NHS England Evidence Review:

Transcatheter edge to edge repair/percutaneous mitral valve leaflet repair for moderately severe or severe secondary mitral regurgitation due to left ventricular dysfunction and/or dilatation

NHS England URN: 2254

NHS England Evidence Review

Transcatheter edge to edge repair/percutaneous mitral valve leaflet repair for moderately severe or severe secondary mitral regurgitation due to left ventricular dysfunction and/or dilatation

Completed: January 2023

Prepared by Solutions for Public Health (SPH) on behalf of NHS England Specialised Commissioning

Contents

1. Introduction

This evidence review examines the clinical effectiveness, safety and cost effectiveness of transcatheter edge to edge repair (TEER)/percutaneous mitral valve leaflet repair combined with current standard care compared with current standard care alone in people with moderately severe to severe secondary mitral regurgitation (SMR).

TEER is a minimally invasive procedure, undertaken via a transfemoral venous approach with trans-oesophageal guidance under general anaesthesia. The procedure involves a clip being secured onto the edges of the mitral valve leaflet.

Current standard of care treatment is guideline directed medical therapy, under the guidance of a cardiac Multi-Disciplinary Team (MDT), which includes beta-blockers, angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB), angiotensin-receptor-neprilysin inhibitors (ARNI) to replace ACEI or ARB, mineralocorticoid receptor antagonists, sodium-glucose co-transporter2 inhibitors, ivabradine, hydralazine-nitrates and diuretics. Cardiac resynchronisation therapy (CRT) may be used in patients who have symptomatic heart failure with reduced ejection fraction and on optimal guideline-directed medical therapy if they are in sinus rhythm and have ventricular dyssynchrony. Mitral valve surgery is recommended in those already undergoing coronary artery bypass graft (CABG) or other cardiac surgery. Mitral valve surgery in the absence of other cardiac surgery is not routinely performed unless a patient without co-morbidities or frailty precluding benefit has severe SMR despite exhaustive pharmacological and device treatment.

In addition, the review scope included the identification of possible subgroups of patients within the included studies who might benefit from TEER more than the wider population of interest.

2. Executive summary of the review

This evidence review examines the clinical effectiveness, safety and cost effectiveness of transcatheter edge to edge repair (TEER) / percutaneous mitral valve leaflet repair combined with current standard care compared with current standard care alone in people with moderately severe to severe secondary mitral regurgitation (SMR). The searches for evidence published since January 2012 were conducted on 28 October 2022 and identified 2,933 potential references. These were screened using their titles and abstracts and 128 full text papers potentially relating to the use of TEER for SMR were obtained and assessed for relevance.

Five studies (published in seven papers) were identified for inclusion. Three systematic review and meta-analyses (SRMAs) and two randomised controlled trials (RCTs) compared TEER plus optimised medical therapy (OMT) to OMT alone in adults with moderate-to-severe to severe SMR. The two RCTs were the Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation trial (COAPT) and the Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation trial (MITRA-FR). The COAPT trial recruited 614 patients in the US and Canada; the MITRA-FR trial recruited 307 trial participants across multiple centres in France. The SRMAs included the same two RCTs.

No randomised controlled trial evidence was identified comparing TEER to optimised mitral valve surgery plus OMT.

In addition, two cost-effectiveness studies which are relevant to the UK were selected for inclusion (Cohen et al 2022 & Shore et al 2020).

In terms of clinical effectiveness:

- **Number of hospital admissions due to heart failure (critical outcome)**
  - For patients that had TEER plus OMT, compared to patients that had OMT alone, one RCT provided high certainty evidence of a statically significantly lower risk of hospital admissions due to heart failure at 24 months follow-up and another RCT provided low certainty evidence of the same at 12 months and between 12 and 24 months follow-up. The latter RCT also provided very low certainty evidence of no statistically significant difference at 24 months follow-up. Two SRMAs that meta-analysed results from both RCTs provided very low certainty evidence of no statistically significant difference at between 12 and 24 months follow-up.
- **Survival (critical outcome)**
  - One RCT provided moderate certainty evidence of a statistically significant lower overall mortality at 24 months in the TEER plus OMT group compared to the group on OMT alone and high certainty evidence of lower mortality related to heart failure in the same group; however, a different RCT and an SRMA of the two RCTs provided very low certainty evidence of no statistically significant difference between treatment groups in overall mortality or cardiovascular mortality at 2 years follow up. One of the RCTs and two different SRMAs of the two RCTs between them provided very low to moderate certainty evidence that compared to OMT alone, TEER does not decrease overall mortality at up to 23 months follow-up or cardiovascular mortality at between 12 and 24 months.

- **NYHA grade[1] (critical outcome)**
  - One RCT provided moderate certainty evidence that in those receiving TEER and OMT compared with those on OMT alone, NYHA grade is improved for up to 2 years follow up; a second RCT provided low certainty evidence of no significant difference in NYHA grades between the treatment groups at 12 and 24 months follow up.
- **Health related quality of life (important outcome)**
  - One RCT provided moderate certainty evidence that those receiving TEER and OMT had a statistically significantly improved health related quality of life (HRQL) at 12 months follow-up compared with those on OMT alone; a second RCT provided low certainty evidence of no difference in HRQL between the treatment groups at 12 months follow up (the two groups were not statistically compared).
- **Pre discharge grading of mitral regurgitation (important outcome)**
  - Two RCTs provided very low to moderate certainty evidence suggesting that the TEER procedure reduces mitral regurgitation grade in those with SMR; the data were not statistically compared.
- **Duration/ durability of mitral regurgitation reduction (important outcome)**
  - One RCT provided moderate certainty evidence of a statistically significantly lower mitral regurgitation severity in those with SMR following the TEER procedure compared to the group on OMT alone, and this was sustained for up to 24 months; the same study also provided low certainty evidence of no statistically significant difference in the number of unplanned mitral valve interventions.
- **Functional outcomes (important outcome)**
  - One RCT provided moderate certainty evidence of a statistically significantly smaller deterioration in functional outcomes as measured by the six minute walk test at 12 months for those who had TEER plus OMT compared with OMT alone. A second RCT provided low certainty evidence of little difference between the two groups in six minute walk test distance at 12 and 24 months; the groups were not compared statistically.

In terms of safety:

- **Procedural complications**
  - These studies provided very low to moderate certainty evidence of little difference in adverse event rates between those receiving TEER and those on OMT alone (statistical tests were only carried out for rates of MI and stroke). One RCT provided moderate certainty evidence that the rate of freedom from device related complications at 12 months was in the region of 96.9%, which was higher than the safety goal of 80.0% adopted by the study. A second RCT reported procedural surgical complications in 14.6% of patients (moderate certainty evidence).

In terms of cost effectiveness:

- In total, two studies were found reporting on the cost effectiveness of TEER with current standard care compared with current standard care alone in people with moderately severe to severe secondary mitral regurgitation from a UK NHS perspective. Both

[1] New York Heart Association functional classification.

studies were mostly based on 2-year clinical and resource inputs from the COAPT trial[2] (n=614).

- These studies provided evidence that the incremental cost effectiveness ratio of TEER with OMT compared with OMT alone in people with moderately severe to severe secondary mitral regurgitation from a UK NHS perspective ranged from £23,270 to £30,057 per quality-adjusted-life-year (QALY) gained over a lifetime, £37,440 per QALY gained over 10 years and £63,608 per QALY gained over 5 years. In terms of life years gained, one study reported an incremental cost effectiveness ratio (ICER) of £17,140 per life year gained over a lifetime time horizon.

In terms of subgroups:

- Subgroup results for NYHA baseline classification grades were reported from one RCT (COAPT trial) for all the critical, important and safety outcomes. Subgroup analysis was pre-planned in the RCT and results were reported as TEER plus OMT vs OMT alone for the different patient subgroups.
- One RCT compared outcomes in patients treated with TEER and OMT compared with OMT alone stratified by baseline NYHA grade and reported no difference in the effectiveness of TEER in terms of hospitalisations for heart failure, survival or unplanned mitral valve interventions or in the risk of MI in different baseline NYHA subgroups (no statistically significant interaction). For other effectiveness and safety outcomes, results by baseline NYHA grade were presented without statistical comparison.

Please see the results table (section 5) in the review for further details of outcomes and definitions

Limitations

Limitations reducing certainty in the comparison of TEER plus OMT and OMT alone for some outcomes included lack of similarity of the groups at baseline, lack of statistical comparison and wide confidence intervals around a hazard ratio. The RCTs could not be blinded, due to the nature of the intervention, and information about the blinding of analysts was missing from both trials. The two clinical trials had significant inconsistency in their results which led to generally very low or low certainty meta-analysis results.

Conclusion

This evidence review considered the clinical effectiveness and safety of TEER combined with OMT compared to OMT alone for the treatment of patients with moderate-to-severe or severe SMR due to left ventricular dysfunction or dilation.

There were meta-analysed RCT data or individual RCT data comparing TEER plus OMT with OMT alone for all the critical and important clinical effectiveness outcomes of interest. There was high certainty evidence of statistically significant reductions in heart failure related hospital admissions and deaths related to heart failure at 24 months follow-up. There was moderate certainty evidence of a statistically significant reduction in all-cause mortality and an improvement in NYHA grade at 24 months follow-up. Additional low to moderate certainty evidence from other studies did not always support these findings. There was no evidence of a

[2] COAPT: Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation Trial.

difference between the groups at 12 months follow-up for mortality or heart failure hospitalisations.

There was moderate certainty evidence of reductions in MR grading persisting to 24 months and of improvements in health related quality of life and six minute walk test distance at 12 months in the TEER plus OMT group when compared to OMT alone. The difference was statistically significant when groups were statistically compared, although statistical analysis was not performed by all studies.

The two RCTs both reported procedural or device related complications with one reporting 14.6% of TEER patients having a procedural surgical complication and the other reporting an estimated 97% of patients free from device related complications at 12 months. For other safety outcomes, there was no evidence of a difference in the number of adverse events reported for TEER plus OMT compared to OMT alone; apart from stroke and myocardial infarction, the groups were not statistically compared.

Limitations reducing certainty in the comparison of TEER plus OMT and OMT alone for some outcomes included lack of similarity of the groups at baseline, lack of statistical comparison and wide confidence intervals around a hazard ratio. The RCTs could not be blinded, due to the nature of the intervention, and information about the blinding of analysts was missing from both trials. The two clinical trials had significant inconsistency in their results which led to generally low or very low certainty meta-analysis results.

The results of the subgroup analysis did not indicate a clear advantage for any subgroup of patients over the wider population of interest.

The cost-effectiveness evidence indicated that the incremental cost effectiveness ratio of TEER with OMT compared with OMT alone in people with moderately severe to severe SMR from a UK NHS perspective ranged from £23,270 to £30,440 per QALY over a lifetime time horizon.

The studies identified for this review therefore provide high to moderate evidence of better outcomes with transcatheter edge to edge repair plus OMT compared to OMT alone in adults with moderate-to-severe to severe SMR.

3. Methodology

Review questions

The review question(s) for this evidence review are:

1. In people with moderately severe to severe secondary mitral regurgitation what is the clinical effectiveness of TEER combined with current standard care compared with current standard care alone?
2. In people with moderately severe to severe secondary mitral regurgitation what is the safety of TEER combined with current standard care compared with current standard care alone?
3. In people with moderately severe to severe secondary mitral regurgitation what is the cost-effectiveness of TEER combined with current standard care compared with current standard care alone?
4. From the evidence selected, are there any subgroups of patients that may benefit from TEER more than the wider population of interest?

See Appendix A for the full PICO document.

Review process

The methodology to undertake this review is specified by NHS England in its 'Guidance on conducting evidence reviews for Specialised Services Commissioning Products' (2020).

The searches for evidence were informed by the PICO document and were conducted on 28 October 2022.

See Appendix B for details of the search strategy.

Results from the literature searches were screened using their titles and abstracts for relevance against the criteria in the PICO document. Full text of potentially relevant studies were obtained and reviewed to determine whether they met the inclusion criteria for this evidence review.

See Appendix C for evidence selection details and Appendix D for the list of studies excluded from the review and the reasons for their exclusion.

Relevant details and outcomes were extracted from the included studies and were critically appraised using a checklist appropriate to the study design. See Appendices E and F for individual study and checklist details.

The available evidence was assessed by outcome for certainty using modified GRADE. See Appendix G for GRADE profiles.

4. Summary of included studies

Five studies (published in seven papers) were identified for inclusion. Three systematic review and meta-analyses (SRMAs) (Bertaina et al 2019, Lodhi et al 2019 & Zimarino et al 2020) and two randomised controlled trials (RCTs). The two RCTs were the Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation trial (COAPT; Giustino et al 2020 and Stone et al 2018) and the Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation trial (MITRA-FR; Iung et al 2019 and Obadia et al 2018). The RCTs compared transcatheter edge to edge repair (TEER)[3] plus optimised medical therapy (OMT)[4] to OMT alone in adults with moderate-to-severe to severe SMR. No randomised controlled trial evidence was identified comparing TEER to optimised mitral valve surgery plus OMT.

In addition, two cost-effectiveness studies which are relevant to the UK were selected for inclusion (Cohen et al 2022 & Shore et al 2020).

Table 1 provides a summary of the included studies and full details are given in Appendix E.

