chart review n=115 FU 1 month	PMVR successful in all patients with a 30-day mortality of 2.6%. 80.7% of patients had trace or MR grade 1+ at hospital discharge. NYHA class was class III/IV in 79% of patients exhibiting class III pre-procedure and class 1/II in 81% of patients at 1 month follow-up.	Small retrospective study with short-term follow up.
Eggebrecht H, Schelle S, Puls m et al. (2015) Risk and outcomes of complications during and after MitraClip implantation: Experience in 828 patients from the German TRAnscatheter mitral valve interventions (TRAMI) registry. Catheterization and Cardiovascular Interventions 86: 728–735	Registry data n=828	MitraClip implantation appears to be a safe treatment option with low rates of MACCE and clip-specific complications.	Data from the TRAMI registry are already included in table 2 (study 5).
Estevez-Loureiro R, Franzen O, Winter R, et al. Echocardiographic and clinical outcomes of central versus noncentral percutaneous edge-to-edge repair of degenerative mitral regurgitation. Journal of the American College of Cardiology. 2013 Dec 24;62(25):2370-7.	Retrospective analysis of registry n=173 Mean 15.2 months (±11.0 months SD) FU	Comparison of central and non-central DMR. Patients with non-central DMR had a statistically wider pre-procedural vena contracta (8.5 mm vs. 6.9 mm) and higher systolic pulmonary pressure (57.9mmHg vs. 47.3 mmHg). Procedural success, post-procedural MR, and NYHA class were similar in both groups.	Small retrospective study in DMR patients. Subgroup comparison not defined in scope.
Giannini C, Fiorelli F, Colombo A, et al. Right ventricular evaluation to improve survival outcome in patients with severe functional mitral regurgitation and advanced heart failure undergoing MitraClip therapy. International Journal of Cardiology. 2016 Nov 15;223:574-80.	Prospective case series n=169 (FMR) 3 year FU	Survival free from cardiac death was 97.6% at 30 days, 86.7% at 1 year, 71.5% at 2 years and 61.6% at 3 years. Patient death was related to age and number of comorbidities. Independent predictors of cardiovascular mortality were severely impaired renal function (OR 5.5, p=0.01), and RV systolic dysfunction (OR 0.57, p=0.003).	Smaller observational study that did not compare alternative management strategies. Only larger observational studies included in table 2 (n>500).
Glower DD, Kar S, Trento A, Lim DS, Bajwa T, Quesada R, et al. Percutaneous mitral valve repair for mitral regurgitation in high-risk patients: results of the EVEREST II study. Journal	Retrospective analysis n=353 (high risk patients from EVEREST II and REALISM studies) 12 months FU	PMVR reduced MR to grade ≤2+ in 86% of patients at discharge (p<0.0001). Major adverse events at 30 days included death in 4.8%, myocardial infarction in 1.1%, and stroke in 2.6%. At 12 months, MR was grade ≤2+in	Patients had exclusively DMR. Analysis includes patients reported in study 1 (Feldman 2011) and study 8 Whitlow (2012).

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
of the American College of Cardiology. 2014 Jul 15;64(2):172-81.		84% of patients. NYHA was class III/IV in 82% patients pre-procedure and class I/II in 83% patients post-procedure (p<0.00001). There were significant improvements in QoL (mental and physical) at 12 months.	
Grasso C, Capodanno D, Scandura S, et al. One- and twelve-month safety and efficacy outcomes of patients undergoing edge-to-edge percutaneous mitral valve repair (from the GRASP Registry). American Journal of Cardiology. 2013 May 15;111(10):1482-7.	Report on GRASP registry n=117 1 year FU	There were no procedural deaths. Major adverse events after 30 days was 4.3%. There was more deterioration to MR grade ≥3+ in patients with DMR (25%) compared with FMR (7%). Freedom from death, surgery for mitral valve dysfunction, or grade ≥3+ MR was 96.4% at 30 days and 75.8% at 1 year. There was no significant difference in this outcome between DMR and FMR.	Smaller observational study (GRASP registry) that did not compare alternative management strategies. Only larger observational studies included in table 2 (n>500).