Table 1: Summary of included studies

Study	Population	Intervention and comparison	Outcomes reported

Bertaina et al 2019
 	
SRMA
 	
International
	n=918 (2 RCTs[a])
	• PMVR: n=454
	• OMT: n=464
	
	RCTs or observational studies with multivariate analysis of patients with left ventricular dysfunction and FMR (≤30% with PMR)[a]
	
	No subgroups reported
		Intervention
		
		PMVR (MitraClip)
		
		Comparison
		
		OMT
			Outcomes reported at median follow-up of 438 days (IQR 360 to 625)[b] unless otherwise stated
			
			Critical outcomes
			
			• Number of hospital admissions due to heart failure
			• Survival
			  • All-cause mortality at 1 month, 12 months & median follow-up
			  • Cardiovascular mortality at median follow-up

Cohen et al 2022 Cost effectiveness study UK perspective	n=614 (COAPT trial) • TEER: n=302 • GDMT: 312 People with symptomatic heart failure, LVEF 20% to 50% and severe (3+ or 4+) secondary mitral regurgitation Subgroups: • Baseline mitral regurgitation 3+; 4+ • NYHA class I or II; III; IV • Baseline LVEF <30%; ≥30%	**Intervention** Mitral valve TEER (MitraClip) plus GDMT **Comparison** GDMT alone	**Important outcomes** • Cost effectiveness • ICER (cost per life-year & cost per QALY) over lifetime time horizon

[3] Included studies appeared to use the terms TEER, percutaneous mitral valve repair (PMVR), and MitraClip device procedure to refer to the same intervention; for the main text of this review, TEER has been used.
[4] Included studies appeared to use the terms OMT and guideline directed medical therapy (GDMT) interchangeably; for the main text of this review, OMT has been used.

Lodhi et al 2019
 	
SRMA
 	
International
	n=918 (2 RCTs[a])
	• PMVR: n=454
	• OMT: n=464
	
	RCTs and non-randomised studies of adult patients where at least 70% of the patients had heart failure complicated by FMR
	
	No subgroups reported
		Intervention
		PMVR
		Comparison
		OMT
			Outcomes reported at mean follow-up of 1.64 years[b] unless otherwise reported
			Critical outcomes
			• Number of hospital admissions due to heart failure
			• Survival
			  • All-cause mortality at 30 days & 1 year
			  • Cardiovascular mortality

Obadia et al 2018
 	
RCT (MITRA-FR trial)
 	
Iung et al 2019 reports 24 month results
 	
France (37 centres)
	n=304
	• PMVR: n=152
	• OMT: n=152
	
	Adults with heart failure and severe secondary mitral regurgitation
	
	No subgroups reported
		Interventions
		PMVR (MitraClip) plus OMT
		Comparators
		OMT alone
			Critical outcomes
			• Number of hospital admissions due to heart failure at 12, 12-24 & 24 months
			• Survival
			  • Death from any cause at 30 days, 12, 12-24 & 24 months
			  • Cardiovascular death at 12, 12-24 & 24 months
			• NYHA grade at 12 & 24 months
			
			Important outcomes
			• Health related quality of life
			  • EQ5D global score[c] at 12 months
			• Pre discharge grading of mitral regurgitation
			  • Reduction of mitral regurgitation of at least one grade at the time of discharge
			  • Reduction of mitral regurgitation to 2+ (mild to moderate) or lower at the time of discharge
			  • Reduction of mitral regurgitation to 0+ (none or trace) to 1+ (mild) at the time of discharge
			• Functional outcomes
			  • 6-minute walk test distance[d] at 12 & 24 months
			• Safety
			  • Procedural complications
			  • Prespecified serious adverse events[e] at 12, 12-24 and 24 months

Shore et al 2020 Cost effectiveness study UK perspective	n=614 (COAPT trial) Transcatheter mitral valve repair plus GDMT: n=302 GDMT alone: n=312 People with secondary mitral valve regurgitation at high risk	**Interventions** Transcatheter mitral valve repair (MitraClip) plus GDMT **Comparators** GDMT alone	**Important outcomes** • Cost effectiveness • ICER (cost per QALY) over 5 year, 10 year & lifetime time horizon

	of surgical mortality or deemed inoperable No subgroups reported		

Stone et al 2018
 	
RCT (COAPT trial)
 	
Giustino et al 2020 reports subgroup results
 	
United States and Canada (78 centres)
	n=614
	• TEER: n=302
	• GDMT: n=312
	
	Adults with ischaemic or nonischaemic cardiomyopathy with a left ventricular ejection fraction of 20 to 50%, had moderate-to-severe (grade 3+) or severe (grade 4+) secondary mitral regurgitation, and remained symptomatic despite the use of stable maximal doses of guideline-directed medical therapy.
	
	Subgroups:
	• Baseline mitral regurgitation 3+; 4+
	• NYHA class I or II; III; IV
		Interventions
		Transcatheter mitral valve repair (MitraClip) plus GDMT
		Comparators
		GDMT alone
			Median follow-up 22.7 months (IQR 12.4 to 24.0) v 16.5 months (IQR 10.1 to 24.0)
			Critical outcomes
			• Number of hospital admissions due to heart failure at 24 months
			• Survival
			  • Death from any cause at 12 & 24 months
			  • Cardiovascular death at 24 months
			• NYHA grade at 30 days, 6, 12, 18 & 24 months
			
			Important outcomes
			• Health related quality of life
			  • KCCQ score[f] at 12 months
			  • Change in KCCQ from baseline to 12 months
			• Pre discharge grading of mitral regurgitation
			• Duration/durability of mitral regurgitation
			  • Grading of MR at 30 days, 6, 12, 18 & 24 months
			  • Unplanned mitral valve intervention at 24 months
			• Functional outcomes
			  • 6-minute walk test distance[d] at 12 months
			  • Change in 6-minute walk test distance from baseline to 12 months
			• Safety
			  • Procedural complications at 12 months
			  • Adverse events at 30 days & 24 months

Zimarino et al 2020
 	
SRMA
 	
International
	n=918 (2 RCTs[a])
	• PMVR: n=454
	• OMT n=464
	
	RCTs or non-randomised longitudinal observational studies with follow-up ≥12 months and reporting all-cause mortality data in patients with moderately severe or severe predominantly (enrolment >60%) secondary mitral regurgitation
	
	No subgroups reported
		Interventions
		PMVR (MitraClip) plus OMT
		Comparators
		OMT alone
			Mean follow-up of 24 (+/- 15 months)[b]
			Critical outcomes
			• Survival
			  • All-cause mortality
			  • Cardiovascular mortality

Abbreviations
COAPT: Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation Trial; f/up: follow-up; FMR: functional mitral valve regurgitation; GDMT: guideline directed medical therapy; ICER: incremental cost effectiveness ratio; IQR: interquartile range; KCCQ: Kansas City Cardiomyopathy Questionnaire; LVEF: left ventricular ejection fraction; MITRA-FR; Multicentre Study of Percutaneous Mitral Valve Repair MitraClip Device in Patients with Severe Secondary Mitral Regurgitation; PMR: primary mitral regurgitation; PMVR: percutaneous mitral valve repair; QALY: quality-adjusted life-year; RCT: randomised controlled trial; NYHA: New York Heart Association; OMT: optimal medical therapy; SRMA: systematic review and meta-analysis; TEER: transcatheter edge to edge repair; UK: United Kingdom

a For the SRMAs, only the results for the meta-analyses of RCTs have been extracted as combining observational results with the randomised results will introduce bias reducing the reliability of the randomised evidence.
b Mean follow-up for all studies including observational studies. Mean follow-up for RCTs only was not reported for these outcomes.
c The EQ5D is a measure of quality of life based on 5 dimensions: activities, anxiety, mobility, pain and self-care. A higher score indicates a better quality of life with a visual acuity scale ranging from 0 (worst imaginable health) to 100 (best imaginable health). Higher scores indicate better quality of life
d The six-minute walk distance test is usually performed on a treadmill and is the distance in metres that the patient can walk in six minutes
e A device related complication was defined as any occurrence of single-leaflet device attachment, embolization of the device, endocarditis that led to surgery, mitral stenosis (as confirmed by the echocardiographic core laboratory) that led to mitral-valve surgery, implantation of a left ventricular assist device, heart transplantation, or any other device-related event that led to nonelective cardiovascular surgery.
f The Kansas City Cardiomyopathy Questionnaire (KCCQ) is a 23-item self-administered questionnaire developed to independently measure the patient's perception of their health status, which includes heart failure symptoms, impact on physical and social function, and how their heart failure impacts their quality of life (QoL) within a 2-week recall period. KCCQ responses are provided along a rating scale continuum (0 to 100) and frequently summarized in 25-point ranges: 0 to 24: very poor to poor; 25 to 49: poor to fair; 50 to 74: fair to good; and 75 to 100: good to excellent.

5. Results

In people with moderately severe to severe secondary mitral regurgitation, what is the clinical effectiveness and safety of TEER combined with current standard care compared with current standard care alone?

Outcome	Evidence statement
Clinical Effectiveness	
Critical outcomes	
Number of hospital admissions due to heart failure **Certainty of evidence:** Very low to high	This outcome is important to patients as it reflects how effective the treatment is compared to current standard of care and is a surrogate for control of symptoms and quality of life. In total, three SRMAs and two RCTs provided evidence relating to hospital admissions due to heart failure in patients with SMR. All studies compared TEER combined with optimal medical therapy (OMT) with OMT alone. At 12 months: • One RCT (Obadia et al 2018) showed *no statistically significant difference* between those that received TEER (74/152, 48.7%) and those on OMT alone (72/152, 47.4%) in the risk of a hospital admission for heart failure at one year (HR 1.13, 95% CI 0.81 to 1.56). **(LOW)** Between 12 and 24 months: • One meta-analysis of two RCTs (Bertaina et al 2019) reported *no statistically significant difference* between treatment groups in the odds of hospital admission for heart failure (aOR 0.77, 95% CI 0.37 to 1.62, p=0.49). The model was adjusted for confounding factors; the confounders were not reported. Length of follow-up for the RCTs was not reported.[5] **(VERY LOW)** • A second meta-analysis of the same two RCTs (Lodhi et al 2019) reported *no statistically significant difference* between treatment groups in the risk of hospital admission for heart failure (HR 0.76, 95% CI 0.36 to 1.63, p=0.48). The median follow-up[6] for the RCTs was not reported. **(VERY LOW)** • One RCT (Iung al 2019) showed a *statistically significant* lower risk of hospital admission for heart failure between 12 and 24 months in those that received TEER (18.6/100 patient-years) compared to those on OMT alone (39.3/100 patient-years) (HR 0.47, 95% CI 0.22 to 0.98). **(LOW)** At 24 Months: • One RCT (Iung al 2019) reported *no statistically significant difference* between those that received TEER (55.9/100 patient-years) and those on OMT alone (62.3/100 patient-years) in the risk of a hospital admission for heart failure at two years (HR 0.97, 95% CI 0.72 to 1.30). **(VERY LOW)** • One RCT (Stone al 2018) reported a *statistically significant lower* risk of a hospital admission for heart failure at two years in those that received TEER (160/446.5 patient-years) compared to those on OMT alone (283/416.8 patient-years) (HR 0.53, 95% CI 0.40 to 0.70, p<0.001). Three patients needed to be treated with TEER compared with OMT alone to prevent one heart failure hospitalisation (NNT=3.1, 95% CI 1.9 to 7.9). **(HIGH)** **For patients that had TEER plus OMT, compared to patients that had OMT alone, one RCT provided high certainty evidence of a statically significantly lower risk of hospital admissions due to heart failure at 24 months follow-up and another RCT provided low certainty evidence of the same at 12 months and between 12 and 24 months follow-up. The latter RCT also provided very low certainty evidence of no statistically significant difference at 24 months**

[5] For all studies reported in Bertaina et al, 2 RCTs and 6 observational studies, the median follow-up was 438 days (IQR 360 to 625 days). Median follow-up for RCTs only was not reported for this outcome.
[6] For all studies reported in Lodhi et al, 2 RCTs and 5 observational studies, the median follow-up was 1.64 years. Median follow-up for RCTs only was not reported for this outcome.

	follow-up. Two SRMAs that meta-analysed results from both RCTs provided very low certainty evidence of no statistically significant difference at between 12 and 24 months follow-up.
Survival **Certainty of evidence:** Very low to high	This outcome is important to patients because it reflects how long people live after treatment, although it does not provide information about their health and wellbeing during that time. In total, three SRMAs and two RCTs provided evidence relating to survival in patients with SMR over a two-year follow-up period. The same studies provided evidence of cardiovascular mortality in patients with SMR from 12 to 24 months. All studies compared TEER combined with OMT with OMT alone. *All-Cause Mortality* At 30 days**:** • Two meta-analyses of two RCTs (Bertaina et al 2019 & Lodhi et al 2019) reported *no statistically significant difference* in odds of death at one month follow-up between those that received TEER and those on OMT alone (Bertaina: aOR 1.74, 95% CI 0.67 to 4.50, p=0.25) **(LOW)**; (Lodhi: OR 1.74, 95% CI 0.67 to 4.52, p=0.25). **(MODERATE)** • One of the SRMAs (Lodhi et al 2019) also reported *no statistically significant difference* in the risk of death at one month follow-up between those that received TEER and those on OMT alone (RR 1.72, 95% CI 0.66 to 4.36, p=0.26). **(VERY LOW)** At 12 months: • Two meta-analyses of two RCTs (Bertaina et al 2019 & Lodhi et al 2019) reported *no statistically significant difference* in odds of death at 12 months follow-up between those that received TEER and those on OMT alone (Bertaina: aOR 0.91, 95% CI 0.68 to 1.22, p=0.53) **(LOW)**; (Lodhi: OR 0.87, 95% CI 0.59 to 1.29, p=0.50). **(MODERATE)** • One of the SRMAs (Lodhi et al 2019) also reported *no statistically significant difference* in the risk of death at 12 months follow-up between those that received TEER and those on OMT alone (RR 0.90, 95% CI 0.66 to 1.23, p=0.51). **(LOW)** Between 12 and 24 months: • One meta-analysis of two RCTs (Bertaina et al 2019) reported *no statistically significant difference* between treatment groups in the risk of mortality (aOR 0.80, 95% CI 0.46 to 1.42, p=0.45). The model was adjusted for confounding factors; the confounders are not reported. Length of follow-up for the RCTs was not reported.[7] **(VERY LOW)** • One RCT (Iung al 2019) showed *no statistically significant difference* between those that received TEER (15.5/100 patient-years) and those on OMT alone (18.2/100 patient-years) in the risk of all cause mortality between 12 and 24 months (HR 0.86, 95% CI 0.44 to 1.69). **(VERY LOW)** At 24 Months: • One meta-analysis of two RCTs (Zimarino et al 2020) showed *no statistically significant difference* between treatment groups in the risk of all-cause mortality at 24 months (HR 0.80, 95% CI 0.46 to 1.42, p=0.45). **(VERY LOW)** • One RCT (Iung al 2019) reported *no statistically significant difference* between those that received TEER (23.1/100 patient-years) and those on OMT alone (22.8/100 patient-years) in the risk of a mortality at two years (HR 1.02, 95% CI 0.70 to 1.50). **(VERY LOW)** • One RCT (Stone et al 2018) reported a *statistically significantly lower* risk of mortality in those that received TEER + OMT (80/302, 29.1%[8]) compared to those on OMT alone (121/312, 46.1%) at 24 months (HR 0.62, 95% CI 0.46 to 0.82, p<0.001). **(MODERATE)**

[7] For all studies reported in Bertaina et al, 2 RCTs and 6 observational studies, the median follow-up was 438 days (IQR 360 to 625 days). Median follow-up for RCTs only was not reported for this outcome.
[8] Percentages are calculated using Kaplan-Meier methodology (estimates of event rate).

	Cardiovascular Mortality Between 12 and 24 months: • One meta-analysis of two RCTs (Bertaina et al 2019) reported *no statistically significant difference* between treatment groups in the odds of cardiovascular mortality (aOR 0.78, 95% CI 0.43 to 1.42, p=0.41). The model was adjusted for confounding factors; the confounders were not reported. Length of follow-up was not reported for RCT studies.[9] **(VERY LOW)** • A second meta-analysis of the same two RCTs (Lodhi et al 2019) reported *no statistically significant difference* between treatment groups in the odds of cardiovascular mortality (OR 0.75, 95% CI 0.40 to 1.43, p=0.39). **(LOW)** The same meta-analysis reported *no statistically significant difference* between those that received TEER and OMT compared with those that had OMT only in the risk of cardiovascular mortality at the same time point (RR 0.81, 95% CI 0.50 to 1.31, p=0.38). Length of follow-up for the RCTs alone was not reported.[10] **(VERY LOW)** • One RCT (Iung al 2019) reported *no statistically significant difference* between those that received TEER (13.6/100 patient-years) and those on OMT alone (17.2/100 patient-years) in the risk of cardiovascular mortality between 12 and 24 months (HR 0.80, 95% CI 0.39 to 1.63). **(VERY LOW)** At 24 Months: • One SRMA including two RCTs (Zimarino et al 2020) reported *no statistically significant difference* in the risk of cardiovascular mortality between those that received TEER and OMT compared to those on OMT only at 24 months[11] (HR 0.78, 95% CI 0.43 to 1.42, p=0.41). **(VERY LOW)** • One RCT (Iung al 2019) reported *no statistically significant difference* between those that received TEER (20.5/100 patient-years) and those on OMT alone (21.1/100 patient-years) in the risk of cardiovascular mortality at two years (HR 0.99, 95% CI 0.66 to 1.48). **(VERY LOW)** • One RCT (Stone et al 2018) reported a *statistically significantly* lower risk of death related to heart failure in those that received TEER (28/302, 12.0%)[12] compared to those on OMT alone (61/312, 25.9%) at two years (HR 0.43, 95% CI 0.27 to 0.67, p <0.001). **(HIGH)** **One RCT provided moderate certainty evidence of a statistically significant lower overall mortality at 24 months in the TEER plus OMT group compared to the group on OMT alone and high certainty evidence of lower mortality related to heart failure in the same group; however, a different RCT and an SRMA of the two RCTs provided very low certainty evidence of no statistically significant difference between treatment groups in overall mortality or cardiovascular mortality at 2 years follow up. One of the RCTs and two different SRMAs of the two RCTs between them provided very low to moderate certainty evidence that compared to OMT alone, TEER does not decrease overall mortality at up to 23 months follow-up or cardiovascular mortality at between 12 and 24 months.**
NYHA grade **Certainty of evidence:** Low to moderate	This outcome is important to patients because reduction of grade will also mean reduction of symptoms. This directly improves the patient's quality of life. In total, two RCTs provided evidence relating to NYHA grade[13] at five time points across 24 months of follow up. Both studies compared TEER combined with OMT with OMT alone.

[9] For all studies reported in Bertaina et al, 2 RCTs and 6 observational studies, the median follow-up was 438 days (IQR 360 to 625 days). Median follow-up for RCTs only was not reported for this outcome.
[10] For all studies reported in Lodhi et al, 2 RCTs and 5 observational studies, the median follow-up was 1.64 years. Mean follow-up for RCTs only was not reported for this outcome.
[11] Mean follow-up 24 months (+/-15) months for all studies including observational studies. Mean follow-up for RCTs only was not reported for this outcome.
[12] Percentages are calculated using Kaplan-Meier methodology (estimates of event rate).
[13] The New York Heart Association (NYHA) functional classification is a widely used tool for risk stratification on the basis of severity of symptoms and limitation of physical activity. It places patients in one of four categories: Class

	At 30 days: • One RCT (Stone et al 2018) showed a *statistically significantly better* NYHA grade at 30 days in those that received TEER + OMT (n=283; NYHA I: 15.5%, II: 60.8%, III: 19.4%, IV: 3.5%) compared to those on OMT alone (n=281; NYHA I: 5.0%, II: 42.7%, III: 41.6%, IV: 9.6%) (p<0.001). **(MODERATE)** At 6 months: • One RCT (Stone et al 2018) showed a *statistically significantly better* NYHA grade at 6 months in those that received TEER + OMT (n=263; NYHA I: 19.4%, II: 52.9%, III: 21.3%, IV: 2.7%) compared to those on OMT alone (n=261; NYHA I: 5.4%, II: 44.8%, III: 38.3%, IV: 2.7%) (p<0.001). **(MODERATE)** At 12 months: • One RCT (Stone et al 2018) showed a *statistically significantly better* NYHA grade at 12 months in those that received TEER + OMT (n=237; NYHA I: 16.9%, II: 55.3%, III: 17.7%, IV: 2.5%) compared to those on OMT alone (n=232; NYHA I: 7.8%, II: 41.8%, III: 28.0%, IV: 4.7%) (p<0.001). **(MODERATE)** • One RCT (Obadia et al 2018) reported that there was no significant difference between NYHA groups at 12 months (TEER n=114; OMT, n=112) (p value not reported). **(LOW)** At 18 months: • One RCT (Stone et al 2018) showed a *statistically significantly better* NYHA grade at 18 months in those that received TEER + OMT (n=183; NYHA I: 12.6%, II: 53.6%, III: 20.2%, IV: 1.1%) compared to those on OMT alone (n=183; NYHA I: 8.2%, II: 38.3%, III: 20.2%, IV: 4.4%) (p<0.001). **(MODERATE)** At 24 Months: • One RCT (Stone et al 2018) showed a *statistically significantly better* NYHA grade at 24 months in those that received TEER + OMT (n=157; NYHA I: 12.1%, II: 42.7%, III: 21.7%, IV: 5.7%) compared to those on OMT alone (n=153; NYHA I: 5.2%, II: 28.1%, III: 23.5%, IV: 3.3%) (p<0.001). **(MODERATE)** • One RCT (lung et al 2019) reported that there was no significant difference between NYHA groups at 24 months (TEER n=90; OMT, n=87) (p value not reported). **(LOW)** **One RCT provided moderate certainty evidence that in those receiving TEER and OMT compared with those on OMT alone, NYHA grade is improved for up to 2 years follow up; a second RCT provided low certainty evidence of no significant difference in NYHA grades between the treatment groups at 12 and 24 months follow up.**
Important outcomes	
Health related quality of life (HRQL) **Certainty of evidence:** Low to moderate	This outcome is important to patients because it provides a holistic evaluation and indication of the patient's general health and their perceived well-being and their ability to participate in activities of daily living. This outcome is both a key indicator of the effectiveness of treatment and provides an insight into the patient's perception of the effectiveness of treatment. In total, two RCTs provided evidence relating to health-related quality-of-life (HRQL) at one year. Both studies compared TEER combined with OMT with OMT alone.

I — no limitation of physical activity. Ordinary physical activity does not cause undue fatigue, breathlessness, or palpitations; Class II — slight limitation of physical activity. Comfortable at rest but ordinary physical activity results in undue breathlessness, fatigue, or palpitations; Class III — marked limitation of physical activity. Comfortable at rest but less than ordinary physical activity results in undue breathlessness, fatigue, or palpitations; Class IV — unable to carry out any physical activity without discomfort. Symptoms at rest can be present. If any physical activity is undertaken discomfort is increased.

	At 12 months: • One RCT (Stone et al 2018) showed a *statistically significantly greater improvement* in patients' KCCQ scores[14] from baseline to 12 months in those that received TEER and OMT (n=237; mean score at 12 months: 66.4, sd: 28.6) compared to those on OMT alone, whose average score worsened (n=228; mean score at 12 months: 49.6, sd: 32.0)(adjusted mean change TEER: 12.5, sd 1.8; OMT: -3.6, sd 1.9; p<0.001). **(MODERATE)** • One RCT (Obadia et al 2018) reported similar results in EQ5D scores[15] for those that received TEER and OMT compared with those that had OMT alone at 12 months (60.8, sd 20.3 compared to 58.6, sd 18.2). The groups were not statistically compared. **(LOW)** **One RCT provided moderate certainty evidence that those receiving TEER and OMT had a statistically significantly improved HRQL at 12 months follow-up compared with those on OMT alone; a second RCT provided low certainty evidence of no difference in HRQL between the treatment groups at 12 months follow up (the two groups were not statistically compared).**
Pre discharge grading of mitral regurgitation **Certainty of evidence:** Very low to moderate	This outcome is important to patients because reduction of severity will reflect how effective the treatment is, although it does not provide information about their symptom control and quality of life. In total, two RCTs provided evidence relating to pre-discharge grading of mitral regurgitation[16]. One RCT presented data only from the treatment group (TEER), the second RCT compared the TEER group with 30 day follow-up MR grading in those receiving OMT alone. • One RCT (Obadia et al 2018) reported that 95.1% of TEER patients had a reduction of at least one MR grade at the time of discharge (117/123); 91.9% had an MR grade of 2+ or lower following TEER (113/123) and 75.6% had an MR grade from 0+ to 1+ at the time of discharge following the TEER procedure (93/123). The groups were not statistically compared to OMT or baseline measures. **(VERY LOW)** • One RCT (Stone et al 2018) reported lower MR grading in patients treated with TEER at discharge (n=260, Grade 1+ or lower: 82.3%, 2+: 12.7%, 3+: 3.5%, 4+: 1.5%) compared with patients on OMT alone at 30 days (n=257, Grade 1+ or lower: 8.2%, 2+: 26.1%, 3+: 37.4%, 4+: 28.4%). The groups were not statistically compared. **(MODERATE)** **Two RCTs provided very low to moderate certainty evidence suggesting that the TEER procedure reduces mitral regurgitation grade in those with SMR; the data were not statistically compared.**
Duration/ durability of mitral regurgitation reduction **Certainty of evidence:** Low to Moderate	This outcome is important to patients because it gives an indicator of how long any changes in grade or symptom burden of SMR may last. One RCT provided evidence relating to durability of mitral regurgitation reduction at five time points and using two variables across 24 months of follow up. The study compared TEER combined with OMT therapy with OMT alone. *Mitral Regurgitation Severity* At 30 days:

[14] The Kansas City Cardiomyopathy Questionnaire (KCCQ) is a 23-item self-administered questionnaire developed to independently measure the patient's perception of their health status, which includes heart failure symptoms, impact on physical and social function, and how their heart failure impacts their quality of life (QoL) within a 2-week recall period. KCCQ responses are provided along a rating scale continuum (0 to 100) and frequently summarized in 25-point ranges: 0 to 24: very poor to poor; 25 to 49: poor to fair; 50 to 74: fair to good; and 75 to 100: good to excellent.

[15] The EQ5D is a measure of quality of life based on 5 dimensions: activities, anxiety, mobility, pain and self-care. A higher score indicates a better quality of life with a visual acuity scale ranging from 0 (worst imaginable health) to 100 (best imaginable health).

[16] MR is graded using echocardiogram on a scale of 0 to 4+: 0 (none or trace), 1+ (mild), 2+ (mild-to-moderate), 3+ (moderate-to-severe), 4+ (severe).