Hamm K, Zacher M, Hautmann M, et al. Influence of experience on procedure steps, safety, and functional results in edge to edge mitral valve repair-a single center study. Catheterization & Cardiovascular Interventions. 2017 Aug 01;90(2):313-20.	Prospective observational study n=126 3 months FU	Comparison of 3 consecutive cohorts of patients (learning curve). The authors concluded that safety and duration of procedure steps improved substantially with experience, but MR reduction was not further improved. Patient selection was considered a key factor for success	Smaller observational study that did not compare alternative management strategies. Only larger observational studies included in table 2 (n>500).
Lesevic H, Sonne C, Braun D, et al. Acute and Midterm Outcome After MitraClip Therapy in Patients With Severe Mitral Regurgitation and Left Ventricular Dysfunction. American Journal of Cardiology. 2015 Sep 1;116(5):749-56.	Prospective observational study n=136 Median FU 371 days	Comparison of 2 groups (group 1 with significant LVEF, group 2 without). The primary efficacy endpoint (death of any cause, repeat mitral valve intervention, and/or NYHA class ≥III) was 31% of patients in group 1 compared with 40% in group 2 (p=0.719). There were significant reductions in MR grade and NYHA class in both groups.	Smaller observational study that did not compare alternative management strategies. Only larger observational studies included in table 2 (n>500).
Iliadis C, Lee S, Kuhr K, Metze C, et al. Functional status and quality of life after transcatheter mitral valve repair: a prospective cohort study and systematic review. Clin. 2017 07 Aug:1-13.	Prospective case series matched with published data from systematic review n=215 (prospective component)	All studies reported improvements of mean NYHA class (0.5 to 1.9 classes), Short-Form (SF)-12/36 scores (4.4 to 9.2 for physical component score, 2.6 to 8.9 for mental component score), 6-MWT, MLHFQ scores.	Hybrid case series and systematic review. A comparative systematic review was included (study 7, Tagaki 2017).

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Lubos E, Schluter M, Vettorazzi E, et al. MitraClip therapy in surgical high-risk patients: identification of echocardiographic variables affecting acute procedural outcome. Jacc: Cardiovascular Interventions. 2014 Apr;7(4):394-402.	Prospective case series of high risk patients n=300	Aimed to identify predictors of acute procedural success. High mean transmitral pressure gradient, high effective regurgitant orifice area, and high mitral valve orifice area were identified as increasing the risk of procedural failure.	Smaller prognostic observational study that did not compare alternative management strategies. Only larger observational studies included in table 2 (n>500).
Mendirichaga R, Singh V, Blumer V, et al. Transcatheter Mitral Valve Repair With MitraClip for Symptomatic Functional Mitral Valve Regurgitation. American Journal of Cardiology. 2017; 120: 708-15.	Systematic review and meta-analysis N=12 studies n=1,695 patients with FMR.	Aim was to evaluate the use of PMVR in high-risk FMR patients. Survival to hospital discharge: 98% (IQR 97 to 100) 30-day survival: 97% (IQR 96 to 98). Overall survival at 12 months: 82% (IQR 77 to 87). Mitral valve re-intervention (12 months): 3% (IQR 2 to 6.5).	Restricted to patients with FMR. Another systematic review and meta-analysis in mixed aetiology of patients was include (study 7).
Munkholm-Larsen S, Wan B, Tian DH, et al. A systematic review on the safety and efficacy of percutaneous edge-to-edge mitral valve repair with the MitraClip system for high surgical risk candidates. Heart. 2014; 100: 473-8.	Systematic review N=12 studies n=878 patients receiving PMVR	Procedural success: 72 to 100%; 30 day mortality: 0 to 7.8%. One year survival: 75 to 90%. There was a significant improvement in haemodynamic profile and functional status after implantation. No meta-analysis attempted.	Older systematic review without meta-analysis. More recent systematic review included (Study 7).