	• One RCT (Stone et al 2018) showed a *statistically significantly lower* MR severity at 30 days in those that received TEER + OMT (n=273; Grade 0: 0.7%, 1+: 72.2%, 2+: 19.8%, 3+: 5.9%, 4+: 1.5%) compared to those on OMT alone (n=257; Grade 0: 0.8%, 1+: 7.4%, 2+: 26.1%, 3+: 37.4%, 4+: 28.4%) (p<0.001). **(MODERATE)** At 6 months: • One RCT (Stone et al 2018) showed a *statistically significantly lower* MR severity at 6 months in those that received TEER + OMT (n=240; Grade 0: 0.4%, 1+: 66.3%, 2+: 27.1%, 3+: 4.6%, 4+: 1.7%) compared to those on OMT alone (n=218; Grade 0: 0.5%, 1+: 8.7%, 2+: 28.9%, 3+: 42.2%, 4+: 19.7%) (p<0.001). **(MODERATE)** At 12 months: • One RCT (Stone et al 2018) showed a *statistically significantly lower* MR severity at 12 months in those that received TEER + OMT (n=210; Grade 0: 0.5%, 1+: 68.6%, 2+: 25.7%, 3+: 4.3%, 4+: 1.0%) compared to those on OMT alone (n=175; Grade 0: 1.1%, 1+: 10.3%, 2+: 35.4%, 3+: 34.3%, 4+: 18.9%) (p<0.001). **(MODERATE)** At 18 months: • One RCT (Stone et al 2018) showed a *statistically significantly lower* MR severity at 18 months in those that received TEER + OMT (n=141; Grade 0: 0.7%, 1+: 74.5%, 2+: 19.9%, 3+: 4.3%, 4+: 0.7%) compared to those on OMT alone (n=114; Grade 0: 0.9%, 1+: 11.4%, 2+: 28.1%, 3+: 41.2%, 4+: 18.4%) (p<0.001). **(MODERATE)** At 24 Months: • One RCT (Stone et al 2018) showed a *statistically significantly lower* MR severity at 24 months in those that received TEER + OMT (n=114; Grade 0: 0.9%, 1+: 76.3%, 2+: 21.9%, 3+: 0%, 4+: 0.9%) compared to those on OMT alone (n=76; Grade 0: 2.6%, 1+: 13.2%, 2+: 27.6%, 3+: 40.8%, 4+: 15.8%) (p<0.001). **(MODERATE)** *Unplanned mitral valve intervention* At 24 Months: • One RCT (Stone et al 2018) showed *no statistically significant difference* between those that received TEER + OMT (n=10/114) and those on OMT alone (n=15/76) in the risk of unplanned mitral-valve interventions[17] at 2 years. (HR 0.61, 95% CI 0.27 to 1.36, p=0.23). **(LOW)** **One RCT provided moderate certainty evidence of a statistically significantly lower mitral regurgitation severity in those with SMR following the TEER procedure compared to the group on OMT alone, and this was sustained for up to 24 months; the same study also provided low certainty evidence of no statistically significant difference in the number of unplanned mitral valve interventions.**
Functional outcomes **Certainty of evidence:** Low to moderate	This outcome is important to patients because it directly impacts independence and quality of life. In total, two RCTs provided evidence relating to functional outcomes, both using the 6-minute walk test[18] at one year. Both studies compared TEER combined with OMT therapy with OMT alone. At 12 months: • One RCT (Obadia et al 2018) showed little difference between those that received TEER and OMT (n=120; mean distance (metres) at 12 months: 339, sd: 151) and those on OMT alone (n=103; mean distance (metres) at 12 months: 363, sd: 157) in the change in the patients' 6 min walk test

[17] Additional / new MitraClip implantation and/or mitral-valve surgery.
[18] The six-minute walk distance test is usually performed on a treadmill and is the distance in metres that the patient can walk in 6 minutes. Benefit is indicated by a higher result.

	distance from baseline to 12 months (TEER: 25, IQR -40 to 71; OMT: 19, IQR -27 to 75). The groups were not statistically compared. **(LOW)** • A different RCT (Stone et al 2018) showed a *statistically significantly smaller deterioration* in patients' 6 min walk test distance from baseline to 12 months in those that received TEER and OMT (n=230; mean distance (m) at 12 months: 256.7, sd: 157.7) compared to those on OMT alone (n=237; mean distance (m) at 12 months: 188.8, sd: 166.7) (adjusted mean change TEER: -2.2, sd 9.1; OMT: -60, sd 9.0; p <0.001). **(MODERATE)** At 24 months: • One RCT (Iung et al 2019) reported similar results in 6 min walk tests for those that received TEER and OMT (n=120; mean distance (metres) at 24 months: 335, IQR 280 to 462) compared with those that had OMT only (n=103; mean distance (metres) at 24 months: 398, IQR 280 to 462[19]) and also in the change in the patients' 6 min walk test distance from baseline to 24 months (change from baseline to 24 months, TEER: 15, IQR -18 to 67; OMT: 22, IQR -6 to 94). The groups were not statistically compared. **(LOW)** **One RCT provided moderate certainty evidence of a statistically significantly smaller deterioration in functional outcomes as measured by the six minute walk test at 12 months for those who had TEER plus OMT compared with OMT alone. A second RCT provided low certainty evidence of little difference between the two groups in six minute walk test distance at 12 and 24 months; the groups were not compared statistically.**
Safety	
Procedural complications **Certainty of evidence:** Very low to moderate	Safety is important to patients as it reflects the risks involved in undergoing TEER and allows a risk to benefit assessment to be undertaken. In total, two RCTs provided evidence relating to safety. Some outcomes were reported only for the treatment group (TEER); all other data compared TEER combined with OMT therapy with OMT alone. *Procedural complications* • One RCT (Obadia et al 2018) reported procedural complications for the device group (TEER); a total of 21/144 patients (14.6%) had surgical complications: device implantation failure (4.2%), haemorrhage resulting in transfusion or vascular complication resulting in surgical intervention (3.5%), atrial septum lesion or defect (2.8%), cardiogenic shock resulting in intravenous inotropic support (2.8%), cardiac embolism (1.4%), tamponade (1.2%). None of the patients required urgent conversion to heart surgery. **(MODERATE)** *Device related complications*[20] At 12 months: • One RCT (Stone et al 2018) reported that the rate of freedom from device related complications at 12 months of 96.9% (95% CI lower boundary 94.8%) was statistically significantly higher at 12 months than the safety goal of 80.0% adopted by the study (p <0.001). **(MODERATE)** *Adverse event rates* At 30 days: • One RCT (Stone et al 2018) reported little difference in adverse events at 30 days in patients in the TEER plus OMT group (n=302) compared to those treated with OMT alone (n=312) (Stroke: TEER 2, OMT 0; MI: TEER 3, OMT: 0) The groups were not statistically compared. **(MODERATE)** At 12 months:

[19] Likely to be incorrectly reported as the IQR is the same as reported for the TEER group.
[20] A device related complication was defined as any occurrence of single-leaflet device attachment, embolization of the device, endocarditis that led to surgery, mitral stenosis (as confirmed by the echocardiographic core laboratory) that led to mitral-valve surgery, implantation of a left ventricular assist device, heart transplantation, or any other device-related event that led to nonelective cardiovascular surgery.

	• One RCT (Obadia et al 2018) reported a set of pre-specified adverse events in those that received TEER plus OMT (n=152; total adverse events: 82.2%, heart transplantation or mechanical cardiac assistance: 3.9%, ischaemic or haemorrhagic stroke: 4.6%, MI: 0%, renal-replacement therapy: 3.3%, severe haemorrhage: 7.2%, infections: 18.4%) compared with those that received OMT alone (n=152; total adverse events: 79.6%, heart transplantation or mechanical cardiac assistance: 5.9%, ischaemic or haemorrhagic stroke: 0.7%, MI: 1.3%, renal-replacement therapy: 0.7%, severe haemorrhage: 3.9%, infections: 17.8%) at 12 months. The groups were not statistically compared. **(LOW)** At more than1 year: • One RCT (Iung et al 2019) reported the rate of a set of pre-specified adverse events at between 12 and 24 months follow up in those that received TEER plus OMT (n=152; rates per 100 patient-years; total adverse events: 6.8, heart transplantation or mechanical cardiac assistance: 1.7, ischaemic or haemorrhagic stroke: 0, MI: 0, renal-replacement therapy: 1.7, severe haemorrhage: 3.4, infections: 6.8) compared with those that received OMT alone (n=152; rates per 100 patient-years; total adverse events: 12.5, heart transplantation or mechanical cardiac assistance: 0, ischaemic or haemorrhagic stroke: 3.6, MI: 1.8, renal-replacement therapy: 1.8, severe haemorrhage: 0, infections: 5.4). The groups were not statistically compared. **(LOW)** • One RCT (Iung et al 2019) reported a set of pre-specified adverse events at 24 months follow-up in those that received TEER plus OMT (n=152; rates per 100 patient-years; total adverse events: 84.9, heart transplantation or mechanical cardiac assistance: 4.6, ischaemic or haemorrhagic stroke: 4.6, MI: 0, renal-replacement therapy: 3.9, severe haemorrhage: 8.6, infections: 21.1) compared with those that received OMT alone (n=152; total adverse events: 82.1, heart transplantation or mechanical cardiac assistance: 5.8, ischaemic or haemorrhagic stroke: 1.9, MI: 1.9, renal-replacement therapy: 1.3, severe haemorrhage: 3.8, infections: 19.2). The groups were not statistically compared. **(LOW)** • One RCT (Stone et al 2018) reported *no statistically significant difference* in adverse events at 24 months in patients in the TEER plus OMT group (n=302) compared to those treated with OMT alone (n=312) for stroke and MI (Stroke: HR 0.96, 95% CI 0.42 to 2.22, p=0.93; MI: HR 0.82, 95% CI 0.38 to 1.78, p=0.62). **(VERY LOW)** **These studies provided very low to moderate certainty evidence of little difference in adverse event rates between those receiving TEER and those on OMT alone (statistical tests were only carried out for rates of MI and stroke). One RCT provided moderate certainty evidence that the rate of freedom from device related complications at 12 months was in the region of 96.9%, which was higher than the safety goal of 80.0% adopted by the study. A second RCT reported procedural surgical complications in 14.6% of patients (moderate certainty evidence).**
Abbreviations aOR: adjusted odds ratio; CI: confidence interval; COAPT: Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation Trial; HR: hazard ratio; HRQL: health related quality-of-life; IQR: interquartile range; KCCQ: The Kansas City Cardiomyopathy Questionnaire; m: metres; MI: myocardial infarction; MR: mitral regurgitation; NNT: number needed to treat; NYHA: New York Heart Association; OMT: optimal medical therapy; OR: odds ratio; RCT: randomised controlled trial; RR: relative risk; sd: standard deviation; SMR: secondary mitral regurgitation; SRMA: systematic review and meta-analysis; TEER: transcatheter edge to edge repair; TIA: transient ischaemic attack	

In people with moderately severe to severe secondary mitral regurgitation what is the cost effectiveness of TEER combined with current standard care compared with current standard care alone?

Outcome	Evidence statement
Cost effectiveness	In total, two studies were found reporting on the cost effectiveness of TEER with OMT compared OMT alone in people with moderately severe to severe secondary mitral regurgitation from a UK NHS perspective. Both studies were mostly based on 2-year clinical and resource inputs from the COAPT trial (n=614). 5-year time horizon: • One cost effectiveness study (Shore et al 2020) reported an incremental cost effectiveness ratio (ICER) of £63,608 per quality-adjusted life-year (QALY) gained. 10-year time horizon: • One cost effectiveness study (Shore et al 2020) reported an ICER of £37,440 per QALY gained. Lifetime time horizon: • One cost effectiveness study (Shore et al 2020) reported an ICER of £30,057 per QALY gained. • One cost effectiveness study (Cohen et al 2022) reported an ICER of £23,270 per QALY gained and 18% probably that the ICER was <£20,000 per QALY gained and 89% probability that it was <£30,000 per QALY gained. • Cohen et al (2022) also reported an ICER of £17,140 per life year gained and 76% probability that the ICER was <£20,000 per life year gained and 96% probability that it was <£30,000 per life year gained. **These studies provided evidence that the incremental cost effectiveness ratio of TEER with OMT compared with OMT alone in people with moderately severe to severe secondary mitral regurgitation from a UK NHS perspective ranged from £23,270 to £30,057 per QALY gained over a lifetime, £37,440 per QALY gained over 10 years and £63,608 per QALY gained over 5 years. In terms of life years gained, one study reported an ICER of £17,140 per life year gained over a lifetime time horizon.**
Abbreviations COAPT: Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation Trial; ICER: incremental cost effectiveness ratio; NHS: National Health Service; OMT: optimised medical therapy; QALY: quality-adjusted life-year; TEER: transcatheter edge to edge repair; UK: United Kingdom	

From the evidence selected, are there any subgroups of patients that may benefit from TEER more than the wider population of interest?

Outcome	Evidence statement
Subgroups	Subgroup results by baseline NYHA grade[21] were reported from one RCT for all the critical, important and safety outcomes. Subgroup analysis was pre-planned in the RCT, and results were reported as TEER plus OMT vs OMT alone for the different patient subgroups. **Critical Outcomes** **Number of hospital admissions due to heart failure** • One RCT (Giustino et al 2020) reported a lower rate of hospitalisations related to heart failure at 24 months for patients that received TEER and OMT compared to patients on OMT alone across all NYHA baseline grades; NYHA Class II (TEER: 40 hospitalisations, 33.0%[22]; OMT: 51 hospitalisations, 51.3%; HR 0.57, 95% CI 0.38 to 0.86), NYHA III (TEER: 49, 35.9%; OMT: 84, 55.6%; HR 0.53, 95% CI 0.37 to 0.76), NYHA IV (TEER: 6,

[21] The New York Heart Association (NYHA) functional classification is a widely used tool for risk stratification on the basis of the burden of heart failure symptoms related to the activities of daily life.
[22] Percentages are estimated using the Kaplan-Meier time-to-event methodology.

	40.9%; OMT: 22, 78.3%; HR 0.34, 95% CI 0.14 to 0.86). The RCT reported *no statistically significant interaction* for the NYHA subgroups at 24 months; patients in the TEER plus OMT group had fewer hospitalisations than the OMT group and this was not influenced by baseline NYHA grade (p=0.55 for interaction). **Survival** • One RCT (Giustino et al 2020) reported a lower rate of death from any cause at 24 months for patients that received TEER and OMT versus patients on OMT alone across all NYHA baseline classifications; NYHA II (TEER: 31 deaths, 24.4%[23]; OMT: 42 deaths, 40.8%; HR 0.55, 95% CI 0.35 to 0.88), NYHA III (TEER: 44, 29.4%; OMT: 64, 41.2%; HR 0.71, 95% CI 0.48 to 1.04), NYHA IV (TEER: 8, 44.4%; OMT: 19, 61.2%; HR 0.64, 95% CI 0.28 to 1.46). The RCT reported *no statistically significant interaction* for the NYHA subgroups at 24 months; patients in the TEER plus OMT group had fewer deaths than the OMT group and this was not influenced by baseline NYHA grade (p=0.74 for interaction). • One RCT (Giustino et al 2020) reported a lower rate of death from heart failure at 24 months for patients that received TEER and OMT versus patients on OMT alone across all NYHA baseline classes; NYHA II (TEER: 9 deaths, 8.0%[24]; OMT: 18 deaths, 19.8%; HR 0.37, 95% CI 0.17 to 0.83), NYHA III / IV (TEER: 21, 14.4%; OMT: 45, 26.9%; HR 0.50, 95% CI 0.30 to 0.84). The baseline NYHA subgroups were not statistically compared. **NYHA Grade** • One RCT (Giustino et al 2020) reported *a statistically significantly better* NYHA grade at 24 months in those that received TEER combined with OMT compared with patients on OMT alone. This difference remained when stratifying by NYHA grade at baseline; For those in NYHA Class II at baseline (TEER n=88, OMT=74), numbers in each NYHA Class at 24 months were: NYHA I: TEER: 19, 21.6%; OMT: 8, 10.8%; NYHA II: TEER: 42, 47.7%; OMT: 28, 37.8%; NYHA III: TEER: 16, 18.2%; OMT: 19, 25.7%; NYHA IV: TEER: 11, 12.5%; OMT: 19, 25.7% (p=0.04); For those in NYHA Class III or IV at baseline (TEER n=118, OMT=130), numbers in each NYHA Class at 24 months were: NYHA I: TEER: 12, 10.2%; OMT: 4, 3.1%; NYHA II: TEER: 49, 41.5%; OMT: 41, 31.5%; NYHA III: TEER: 28, 23.7%; OMT: 34, 26.2%; NYHA IV: TEER: 29, 24.6%; OMT: 51, 39.2% (p=0.01). The baseline NYHA subgroups were not statistically compared. **Important Outcomes** **Health related quality of life (HRQL)** • One RCT (Giustino et al 2020) reported a *statistically significantly greater* improvement in patients' KCCQ scores[25] from baseline to 12 months in those that received TEER and OMT compared to those on OMT alone (whose average score worsened) for those who were in NYHA Class II at baseline (paired change TEER: 0.8, sd 31.5; OMT: -20.0, sd 33.2; p<0.0001), and in those in NYHA Class III or IV at baseline (paired change TEER: 12.8, sd 36.5; OMT: -7.4, sd 34.2; p<0.0001). The baseline NYHA subgroups were not statistically compared. **Pre-discharge grading of mitral regurgitation** • One RCT (Giustino et al 2020) reported pre-discharge MR grading for the 260 COAPT trial patients that received the TEER intervention, stratified by NYHA grade at baseline. (All patients had an MR grade of 3+ or higher at baseline.) Of those categorised as NHYA Class II at baseline, 95.7% had an

[23] Percentages are estimated using the Kaplan-Meier time-to-event methodology.
[24] Percentages are estimated using the Kaplan-Meier time-to-event methodology.
[25] The Kansas City Cardiomyopathy Questionnaire (KCCQ) is a 23-item self-administered questionnaire developed to independently measure the patient's perception of their health status, which includes heart failure symptoms, impact on physical and social function, and how their heart failure impacts their quality of life (QoL) within a 2-week recall period. KCCQ responses are provided along a rating scale continuum (0 to 100) and frequently summarized in 25-point ranges: 0 to 24: very poor to poor; 25 to 49: poor to fair; 50 to 74: fair to good; and 75 to 100: good to excellent.

	MR grade of 2+ or lower at hospital discharge (111/116); of those in NYHA Class III at baseline, the corresponding figures were 95.4% (122/128), and for those in NYHA Class IV at baseline they were 87.5% (14/16). Data for the OMT group were not reported. The baseline NYHA subgroups were not statistically compared. **Duration/durability of mitral regurgitation reduction** *Mitral Regurgitation Severity* • One RCT (Giustino et al 2020) reported *a statistically significantly lower* MR severity at 24 months in those that received TEER + OMT compared to those on OMT alone. This difference remained when stratifying by NYHA grade at baseline: For those in NYHA Class II at baseline: MR grade at 24 months was for the TEER group (n=76), Grade 0+: 1.3%, 1+: 80.3%, 2+: 17.1%, 3+: 0%, 4+: 1.3%; and for the OMT group (n=50) MR grade at 24 months was Grade 0+: 2.0%, 1+: 12.0%, 2+: 28.0%, 3+: 30.0%, 4+: 28.0%; p<0.0001; For those in NYHA Class III or IV at baseline: in the TEER group (n=86), MR grade at 24 months was Grade 0+: 1.2%, 1+: 74.4%, 2+: 24.4%, 3+: 0%, 4+: 0%; and in the OMT group (n=73), MR grade at 24 months was Grade 0+: 1.4%, 1+: 20.5%, 2+: 27.4%, 3+: 37.0%, 4+: 13.7%; p<0.0001. *Unplanned mitral-valve intervention* • One RCT (Giustino et al 2020) showed *a statistically significantly lower* risk of unplanned mitral-valve interventions[26] at 2 years in those that received TEER + OMT compared to those on OMT alone in those patients that were NYHA Class II at baseline (HR 0.12, 95% CI 0.01 to 0.97). The RCT reported *no statistically significant difference* between those that received TEER + OMT and those on OMT alone in the risk of unplanned mitral-valve interventions at 2 years in those patients that were NYHA Class III or IV at baseline (HR 0.89, 95% CI 0.37 to 2.15). The difference between the two baseline NYHA subgroups was *not statistically significant* (p=0.09 for interaction). **Functional Outcomes** *6 min walk test* • One RCT (Giustino et al 2020) showed *no statistically significant difference* between those that received TEER and OMT and those on OMT alone in the change in the patients' 6-minute walk test distance[27] from baseline to 12 months in those with an NYHA Class II at baseline (paired change from baseline: TEER (metres): -88.3, sd 161.3; OMT: -97.4, sd 175.4; p=0.64). For those with an NYHA Class III or IV at baseline, the RCT reported a *statistically significantly smaller* deterioration in 6-minute walk test distance at 12 months in those that received TEER + OMT compared to those that received OMT alone (paired change from baseline: TEER (m): -33.3, sd 147.0; OMT: -86.4, sd 160.5; p=0.005). The baseline NYHA subgroups were not statistically compared. **Safety** *Adverse event rates* • One RCT (Giustino et al 2020) reported adverse events in the two patient groups, stratified by NYHA Classification (NYHA Class II: TEER n=130, OMT n=110; NYHA Class III/IV: TEER=172, OMT=201). The RCT reported *no statistically significant difference* in adverse events of stroke and MI at 24 months in patients in the TEER plus OMT group compared to those treated with OMT alone, stratified by baseline NYHA class. • Stroke: NYHA Class II: TEER 4.2%[28], OMT 6.3%, HR 0.77 (95% CI 0.22 to 2.66); NYHA Class III/IV: TEER 4.3%, OMT 6.6%, HR 0.66 (95% CI 0.24 to 1.81). The baseline NYHA subgroups were not statistically compared.

[26] Additional / new MitraClip implantation and/or mitral-valve surgery.
[27] The six-minute walk distance test is usually performed on a treadmill and is the distance in metres that the patient can walk in 6 minutes. Subjects who experienced a heart failure-related death prior to follow-up (or were unable to walk due to cardiac reasons) were assigned a score of 0 for the 6-min walk test.
[28] Percentages are estimated using the Kaplan-Meier time-to-event methodology.

	• MI: NYHA Class II: TEER 5.2%, OMT 7.3%, HR 0.75 (95% CI 0.24 to 2.34); NYHA Class III / IV: TEER 4.6%, OMT 7.7%, HR 0.70 (95% CI 0.27 to 1.80); p=0.90 for interaction **One RCT compared outcomes in patients treated with TEER and OMT compared with OMT alone stratified by baseline NYHA grade and reported no difference in the effectiveness of TEER in terms of hospitalisations for heart failure, survival or unplanned mitral valve interventions or in the risk of MI in different baseline NYHA subgroups (no statistically significant interaction). For other effectiveness and safety outcomes, results by baseline NYHA grade were presented without statistical comparison.**
Abbreviations CI: confidence interval; COAPT: Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation Trial; HR: hazard ratio; HRQL: health related quality-of-life; KCCQ: The Kansas City Cardiomyopathy Questionnaire; K-M: Kaplan-Meier; m: metres; MI: myocardial infarction; MR: mitral regurgitation; NYHA: New York Heart Association; OMT: optimal medical therapy; RCT: randomised controlled trial; SMR: secondary mitral regurgitation; TEER: transcatheter edge to edge repair	

6. Discussion

This evidence review considered the clinical effectiveness and safety of TEER combined with OMT compared to OMT alone for the treatment of patients with moderate-to-severe or severe SMR due to left ventricular dysfunction or dilation. The critical outcomes of interest were number of hospital admissions due to heart failure, survival and NYHA grade. Important outcomes were health related quality of life, pre-discharge grading of mitral regurgitation, duration/durability of mitral regurgitation reduction, functional outcomes, and safety. Evidence on cost effectiveness was also sought.

Evidence was available from three SRMAs, two RCTs and two cost-effectiveness studies. All studies compared TEER combined with OMT compared to OMT alone. No randomised controlled studies were identified comparing TEER plus OMT with open mitral valve surgery plus OMT in people with SMR. After paper selection was completed, NHS England confirmed that the priority comparator was OMT.

The SRMAs included data from both observational studies and RCTs; however, only the results for the meta-analyses of RCTs have been extracted as combining observational results with the randomised results will introduce bias reducing the reliability of the randomised evidence. All three SRMAs used data from the same two RCTs, the COAPT trial and the MITRA-FR trial; data from these trials are also presented separately in this report. Both RCTs were large multi-centre international studies; COAPT included 78 centres in the United States and Canada, MITRA-FR recruited from 37 centres in France. It is not clear to what extent the results of these studies might be generalisable to the UK population.

Both RCTs included adult patients that were diagnosed with moderate-to-severe to severe SMR based on the results of echocardiography grading. The TEER procedure was conducted at baseline and all patients maintained optimal medical therapy throughout the follow-up period. Maximum follow-up for both RCTs was 24 months. Further follow-up for the COAPT trial is unavailable as cross-over of the groups was allowed following the 24-month data collection.

The COAPT trial enrolled 302 patients in the TEER plus OMT group and 312 patients in the OMT only group. The demographic and clinical characteristics, and medical therapy of the two groups were broadly similar at baseline. The trial was appropriately powered to measure a difference between treatment groups (for the primary outcome of heart failure related hospitalisations) with a two-sided significance level of 5% and 80% power. Given the nature of the intervention, it was not possible to blind participants or those delivering the intervention to treatment allocation. The RCT used standardised assessment measures where possible and a centralised echocardiography laboratory to minimise bias. The paper does not report whether outcome assessors were blinded.

The COAPT trial was well conducted, and no risk of bias issues were identified for many of the outcomes reported. Statistical comparison between the groups was not reported for safety outcomes and some outcomes were downgraded for imprecision due to wide confidence intervals around a hazard ratio. The study was funded by Abbott, the maker of the TEER device (MitraClip) used in the trial. The protocol was designed by the principal investigators and funder in accordance with the principles of the Mitral Valve Academic Research Consortium. The funder participated in site selection, management and data analysis.

The COAPT trial reported pre-planned subgroup analysis stratified by NYHA grade at baseline; however, the subgroups were only directly compared in terms of hospitalisation, survival and unplanned mitral valve interventions, with no statistically significant difference reported for the effectiveness of TEER between the baseline NYHA subgroups. For other outcomes, results for

the two baseline NYHA subgroups of patients were reported separately and not compared statistically. These did not suggest a clear advantage of TEER in any particular baseline NYHA subgroup compared to another.

The French MITRA-FR RCT enrolled 152 patients in each of the two treatment groups, TEER plus OMT and OMT alone, across 37 centres. The trial was only powered to detect a large treatment effect: a primary outcome event rate of 50% in the control group and 33% in the intervention group (the primary outcome in the trial was a composite variable combining death from any cause and hospitalisation due to heart failure). There were some differences in the demographic and clinical characteristics between the two groups at baseline, namely the proportion of males and history of ischaemic cardiomyopathy, myocardial infarction and diabetes, which were more common in the intervention group. Given the nature of the intervention, it was not possible to blind participants or those delivering the intervention to treatment allocation. The paper does not report whether outcome assessors were blinded.

The trial had a high attrition rate which differed between the two groups (28% TEER group and 9% in OMT group). Reasons included patient cross over (8 TEER v 2 OMT); not meeting prespecified criteria or had a protocol deviation (13 v 12); device procedure failure (6); and underwent device implantation more than 21 days after randomisation (21); however, an ITT analysis was performed and a comparison with results from a ‘per protocol’ analysis showed no significant difference. A large amount of follow-up data on echocardiographic, functional and QoL outcomes were missing and the impact of this on results was not explored.

The MITRA-FR trial was well conducted but concerns about bias were identified for many of the outcomes reported; p values were not reported for comparisons between the groups for any outcomes except the primary outcomes. The authors state that p-values were not reported as regression analyses were not used; however, confidence intervals were reported for survival and hospital admission outcomes. The study was funded by the French Ministry of Health and Research with some funding from Abbott Vascular. The paper stated that Abbott Vascular did not have a role in the design of the trial; the selection of participating trial centres; the monitoring or oversight of the centres; the enrolment or care of the patients; the collection, storage, analysis, or interpretation of the data; the writing of the manuscript; or the decision to submit the manuscript for publication; however, three patients were excluded prior to randomisation due to a proctoring decision by Abbott.