Ohno Y, Attizzani GF, Capodanno D, et al. Association of tricuspid regurgitation with clinical and echocardiographic outcomes after percutaneous mitral valve repair with the MitraClip System: 30-day and 12-month follow-up from the GRASP Registry. European heart journal cardiovascular Imaging. 2014 Nov;15(11):1246-55.	Retrospective analysis of registry n=146 12 months FU	Analysis of moderate/severe vs. mild/absent TR. Primary safety endpoint was significantly higher in moderate/severe TR group at 30 days (p=0.035), as was NYHA class at 12 months (p=0.006). The primary efficacy endpoint at12 months (freedom from death, surgery for mitral valve dysfunction, or MR grade ≥3+) was comparable between groups, but combined death and re-hospitalization for heart failure rates were higher in the moderate/severe TR group.	Smaller observational study (GRASP registry) that did not compare alternative management strategies. Only larger observational studies included in table 2 (n>500).
Orban M, Braun D, Sonne C, et al. Dangerous liaison: successful percutaneous edge-to-edge mitral valve repair in patients with end-stage systolic heart failure can cause left ventricular thrombus formation. EuroIntervention. 2014 Jun;10(2):253-9.	Retrospective observational study n=150 12 months FU	New LV thrombus detected in 3/150 patients with end-stage systolic heart failure and LVEF below 20%. No thrombus seen in patients with LVEF >20% (136/150). Frequency of new LV thrombus formation in patient with LVEF ≤20% was 21%.	Smaller retrospective observational study that did not compare alternative management strategies. Only larger observational

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			studies included in table 2 (n>500).
Panaich SS, Arora S, Badheka A, et al. Procedural trends, outcomes, and readmission rates pre-and post-FDA approval for MitraClip from the National Readmission Database (2013-14). Catheterization & Cardiovascular Interventions. 2017; 20: 20.	Time analysis of National Readmission Data. n=2003 analysed	There was a significant increase in procedural volume post-FDA approval, witha corresponding downward trend in mortality and procedural complications. Significant predictors of in-hospital mortality and procedural complications included the use of vasopressors (p<0.001) and hemodynamic support (p<0.001). Higher hospital volume (10 MitraClips/year) was associated with lower in-hospital mortality and complications (P50.02). Elective procedures had lower in-hospital mortality (P<0.001) and lower readmission rates (p=0.011) compared with no-elective procedures.	Study 6 (by Sorajja 2017) provided more robust methodology for analysis of US registry and linked data.
Philip F, Athappan G, Tuzcu EM, et al. MitraClip for severe symptomatic mitral regurgitation in patients at high surgical risk: A comprehensive systematic review. Catheterization & Cardiovascular Interventions. 2014 Oct 1;84(4):581-90.	Systematic review and meta-analysis comparing PMVR with surgery N=21	<u>PMVR vs. surgery</u> *Technical failure:* 3.2% (95% CI 1.4 to 7%) vs. 0.6% (95% CI 0.2 to 1.8%) *Mortality (30 days):* 3% (95% CI 3 to 4%) vs. 16% (95% CI 13 to 20%) *Stroke (30 days):* 1.1% (95% CI 1 to 2%) vs. 4.5% (95% CI 4 to 5%) <u>PMVR only (1 year FU)</u> *Mortality:* 13.0 % (95% CI 9 to 18.3%) *Stroke:* 1.6% (95% CI 0.8 to 3.2%) *Repeat surgery:* 1.6% (95% CI 0.8 to 3.2%); 1.3% (95% CI 0.7 to 2.6%)	More recent systematic review and meta-analysis has been included with similar scope (Study 7, Takagi 2017).
Rahhab Z, Kortlandt FA, Velu JF, et al. Current MitraClip experience, safety and feasibility in the Netherlands. Netherlands Heart Journal. 2017; 25: 394-400.	Multi-centre retrospective analysis of all MitraClip procedures carried out in Netherlands (2009 to 2016) n=1151 Limited FU (immediately post-procedure)	MR grade reduction: 0: 7%,1: 9%, 2: 51%, 3: 33% ≥1MR reduction : 94% Device success: 91% Technical success: 95% Intra-procedural death: 0.3% Emergency surgery: 0.5%	This was a single-armed retrospective study whereas prospective studies were preferred (Studies 3, 4, 5). Only short term outcomes reported.