The meta-analyses all used the same data sources, the two RCTs described above. Two of the SRMAs reported detailed and appropriate search strategies (Bertaina et al 2019 reported a limited search strategy) and all three SRMAs used two reviewers to screen papers for inclusion in the meta-analysis. All included SRMAs presented combined results using a random effects model as significant inconsistency was observed between the results of the two included RCTs. The reasons for these differences are not obvious from the reported study data and there does not appear to be consensus regarding the differing results; however, the authors of all three systematic reviews suggested reasons for the inconsistency, mainly suggesting that the patients recruited for the COAPT trial and the MITRA-FR trial were different sub-sets of SMR patients. Bertaina et al 2019 suggested that the MITRA-FR trial participants were simply “sicker” than the COAPT participants but did not provide data to support this; Lodhi et al 2019 pointed out that MITRA-FR patients had more dilated ventricles at baseline; Zimarino et al 2020 highlighted the smaller left ventricular end-diastolic volume index at baseline among COAPT patients.

One SRMA, Lodhi et al 2019, reported the presence of publication bias, suggesting that there could have been increased mortality with TEER plus OMT that was not being reported. Zimarino et al 2020 did not find any publication bias for any outcomes and Bertaina et al 2019 did not test for publication bias.

The cost effectiveness evidence was reported from two studies using a UK NHS perspective over a lifetime time horizon. Although both studies used UK costs, the model inputs were primarily from the COAPT trial (conducted in the US and Canada), and therefore results, particularly costs based on resource allocation data derived from a different healthcare setting, may not be applicable to the UK.

In one cost effectiveness study, survival and quality of life (measured by the SF-36) from the COAPT trial data were converted to UK utility weights and estimated using linear regression. In the second study, quality of life was estimated using the NYHA classes. Limitations include uncertainties around modelled lifetime estimates based on 2-year trial data and a lack of confidence intervals reported for the ICER estimates.

7. Conclusion

This evidence review considered the clinical effectiveness and safety of TEER combined with OMT compared to OMT alone for the treatment of patients with moderate-to-severe or severe SMR due to left ventricular dysfunction or dilation.

There were meta-analysed RCT data or individual RCT data comparing TEER plus OMT with OMT alone for all the critical and important clinical effectiveness outcomes of interest. There was high certainty evidence of statistically significant reductions in heart failure related hospital admissions and deaths related to heart failure at 24 months follow-up. There was moderate certainty evidence of a statistically significant reduction in all-cause mortality and an improvement in NYHA grade at 24 months follow-up. Additional low to moderate certainty evidence from other studies did not always support these findings. There was no evidence of a difference between the groups at 12 months follow-up for mortality or heart failure hospitalisations.

There was moderate certainty evidence of reductions in MR grading persisting to 24 months and of improvements in health related quality of life and six minute walk test distance at 12 months in the TEER plus OMT group when compared to OMT alone. The difference was statistically significant when groups were statistically compared, although statistical analysis was not performed by all studies.

The two RCTs both reported procedural or device related complications with one reporting 14.6% of TEER patients having a procedural surgical complication and the other reporting an estimated 97% of patients free from device related complications at 12 months. For other safety outcomes, there was no evidence of a difference in the number of adverse events reported for TEER plus OMT compared to OMT alone; apart from stroke and myocardial infarction, the groups were not statistically compared.

Limitations reducing certainty in the comparison of TEER plus OMT and OMT alone for some outcomes included lack of similarity of the groups at baseline, lack of statistical comparison and wide confidence intervals around a hazard ratio. The RCTs could not be blinded, due to the nature of the intervention, and information about the blinding of analysts was missing from both trials. The two clinical trials had significant inconsistency in their results which led to generally low or very low certainty meta-analysis results.

The results of the subgroup analysis did not indicate a clear advantage for any subgroup of patients over the wider population of interest.

The cost-effectiveness evidence indicated that the incremental cost effectiveness ratio of TEER with OMT compared with OMT alone in people with moderately severe to severe SMR from a UK NHS perspective ranged from £23,270 to £30,440 per QALY over a lifetime time horizon.

The studies identified for this review therefore provide high to moderate evidence of better outcomes with transcatheter edge to edge repair plus OMT compared to OMT alone in adults with moderate-to-severe to severe SMR.

Appendix A PICO document

The review questions for this evidence review are:

In people with moderately severe to severe secondary mitral regurgitation what is the clinical effectiveness of TEER combined with current standard care compared with current standard care alone?

In people with moderately severe to severe secondary mitral regurgitation what is the safety of TEER combined with current standard care compared with current standard care alone?

In people with moderately severe to severe secondary mitral regurgitation what is the cost-effectiveness of TEER combined with current standard care compared with current standard care alone?

From the evidence selected, are there any subgroups of patients that may benefit from TEER more than the wider population of interest?

P –Population and Indication	People with moderately severe to severe (also known as grade 3 to grade 4[1,2]), secondary mitral regurgitation (SMR) due to left ventricular dysfunction or dilatation, and symptoms of heart failure despite optimised medical therapy which may or may not include cardiac resynchronisation therapy. Subgroups of interest: - Severe (grade 4) - Severe (NYHA IV) symptoms - Ejection fraction >20% and <60% [SMR due to LV dysfunction may also be called ventricular secondary mitral regurgitation (MR) Patients with secondary mitral valve disease due to atrial fibrillation, sometimes known as atrial secondary MR are not relevant to this review]
I – Intervention	Transcatheter Edge to Edge Repair (TEER) combined with optimised medical management [Procedure undertaken by placement of a mitral valve clip via percutaneous transfemoral venous approach under general anaesthesia (Current licenced techniques include MitraClip and PASCAL Mitral Valve Repair System) TEER may be done in combination with revascularisation therapy, e.g. percutaneous coronary intervention, or as a standalone procedure] [Medical management includes beta-blockers, angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB), angiotensin-receptor-neprilysin inhibitors (ARNI) to replace ACEI or ARB, mineralocorticoid receptor antagonists, sodium-glucose co-transporter2 inhibitors,

	ivabradine, hydralazine-nitrates and diuretics. Medical management may involve cardiac resynchronisation therapy as well.]
C – Comparator(s)	Current standard of care: 1. Optimised medical management alone [Medical management includes beta-blockers, angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB), angiotensin-receptor-neprilysin inhibitors (ARNI) to replace ACEI or ARB, mineralocorticoid receptor antagonists, sodium-glucose co-transporter2 inhibitors, ivabradine, hydralazine-nitrates and diuretics. Medical management may involve cardiac resynchronisation therapy as well.] 2. Open mitral valve surgery plus optimised medical management [Mitral valve open heart surgery may be part of open revascularisation surgery e.g. coronary artery bypass graft or may be a standalone procedure]
O – Outcomes	**Clinical Effectiveness** *Unless stated for the outcome, minimum clinically important differences (MCIDs) are unknown. Outcomes ideally measured at 6, 12, 24 months as well as long-term outcomes.* *Critical to decision making* • **Number of hospital admissions due to heart failure** *This outcome is important to patients as it reflects how effective the treatment is compared to current standard of care and is a surrogate for control of symptoms and quality of life.* [This will be measured within 24 months of follow-up, including recurrent events in patients with more than one event, and/or freedom from hospital admission] • **Survival** *This outcome is important to patients because it reflects how long people live after treatment, although it does not provide information about their health and wellbeing during that time.* [Other terms used to describe or indicate survival include, but are not limited to, overall survival, survival rate, freedom from death, death] • **NYHA grade**

	This outcome is important to patients because reduction of grade will also mean reduction of symptoms. This directly improves the patient's quality of life. [NYHA = New York Heart Association heart failure class (I – IV). This will usually be measured 6 to 12 months post procedure] *<u>Important to decision-making:</u>* • **Health related quality of life (HRQL)** *This outcome is important to patients because it provides a holistic evaluation and indication of the patient's general health and their perceived well-being and their ability to participate in activities of daily living. This outcome is both a key indicator of the effectiveness of treatment and provides an insight into the patient's perception of the effectiveness of treatment* [Other terms used to describe or indicate quality of life include but are not limited to; patient-reported quality of life outcomes, health related quality of life. Examples of metrics to assess quality of life include but are not limited to: Short Form (SF-36), EuroQuality of Life Five Dimensions (EQ-5D), Kansas City Cardiomyopathy Questionnaire (KCCQ) score, The Minnesota Living with Heart Failure quality of life questionnaire (MLHFQ). Other methods of assessing quality of life include but are not limited to subjective/self-reported/carer reported quality of life experiences.] • **Pre discharge grading of mitral regurgitation** *This outcome is important to patients because reduction of severity will reflect how effective the treatment is, although it does not provide information about their symptom control and quality of life.* [This outcome will be established on periodic echocardiographic imaging (ECHO), compared to their previous ECHO prior to TEER procedure. A two-grade reduction or a reduction to grade II or less is a key outcome] • **Duration/ durability of mitral regurgitation reduction** *This outcome is important to patients because it gives an indicator of how long any changes in grade or symptom burden of SMR may last.* [Other terms used to describe or indicate 'durability of response include but are not limited to; changes or lack of changes in mitral regurgitation grading on echocardiography, requirement for repeat mitral valve procedures, duration of symptomatic responses, time to

	treatment failure, progression free survival, time to re-intervention, time to repeat surgery] • **Functional outcomes** *This outcome is important to patients because it directly impacts independence and quality of life.* [6-minute walk tests are used to measure functional status (with longer distances indicating more preserved functional capacity)] **<u>Safety</u>** • **Procedural complications** *Safety is important to patients as it reflects the risks involved in undergoing TEER and allows a risk to benefit assessment to be undertaken* [Other terms used to describe or indicate safety include, but are not limited to; adverse events, serious/ major adverse events. This may include but is not limited to; device related complications (such as single leaflet device attachment, embolisation of device, mitral stenosis) death, myocardial infarction, need for intensive care admission, blood loss, endocarditis.] **<u>Cost effectiveness</u>**
Inclusion criteria	
Study design	Systematic reviews, randomised controlled trials, controlled clinical trials, cohort studies. If no higher-level quality evidence is found, case series can be considered.
Language	English only
Patients	Human studies only
Age	Adults
Date limits	2012 – 2022
Exclusion criteria	
Publication type	Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters, editorials and guidelines
Study design	Case reports, resource utilisation studies

1 Lancellotti, P., Pibarot, P., Chambers, J., la Canna, G., Pepi, M., Dulgheru, R., Dweck, M., Delgado, V., Garbi, M., Vannan, M. A., Montaigne, D., Badano, L., Maurovich-Horvat, P., Pontone, G., Vahanian, A., Donal, E., & Cosyns, B. (2022). Multi-modality imaging assessment of native valvular regurgitation: an EACVI and ESC council of valvular heart disease position paper. European Heart Journal, 23(5), pp. 171–232.

2 Zoghbi, W. A., Adams, D., Bonow, R. O., Enriquez-Sarano, M., Foster, E., Grayburn, P. A., Hahn, R. T., Han, Y., Hung, J., Lang, R. M., Little, S. H., Shah, D. J., Shernan, S., Thavendiranathan, P., Thomas, J. D., and Weissman, N. J. (2017). Recommendations for Noninvasive Evaluation of Native Valvular Regurgitation: A Report from the American Society of Echocardiography Developed in Collaboration with the Society for Cardiovascular Magnetic Resonance. Journal of the American Society of Echocardiography, 30(4), pp. 303–371.

Note, after paper selection was completed, NHS England confirmed that the priority comparator was optimised medical management.

Appendix B Search strategy

Medline, Embase, Cochrane, PubMed and TRIP were searched limiting the search to papers published in English language in the last 10 years. Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters, editorials, guidelines, pre-publication prints, case reports and resource utilisation studies were excluded.

Search dates: 1 January 2012 and 28 October 2022

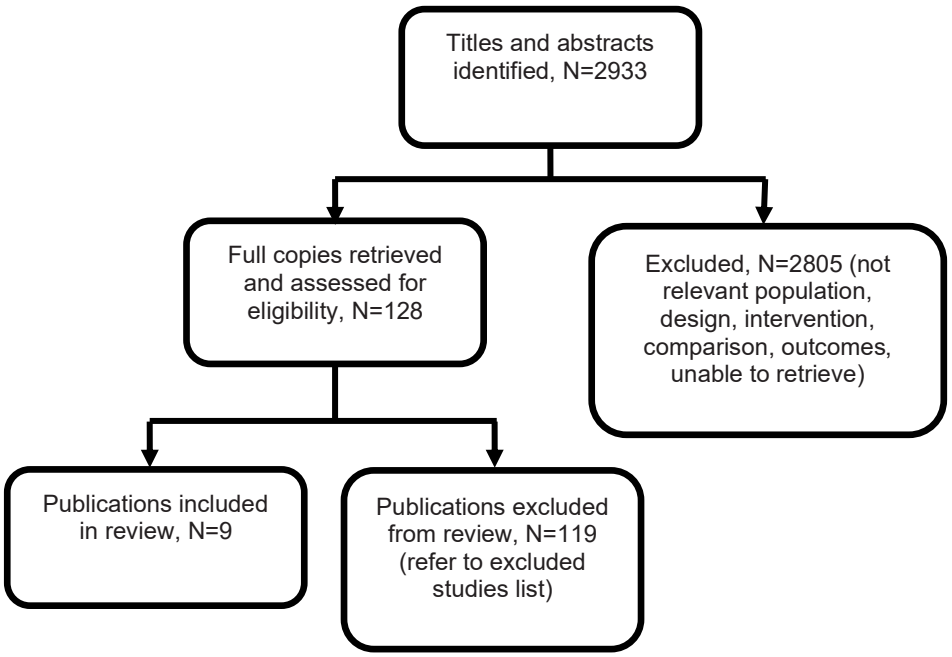
Medline search strategy:

1	Heart Failure/ or Ventricular Dysfunction, Left/
2	(heart failure or (left ventric* adj2 dysfunction)).ti,ab,kf.
3	1 or 2
4	Mitral Valve/
5	mitral valve?.ti.
6	4 or 5
7	3 and 6
8	Mitral Valve Insufficiency/
9	(mitral valve? adj3 (regurgit* or dysfunction or insufficienc* or incompetence or dilation)).ti,ab,kf.
10	7 or 8 or 9
11	Percutaneous Coronary Intervention/ and (Mitral Valve/su or Mitral Valve Insufficienty/su)
12	(percutaneous or transcatheter* or trans-catheter*).ti.
13	((percutaneous or transcatheter* or trans-catheter*) adj5 (repair* or implant* or surg* or clip* or intervention? or leaflet?)).ti,ab,kf.
14	teer.ti,ab,kf.
15	mitraclip.ti,ab,kf.
16	pascal.ti,ab,kf.
17	11 or 12 or 13 or 14 or 15 or 16
18	10 and 17
19	limit 18 to (meta analysis or "systematic review" or "reviews (maximizes specificity)")
20	(comment or editorial or letter or review).pt. or case report.ti.
21	18 not 20
22	exp animals/ not humans.sh.
23	21 not 22
24	19 or 23
25	limit 24 to (english language and yr="2012 -Current")

Appendix C Evidence selection

The literature searches identified 2,933 references. These were screened using their titles and abstracts and 128 references were obtained in full text and assessed for relevance. Of these, 9 references are included in the evidence summary. The remaining 119 references were excluded and are listed in Appendix D.

Figure 1- Study selection flow diagram



References submitted with Preliminary Policy Proposal

Reference	Paper selection - decision and rationale if excluded
G.W. Stone, et al for the COAPT Investigators. (2018) Transcatheter Mitral-Valve Repair in Patients with Heart Failure. The New England Journal of Medicine; 379:2307-18	Included.
Feldman, T et al for the EVEREST II Investigators (2011) Percutaneous Repair or Surgery for Mitral Regurgitation. New England Journal of Medicine, 364(15), 1395-1406	Outside of PICO specified search dates. Does not report outcomes by PICO population (secondary mitral regurgitation).
Maisano, F et al (2013) Percutaneous Mitral Valve Interventions in the Real World Early and 1- Year Results From the ACCESS-EU, A Prospective, Multicenter, Nonrandomized Post-Approval Study of the MitraClip Therapy in Europe. Journal of the American College of Cardiology, 62(12), 1052-61	No comparator group. RCT evidence available for all outcomes of interest.

Appendix D Excluded studies table

Study reference	Reason for exclusion
Alozie A, Paranskaya L, Westphal B, Kaminski A, Sherif M, Sindt M, et al. Clinical outcomes of conventional surgery versus MitraClip R therapy for moderate to severe symptomatic mitral valve regurgitation in the elderly population: an institutional experience. BMC Cardiovasc Disord. 2017;17(1):85.	Does not report outcomes by PICO population (secondary mitral regurgitation (SMR)).
Andalib A, Mamane S, Schiller I, Zakem A, Mylotte D, Martucci G, et al. A systematic review and meta-analysis of surgical outcomes following mitral valve surgery in octogenarians: implications for transcatheter mitral valve interventions. EuroIntervention. 2014;9(10):1225-34.	Does not report outcomes by PICO population (SMR).
Ansari MT, Ahmadzai N, Coyle K, Coyle D, Moher D. Mitral Valve Clip for Treatment of Mitral Regurgitation: An Evidence-Based Analysis. Ont Health Technol Assess Ser. 2015;15(12):1-104.	Does not report outcomes by PICO population (SMR).
Armeni P, Boscolo PR, Tarricone R, Capodanno D, Maggioni AP, Grasso C, et al. Real-world cost effectiveness of MitraClip combined with Medical Therapy Versus Medical therapy alone in patients with moderate or severe mitral regurgitation. Int J Cardiol. 2016;209:153-60.	Non-UK cost effectiveness study. UK based cost effectiveness studies available.
Armoiry X, Obadia JF, Auguste P, Connock M. Conflicting findings between the Mitra-Fr and the Coapt trials: Implications regarding the cost-effectiveness of percutaneous repair for heart failure patients with severe secondary mitral regurgitation. PLoS ONE. 2020;15(11):e0241361.	Non-UK cost effectiveness study. UK based cost effectiveness studies available.
Arnold SV, Chinnakondepalli KM, Spertus JA, Magnuson EA, Baron SJ, Kar S, et al. Health Status After Transcatheter Mitral-Valve Repair in Heart Failure and Secondary Mitral Regurgitation: COAPT Trial. J Am Coll Cardiol. 2019;73(17):2123-32.	Not a specified subgroup of interest. Does not report any additional outcomes that are not already covered by included studies.
Arnold SV, Stone GW, Jain SS, Mack MJ, Saxon JT, Zhang Z, et al. Prognostic Importance of Health Status Versus Functional Status in Heart Failure and Secondary Mitral Regurgitation. JACC Heart Fail. 2021;9(9):684-92.	Not a specified subgroup of interest. Does not report any additional outcomes that are not already covered by included studies.
Arnold SV, Stone GW, Mack MJ, Chhatriwalla AK, Austin BA, Zhang Z, et al. Health Status Changes and Outcomes in Patients With Heart Failure and Mitral Regurgitation: COAPT Trial. J Am Coll Cardiol. 2020;75(17):2099-106.	Not a specified subgroup of interest. Does not report any additional outcomes that are not already covered by included studies.
Asgar AW, Khairy P, Guertin MC, Cournoyer D, Ducharme A, Bonan R, et al. Clinical outcomes and economic impact of transcatheter mitral leaflet repair in heart failure patients. J Med Econ. 2017;20(1):82-90.	Non-UK cost effectiveness study. UK based cost effectiveness studies available.
Baron SJ, Wang K, Arnold SV, Magnuson EA, Whisenant B, Brieke A, et al. Cost-Effectiveness of Transcatheter Mitral Valve Repair Versus Medical Therapy in Patients With Heart Failure and Secondary Mitral Regurgitation: Results From the COAPT Trial. Circulation. 2019;140(23):1881-91.	Non-UK cost effectiveness study. UK based cost effectiveness studies available.
Baron SJ. Clinical trial perspective: Cost-effectiveness of transcatheter mitral valve repair versus medical therapy in patients with heart failure and secondary mitral regurgitation. Results from the COAPT trial. US Cardiology Review. 2020;14:e08.	Non-UK cost effectiveness study. UK based cost effectiveness studies available.

Barros da Silva P, Sousa JP, Oliveiros B, Donato H, Costa M, Goncalves L, et al. Stroke after transcatheter edge-to-edge mitral valve repair: a systematic review and meta-analysis. EuroIntervention. 2020;15(16):1401-8.	Does not report outcomes by PICO population (SMR).
Benito-Gonzalez T, Estevez-Loureiro R, Iglesias-Garriz I, Gualis J, Perez de Prado A, Garrote C, et al. Survival Advantage of MitraClip R Over Medical Treatment in Patients with Mitral Regurgitation: A Meta-Analysis. J Heart Valve Dis. 2017;26(6):651-8.	Includes observational studies. RCT evidence available for all outcomes of interest.
Benito-Gonzalez T, Estevez-Loureiro R, Villablanca PA, Armeni P, Iglesias-Garriz I, Minguito C, et al. Percutaneous Mitral Valve Repair Vs. Stand-Alone Medical Therapy in Patients with Functional Mitral Regurgitation and Heart Failure. Cardiovasc Revasc Med. 2020;21(1):52-60.	Letters excluded in PICO.
Ben-Yehuda O, Shahim B, Chen S, Liu M, Redfors B, Hahn RT, et al. Pulmonary Hypertension in Transcatheter Mitral Valve Repair for Secondary Mitral Regurgitation: The COAPT Trial. J Am Coll Cardiol. 2020;76(22):2595-606.	Not a specified subgroup of interest. Does not report any additional outcomes that are not already covered by included studies.
Borisenko O, Haude M, Hoppe UC, Siminiak T, Lipiecki J, Goldberg SL, et al. Cost-utility analysis of percutaneous mitral valve repair in inoperable patients with functional mitral regurgitation in German settings. BMC Cardiovasc Disord. 2015;15:43.	Non-UK cost effectiveness study. UK based cost effectiveness studies available.
Cameron HL, Bernard LM, Garmo VS, Hernandez JB, Asgar AW. A Canadian cost-effectiveness analysis of transcatheter mitral valve repair with the MitraClip system in high surgical risk patients with significant mitral regurgitation. J Med Econ. 2014;17(8):599-615.	Non-UK cost effectiveness study. UK based cost effectiveness studies available.
Cardoso R, Ansari M, Garcia D, Martucci G, Piazza N. A meta-analysis of controlled studies comparing mitraclip versus surgery for severe mitral regurgitation: Is there a mortality benefit? J Am Coll Cardiol. 2016;67(13 SUPPL. 1):343.	Does not report outcomes by PICO population (SMR).
Chatzistergiou KT, Papanastasiou CA, Kokkinidis DG, Ziakas AG, Karvounis HI, Karamitsos TD. MitraClip device for patients with functional mitral valve regurgitation: A systematic review. HJC Hell. 2019;60(2):101-7.	Non-comparative study. RCT evidence available for all outcomes of interest.
Chiarito M, Pagnesi M, Martino E, Pighi M, Scotti A, Biondi-Zoccai G, et al. Outcome after percutaneous edge-to-edge mitral repair for functional and degenerative mitral regurgitation: A systematic review and meta-analysis. J Am Coll Cardiol. 2017;70(18 Supplement 1):B240-B1.	Incorrect comparator: primary MR vs secondary MR.
Chiarito M, Pagnesi M, Martino EA, Godino C, Monello A, Scotti A, et al. One year outcome after mitraclip procedure for functional and degenerative significant mitral regurgitation: A systematic review and meta-analysis. Eur Heart J. 2016;37(Supplement 1):405.	Does not report outcomes by PICO population (SMR).
Chiarito M, Sanz-Sanchez J, Pighi M, Cannata F, Rubbio AP, Munafò A, et al. Edge-to-edge percutaneous mitral repair for functional ischaemic and non-ischaemic mitral regurgitation: a systematic review and meta-analysis. ESC Heart Fail. 2022.	Includes observational studies. RCT evidence available for all outcomes of interest.

Conradi L, Treede H, Rudolph V, Graumuller P, Lubos E, Baldus S, et al. Surgical or percutaneous mitral valve repair for secondary mitral regurgitation: comparison of patient characteristics and clinical outcomes. Eur J Cardiothorac Surg. 2013;44(3):490-6; discussion 6.	Observational study. RCT evidence available for all outcomes of interest.
Cubero-Gallego H, Hernandez-Vaquero D, Avanzas P, Almendarez M, Adeba A, Lorca R, et al. Outcomes with percutaneous mitral repair vs. Optimal medical treatment for functional mitral regurgitation: Systematic review. Ann. 2020;8(15):962.	Systematic review of included studies with no meta-analysis of results. Eligible studies separately considered for inclusion.
Czarnecki A, Han L, Abuzeid W, Cantor WJ, Chan V, Cohen EA, et al. Impact of Transcatheter Mitral Valve Repair on Preprocedural and Postprocedural Hospitalization Rates. JACC Cardiovasc Interv. 2021;14(20):2274-81.	Does not report outcomes by PICO population (SMR).
D'Ascenzo F, Moretti C, Marra WG, Montefusco A, Omede P, Taha S, et al. Meta-analysis of the usefulness of Mitraclip in patients with functional mitral regurgitation. Am J Cardiol. 2015;116(2):325-31.	Non-comparative study. RCT evidence available for all outcomes of interest.
De Bonis M, Lapenna E, Buzzatti N, La Canna G, Denti P, Pappalardo F, et al. Corrigendum to 'Optimal results immediately after MitraClip therapy or surgical edge-to-edge repair for functional mitral regurgitation: are they really stable at 4 years?' [Eur J Cardiothorac Surg 2016;50:488-494]. Eur J Cardiothorac Surg. 2017;51(4):807.	Observational study. RCT evidence available for all outcomes of interest.
De Bonis M, Lapenna E, Buzzatti N, La Canna G, Denti P, Pappalardo F, 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? Eur J Cardiothorac Surg. 2016;50(3):488-94.	Observational study. RCT evidence available for all outcomes of interest.
De Bonis M, Taramasso M, Lapenna E, Denti P, La Canna G, Buzzatti N, 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. Eur J Cardiothorac Surg. 2016;49(1):255-62.	Observational study. RCT evidence available for all outcomes of interest.
De Rosa R, Silverio A, Baldi C, Di Maio M, Prota C, Radano I, et al. Transcatheter Repair of Functional Mitral Regurgitation in Heart Failure Patients - A Meta-Analysis of 23 Studies on MitraClip Implantation. Circ J. 2018;82(11):2800-10.	Includes observational studies. RCT evidence available for all outcomes of interest.
Del Val D, Ferreira-Neto AN, Wintzer-Wehekind J, Dagenais F, Paradis JM, Bernier M, et al. Early Experience With Transcatheter Mitral Valve Replacement: A Systematic Review. J Am Heart Assoc. 2019;8(17):e013332.	Incorrect intervention: transcatheter mitral valve replacement.
Doshi R, Shlofmitz E, Shah J, Meraj P. Comparison of Transcatheter Mitral Valve Repair Versus Surgical Mitral Valve Repair in Patients With Advanced Kidney Disease (from the National Inpatient Sample). Am J Cardiol. 2018;121(6):762-7.	Observational study. RCT evidence available for all outcomes of interest.
Estler B, Rudolph V, Seleznova Y, Shukri A, Stock S, Muller D. Cost-effectiveness of the MitraClip device in German heart failure patients with secondary mitral regurgitation. European Journal of Health Economics. 2022.	Non-UK cost effectiveness study. UK based cost effectiveness studies available.