Rudolph V, Knap M, Franzen O, Schluter M, et al. Echocardiographic and clinical outcomes of	Case series of patients unsuitable for surgery	Device success was 92%, MR grade ≤2+ was 82.5% at 1 year FU. Left ventricular end-diastolic	Smaller prospective observational study that did not

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MitraClip therapy in patients not amenable to surgery. Journal of the American College of Cardiology. 2011 Nov 15;58(21):2190-5.	n=104 12 months FU	and -systolic volumes were reduced, and forward stroke volumes were significantly increased. Improvements in NYHA class was achieved in 80% of patients (69% in class I/II); 75% had improved 6-MWT, and 74% reported improvements in QoF. One-year estimates of mortality and rehospitalisation were 22% and 31%, respectively. Forward stroke volume at discharge was a predictor of event-free survival.	compare alternative management strategies. Only larger observational studies included in table 2 (n>500).
Scandura S, Capranzano P, Caggegi, et al. Percutaneous mitral valve repair with the MitraClip system in the elderly: One-year outcomes from the GRASP registry. International Journal of Cardiology. 2016 Dec 01;224:440-6	Prospective case series n=180 1 year FU	Compared patients <75 years with patients ≥75 years. Primary efficacy endpoint (composite of death, surgery for MR dysfunction and MR grade ≥3+) occurred in 24.5%, with no difference in age groups (p=0.912). 12.2% deaths after 1 year FU, with no significant difference in age groups (p=0.574). There were significant improvements in MR grade and NYHA in younger and older patients.	Smaller observational study (GRASP registry) that did not compare alternative management strategies. Only larger observational studies included in table 2 (n>500).
Schau T, Isotani A, Neuss M, et al. Long-term survival after MitraClip therapy in patients with severe mitral regurgitation and severe congestive heart failure: A comparison among survivals predicted by heart failure models. Journal of Cardiology. 2016 Mar;67(3):287-94.	Retrospective case series n=194 1 year FU	Compared expected outcomes in patients receiving PMVR with Seattle Heart Failure Model (SHFM) and the heart failure calculator of the meta-analysis global group in chronic heart failure (MAGGIC). The observed mortality after 1 year FU was24%, compared with 18% predicted by SHFM (p =0.185) and 20.9% by MAGGIC (p=0.542). At 2 years, 32% died compared with. 33% predicted by SHFM (p=0.919).	Smaller predictive retrospective observational study that did not compare alternative management strategies. Only larger observational studies included in table 2 (n>500).
Seeger J, Muller P, Gonska B, et al. Percutaneous Mitral Valve Repair With the MitraClip in Primary Compared With Secondary Mitral Valve Regurgitation Using the Mitral Valve Academic Research Consortium Criteria. J Invasive Cardiol. 2017 Apr;29(4):145-50.	Prospective case series n=210 30 days FU	Comparison between DMR and FMR. Device success was high in both groups (93.3% in FMR vs 94.3% in DMR) with no difference observed (p=0.14). Reduction of NYHA class from baseline to 30-day follow-up was 1.7 in secondary FMR group vs, 2.2 DMR (p<0.01). Safety outcomes after 30 days was 4.8% in DMR vs 5.7% in FMR (p=ns).	Smaller prospective observational study that did not compare alternative management strategies. Only larger observational studies included in table 2 (n>500).

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Surder D, Pedrazzini G, Gaemperli O, et al. Predictors for efficacy of percutaneous mitral valve repair using the MitraClip system: the results of the MitraSwiss registry. Heart. 2013 Jul;99(14):1034-40.	Prospective case series n=100 6 months FU	Acute procedural success was achieved in 85% of patients. Overall survival at 6 and 12 months was 89.9% (95% CI 81.8% to 94.6%) and 84.6% (95% CI 74.7% to 91.0%), respectively. Acute procedural success (p=0.0069) and discharge MR grade (p=0.03) as significant predictors of survival.	Smaller prospective observational study that did not compare alternative management strategies. Only larger observational studies included in table 2 (n>500).
Swaans MJ, Bakker ALM, Alipour A, et al. Survival of transcatheter mitral valve repair compared with surgical and conservative treatment in high-surgical-risk patients. Jacc: Cardiovascular Interventions. 2014 Aug;7(8):875-81.	Prospective case series with retrospectively identified comparators (surgery and medical management). n=130 FU PMVR 1.7 years, surgery 3.8 years, medical management 2.7 years	After 1 year of follow-up, the PMVR and surgery groups showed similar survival rates (85.8% and 85.2%, respectively), whereas 67.7% of conservatively treated patients survived. The same trend was observed after the second and third years. After weighting for propensity score and controlling for risk factors, both PMVR (HR 0.41, 95% CI 0.22 to 0.78, p=0.006) and surgical (HR 0.52, 95% CI: 0.30 to 0.88, p=0.014) groups had better survival than the conservatively treated group. The PMVR and surgical groups did not differ (HR: 1.25, 95% CI: 0.72 to 2.16, p=0.430).	Comparative observational study, but the cohorts were not equivalent at baseline. Included in meta-analysis of (Study 7, Takagi 2017).
Taramasso M, Denti P, Buzzatti N, et al. Mitraclip therapy and surgical mitral repair in patients with moderate to severe left ventricular failure causing functional mitral regurgitation: a single-centre experience. European Journal of Cardio-Thoracic Surgery. 2012 Dec;42(6):920-6.	Retrospective observational study of PMVR and matched annuloplasty patients n=143 Median FU: surgery 18 months MitraClip 8.5 months	Major postoperative infection or sepsis occurrence was higher in the surgical group (16.3 vs. 3.8%, p=0.01). In-hospital mortality was 6.6% for surgery and 0% for PMVR (p =0.01). Residual MR grade ≥3+ at discharge was 0% for surgery and 9.6% for PMVR (p=0.002). Survival at 1 year was 89% for surgery and 88% for PMVR (p=0.6). Freedom from MR grade ≥3+ at 1 year was 79% for PMVR and 94% for surgery (p=0.01). At last follow-up, most of the survivors were in NYHA class I/II.	Comparative observational study, but the cohorts were not equivalent at baseline. Included in meta-analysis of Study 7 (Takagi 2017).
Taramasso M, Maisano F, Latib A, et al. Clinical outcomes of MitraClip for the treatment of functional mitral regurgitation. EuroIntervention. 2014 Oct;10(6):746-52.	Retrospective observational study n=109 Up to 4 years FU	Procedural success was 99% and 30-day mortality was 1.8%. At discharge, 87% patients had MR grade ≤2+. At 12 months, EF was 34.7±10.4% (p=0.002 compared to preoperative value). Survival at three years	Smaller retrospective observational study that did not compare alternative management

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		was 75%. Freedom from MR grade ≥3+ at 2.5 years was 70%. At one-year follow-up, 86% of patients were in NYHA class I/II.	strategies. Only larger observational studies included in table 2 (n>500).
Tay E, Muda N, Yap J, et al. The MitraClip Asia-Pacific registry: Differences in outcomes between functional and degenerative mitral regurgitation. Catheterization & Cardiovascular Interventions. 2016 Jun;87(7):E275-81.	Prospective registry (MARS) n=163 1 month FU	Comparison between outcomes in patients with FMR and DMR. Procedural success rates were similar in both groups, as were 30-day mortality rates (4.5% vs. 6.7%, p=0.555) and 30-day major adverse event rates (9.2% vs. 14.7%, p=0.281). There were similar improvement in MR grade and NYHA class in both groups. There was a significantly greater reduction in left ventricular end-diastolic diameter (p =0.002) and end systolic diameter (p=0.017) in DMR than in FMR.	Smaller observational study (MARS registry) that did not compare alternative management strategies. Only larger observational studies included in table 2 (n>500).
Triantafyllis AS, Kortlandt F, Bakker ALM, et al. Long-term survival and preprocedural predictors of mortality in high surgical risk patients undergoing percutaneous mitral valve repair. Catheterization & Cardiovascular Interventions. 2016 Feb 15;87(3):467-75.	Prospective case series n=136 2 year FU	One year post-procedure, cardiac and overall survival rates were 87% and 85%, respectively. At 2 years cardiac and overall survival rates were 78% and 75%, respectively. Predictors of mortality included NYHA class, high logistic EuroSCORE and STS score.	Smaller retrospective observational study that did not compare alternative management strategies. Only larger observational studies included in table 2 (n>500).
Vakil K, Roukoz H, Sarraf M, et al. Safety and efficacy of the MitraClip system for severe mitral regurgitation: a systematic review. Catheterization & Cardiovascular Interventions. 2014 Jul 1;84(1):129-36	Systematic review and meta-analysis N=16 studies No comparator	Acute procedural success: 91.4% Procedural death: 0.1% 30 day mortality: 4.2% Mortality (310 days): 15.8% 51.8% patients had ≥2+ MR at the end of follow-up, while 13.1% had ≥3±MR. QoL score (mean + SE). Baseline 32.5±1.3, follow up 40.1±2.0.	More recent systematic review and meta-analysis reported in study 7 (Takagi 2017).
Wan B, Rahnavardi M, Tian DH, et al. A meta-analysis of MitraClip system versus surgery for treatment of severe mitral regurgitation. Annals of Cardiothoracic Surgery. 2013; 2: 683-92.	Systematic review and meta-analysis N=4 studies PMVR: n=355 Surgery: n=289	Post-procedural MR severity >2 was significantly higher in the PMVR group compared with the surgical group (17.2% vs. 0.4%; p<0.0001). 30-day mortality was not statistically significant (1.7% vs. 3.5%; p=0.54), nor were neurological events (0.85% vs. 1.74%; p=0.43), reoperations for failed MV	A more recent systematic review and meta-analysis (Study 7) was included.

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		procedures (2% vs. 1%; p=0.56), NYHA Class III/IV (5.7% vs. 11.3; p=0.42) and mortality at 12 months (7.4% vs. 7.3%; p=0.66).	
Wang A, Sangli C, Lim S, et al. Evaluation of renal function before and after percutaneous mitral valve repair. Circulation: Cardiovascular Interventions. 2015; 8.	Analysis of patients enrolled into EVEREST family of studies. n=854 I year FU	The aim of the study was to evaluate PMVR in patients with CKD. At 1-year follow-up, the mean change in eGFR was: Overall cohort: -1.0±15.1 mL/min/1.73 m^2; Patients with CKD stage 1 or 2, 4.1±16.6, +2.6±12.4 Stage 3, 4 and 5: +4.8±9.5 mL/min/1.73 m^2. There was a strong association between MR and eGFR, and a statistically significant improvement in eGFR in patients with CKD stage 4 or 5 associated with MR reduction to ≤2+ (p=0.007).	
Yeo KK, Yap J, Yamen E, et al. Percutaneous mitral valve repair with the MitraClip: early results from the MitraClip Asia-Pacific Registry (MARS). EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology. 2014 Sep 22;10(5):620-5.	Report from MARS registry n=142 30 days FU	Acute procedural success rate was 93.7%. 31.7% of the patients were in NYHA Class I/II at baseline, compared with 82.1% at 30 days (p<0.001). No patients had MR grade ≤2+ at baseline, compared with 76.8% at 30 days (p<0.001).	Smaller observational study (MARS registry) that did not compare alternative management strategies. Only larger observational studies included in table 2 (n>500).

Abbreviations: 6-MWT, 6 minute walk test; CI, confidence interval; CKD, chronic kidney disease; DMR, degenerative mitral regurgitation; eGFR, estimated glomerular filtration rate; EuroSCORE II, the European System for Cardiac Operative Risk Evaluation II; EVEREST, Endovascular Valve Edge-to-Edge Repair Study; FMR, functional mitral regurgitation; FU – follow up; GRASP - Getting Reduction of Mitral Insufficiency by Percutaneous Clip Implantation; HR, hazard ratio; ICU, intensive care unit; LVEF – left ventricular ejection fraction; MAC, mitral annular calcification; MACCE, major adverse cerebrovascular and cardiac events; MARS - MitraClip Asia-Pacific Registry; MLHFQ - Minnesota Living With Heart Failure Questionnaire; MR – mitral valve regurgitation; ns, not significant; REALISM, Real World Expanded Multicenter Study of the MitraClip System; SD – standard deviation; SF-36 – short form 36; STS-PROM, the Society of Thoracic Surgeons Predicted Risk of Mortality score; TR, tricuspid regurgitation; vs., versus.