Fabry N, Hendrickson MJ, Arora S, Vavalle JP. Five-year trends in cause-specific readmissions and cost burden of mitral transcatheter edge-to-edge repair. Catheter Cardiovasc Interv. 2022;99(4):1251-6.	Non-UK cost effectiveness study. UK based cost effectiveness studies available.
Feldman T, Kar S, Elmariah S, Smart SC, Trento A, Siegel RJ, et al. Randomized Comparison of Percutaneous Repair and Surgery for Mitral Regurgitation: 5-Year Results of EVEREST II. J Am Coll Cardiol. 2015;66(25):2844-54.	Does not report outcomes by PICO population (SMR).
Flynn CD, Wilson-Smith AR, Yan TD. Novel mitral valve technologies-transcatheter mitral valve implantation: a systematic review. Ann Cardiothorac Surg. 2018;7(6):716-23.	Incorrect intervention: transcatheter mitral valve replacement.
Geis N, Raake P, Lewening M, Mereles D, Chorianopoulos E, Frankenstein L, et al. Percutaneous repair of mitral valve regurgitation in patients with severe heart failure: comparison with optimal medical treatment. Acta Cardiol. 2018;73(4):378-86.	Observational study. RCT evidence available for all outcomes of interest.
Geis NA, Pleger ST, Bekeredjian R, Chorianopoulos E, Kreusser MM, Frankenstein L, et al. Haemodynamic effects of percutaneous mitral valve edge-to-edge repair in patients with end-stage heart failure awaiting heart transplantation. ESC Heart Fail. 2018;5(5):892-901.	Observational study. RCT evidence available for all outcomes of interest.
Giannini C, D'Ascenzo F, Fiorelli F, Spontoni P, Swaans MJ, Velazquez EJ, et al. A meta-analysis of MitraClip combined with medical therapy vs. medical therapy alone for treatment of mitral regurgitation in heart failure patients. ESC Heart Fail. 2018;5(6):1150-8.	Includes observational studies. RCT evidence available for all outcomes of interest.
Giannini C, Fiorelli F, De Carlo M, Guarracino F, Faggioni M, Giordano P, et al. Comparison of Percutaneous Mitral Valve Repair Versus Conservative Treatment in Severe Functional Mitral Regurgitation. Am J Cardiol. 2016;117(2):271-7.	Observational study. RCT evidence available for all outcomes of interest.
Glower D, Ailawadi G, Argenziano M, Mack M, Trento A, Wang A, et al. EVEREST II randomized clinical trial: predictors of mitral valve replacement in de novo surgery or after the MitraClip procedure. J Thorac Cardiovasc Surg. 2012;143(4 Suppl):S60-3.	Does not report outcomes by PICO population (SMR).
Goel S, Pasam RT, Wats K, Chava S, Gotesman J, Sharma A, et al. Mitraclip Plus Medical Therapy Versus Medical Therapy Alone for Functional Mitral Regurgitation: A Meta-Analysis. Cardiology and Therapy. 2020;9(1):5-17.	Includes observational studies. RCT evidence available for all outcomes of interest.
Grayburn PA, Sannino A, Cohen DJ, Kar S, Lim DS, Mishell JM, et al. Predictors of Clinical Response to Transcatheter Reduction of Secondary Mitral Regurgitation: The COAPT Trial. J Am Coll Cardiol. 2020;76(9):1007-14.	Does not include PICO specified outcomes.
Guerin P, Bourguignon S, Jamet N, Marque S. MitraClip therapy in mitral regurgitation: a Markov model for the cost-effectiveness of a new therapeutic option. J Med Econ. 2016;19(7):696-701.	Non-UK cost effectiveness study. UK based cost effectiveness studies available.
Gyoten T, Schenk S, Rochor K, Herwig V, Harnath A, Grimmig O, et al. Outcome comparison of mitral valve surgery and MitraClip therapy in patients with severely reduced left ventricular dysfunction. ESC Heart Fail. 2020;7(4):1781-90.	Observational study. RCT evidence available for all outcomes of interest.

Haberman D, Estevez-Loureiro R, Benito-Gonzalez T, Denti P, Arzamendi D, Adamo M, et al. Conservative, surgical, and percutaneous treatment for mitral regurgitation shortly after acute myocardial infarction. Eur Heart J. 2022;43(7):641-50.	Observational study. RCT evidence available for all outcomes of interest.
Herrmann E, Ecke A, Herrmann E, Eissing N, Fichtlscherer S, Zeiher AM, et al. Daily non-invasive haemodynamic telemonitoring for efficacy evaluation of MitraClip R implantation in patients with advanced systolic heart failure. ESC Heart Fail. 2018;5(5):780-7.	Observational study. RCT evidence available for all outcomes of interest.
Hubert A, Galli E, Leurent G, Corbineau H, Auriane B, Guillaume L, et al. Left ventricular function after correction of mitral regurgitation: Impact of the clipping approach. Echocardiography. 2019;36(11):2010-8.	Observational study. RCT evidence available for all outcomes of interest.
Iliadis C, Lee S, Kuhr K, Metze C, Matzik AS, Michels G, et al. Functional status and quality of life after transcatheter mitral valve repair: a prospective cohort study and systematic review. Clin. 2017;106(12):1005-17.	Does not report outcomes by PICO population (SMR).
Jogu HR, Arora S, Strassle PD, Patel C, Patil N, Venkatesh S, et al. Impact of age and comorbidities on the effect of transcatheter versus surgical mitral valve repair on inpatient outcomes. Catheter Cardiovasc Interv. 2020;95(6):1195-201.	Does not report outcomes by PICO population (SMR).
Kamperidis V, van Wijngaarden SE, van Rosendael PJ, Kong WKF, Regeer MV, van der Kley F, et al. Mitral valve repair for secondary mitral regurgitation in non-ischaemic dilated cardiomyopathy is associated with left ventricular reverse remodelling and increase of forward flow. Eur Heart J Cardiovasc Imaging. 2018;19(2):208-15.	Observational study. RCT evidence available for all outcomes of interest.
Kar S, Mack MJ, Lindenfeld J, Abraham WT, Asch FM, Weissman NJ, et al. Relationship Between Residual Mitral Regurgitation and Clinical and Quality-of-Life Outcomes After Transcatheter and Medical Treatments in Heart Failure: COAPT Trial. Circulation. 2021;144(6):426-37.	Not a specified subgroup of interest. Does not report any additional outcomes that are not already covered by included studies.
Khader AA, Allaf M, Lu OW, Lazopoulos G, Moscarelli M, Kendall S, et al. Does the clinical effectiveness of Mitraclip compare with surgical repair for mitral regurgitation? J Card Surg. 2021;36(3):1103-19.	Does not report outcomes by PICO population (SMR).
Kheiri B, Zayed Y, Barbarawi M, Osman M, Chahine A, Ahmed S, et al. Interventions for Secondary Mitral Regurgitation in Patients With Heart Failure: A Network Meta-Analysis of Randomized Controlled Comparisons of Surgery, Medical Therapy and Transcatheter Intervention. Cardiovasc Revasc Med. 2020;21(2):155-63.	Systematic review of included studies with no meta-analysis of results. Eligible studies separately considered for inclusion.
Kortlandt F, Velu J, Schurer R, Hendriks T, Van den Branden B, Bouma B, et al. Survival After MitraClip Treatment Compared to Surgical and Conservative Treatment for High-Surgical-Risk Patients With Mitral Regurgitation. Circ. 2018;11(6):e005985.	Observational study. RCT evidence available for all outcomes of interest.
Kortlandt F, Velu J, Schurer R, Van den Branden B, Bouma B, Kelder J, et al. Impact of mitral valve treatment choice on mortality according to aetiology. EuroIntervention. 2019;14(17):1733-9.	Observational study. RCT evidence available for all outcomes of interest.

Koschutnik M, Dannenberg V, Dona C, Nitsche C, Kammerlander AA, Koschatko S, et al. Transcatheter Versus Surgical Valve Repair in Patients with Severe Mitral Regurgitation. Journal of Personalized Medicine. 2022;12(1):90.	Does not report outcomes by PICO population (SMR).
Kosmidou I, Lindenfeld J, Abraham WT, Kar S, Lim DS, Mishell JM, et al. Transcatheter Mitral Valve Repair in Patients With and Without Cardiac Resynchronization Therapy: The COAPT Trial. Circ. 2020;13(11):e007293.	Not a specified subgroup of interest. Does not report any additional outcomes that are not already covered by included studies.
Kosmidou I, Lindenfeld J, Abraham WT, Rinaldi MJ, Kapadia SR, Rajagopal V, et al. Sex-Specific Outcomes of Transcatheter Mitral-Valve Repair and Medical Therapy for Mitral Regurgitation in Heart Failure. JACC Heart Fail. 2021;9(9):674-83.	Not a specified subgroup of interest. Does not report any additional outcomes that are not already covered by included studies.
Kumar A, Al-Khafaji J, Shariff M, Vaz IP, Adalja D, Doshi R. Percutaneous mitral valve repair for secondary mitral valve regurgitation: A systematic review and meta-analysis. Eur. 2020;78:107-12.	Includes observational studies. RCT evidence available for all outcomes of interest.
Lavall D, Mehrer M, Schirmer SH, Reil JC, Wagenpfeil S, Bohm M, et al. Long-Term Hemodynamic Improvement after Transcatheter Mitral Valve Repair. J Am Soc Echocardiogr. 2018;31(9):1013-20.	Does not report outcomes by PICO population (SMR).
Lerakis S, Kini AS, Asch FM, Kar S, Lim DS, Mishell JM, et al. Outcomes of transcatheter mitral valve repair for secondary mitral regurgitation by severity of left ventricular dysfunction. EuroIntervention. 2021;17(4):e335-e42.	Not a specified subgroup of interest. Does not report any additional outcomes that are not already covered by included studies.
Leurent G, Auffret V, Donal E, Corbineau H, Grinberg D, Bonnet G, et al. Delayed hospitalisation for heart failure after transcatheter repair or medical treatment for secondary mitral regurgitation: a landmark analysis of the MITRA-FR trial. EuroIntervention. 2022;18(6):514-23.	Post-hoc analysis of RCT, excluding a subset of patients (those that died or needed hospitalisation in first 12 months), so it is no longer a randomisation-based analysis. RCT evidence available for all outcomes of interest.
Lima FV, Kolte D, Rofeberg V, Molino J, Zhang Z, Elmariah S, et al. Thirty-day readmissions after transcatheter versus surgical mitral valve repair in high-risk patients with mitral regurgitation: Analysis of the 2014-2015 Nationwide readmissions databases. Catheter Cardiovasc Interv. 2020;96(3):664-74.	Incorrect population: primary mitral regurgitation.
Lindenfeld J, Abraham WT, Grayburn PA, Kar S, Asch FM, Lim DS, et al. Association of Effective Regurgitation Orifice Area to Left Ventricular End-Diastolic Volume Ratio With Transcatheter Mitral Valve Repair Outcomes: A Secondary Analysis of the COAPT Trial. JAMA Cardiol. 2021;6(4):427-36.	Post-hoc analysis of RCT, excluding a subset of patients, so it is no longer a randomisation-based analysis. RCT evidence available for all outcomes of interest.
Liu XH, Shi JY, Feng XJ, Feng DC, Wang L, Pang HY, et al. Short-term and 1-year outcomes after MitraClip therapy in functional versus degenerative mitral regurgitation patients: A systematic review and meta-analysis. J. 2018;10(7):4156-68.	Incorrect comparator: primary MR vs secondary MR.
Ludwig S, Sedighian R, Weimann J, Koell B, Waldschmidt L, Schafer A, et al. Management of patients with mitral regurgitation ineligible for standard therapy undergoing TMVI screening. EuroIntervention. 2022;18(3):213-23.	Observational study. RCT evidence available for all outcomes of interest.

Mack MJ, Abraham WT, Lindenfeld J, Bolling SF, Feldman TE, Grayburn PA, et al. Cardiovascular Outcomes Assessment of the MitraClip in Patients with Heart Failure and Secondary Mitral Regurgitation: Design and rationale of the COAPT trial. Am Heart J. 2018;205:1-11.	Does not include PICO specified outcomes.
Mack MJ, Lindenfeld J, Abraham WT, Kar S, Lim DS, Mishell JM, et al. 3-Year Outcomes of Transcatheter Mitral Valve Repair in Patients With Heart Failure. J Am Coll Cardiol. 2021;77(8):1029-40.	Post-hoc analysis of RCT, where cross-over of patients was allowed after 3-years, so it is no longer a randomisation-based analysis. RCT evidence available for all outcomes of interest.
Malik UI, Ambrosy AP, Ku IA, Mishell JM, Kar S, Lim DS, et al. Baseline Functional Capacity and Transcatheter Mitral Valve Repair in Heart Failure With Secondary Mitral Regurgitation. JACC Cardiovasc Interv. 2020;13(20):2331-41.	Not a specified subgroup of interest. Does not report any additional outcomes that are not already covered by included studies.
Marmagkiolis K, Hakeem A, Ebersole DG, Iliescu C, Ates I, Cilingiroglu M. Clinical outcomes of percutaneous mitral valve repair with MitraClip for the management of functional mitral regurgitation. Catheter Cardiovasc Interv. 2019;94(6):820-6.	Includes observational studies. RCT evidence available for all outcomes of interest.
Mauri L, Foster E, Glower DD, Apruzzese P, Massaro JM, Herrmann HC, et al. 4-year results of a randomized controlled trial of percutaneous repair versus surgery for mitral regurgitation. J Am Coll Cardiol. 2013;62(4):317-28.	Does not include PICO specified outcomes.
Mealing S, Feldman T, Eaton J, Singh M, Scott DA. EVEREST II high risk study based UK cost-effectiveness analysis of MitraClip R in patients with severe mitral regurgitation ineligible for conventional repair/replacement surgery. J Med Econ. 2013;16(11):1317-26.	Effectiveness data derived from a non-randomised trial which included patients with primary MR. UK based cost effectiveness studies available based on RCT of secondary MR patients.
Medvedofsky D, Milhorini Pio S, Weissman NJ, Namazi F, Delgado V, Grayburn PA, et al. Left Ventricular Global Longitudinal Strain as a Predictor of Outcomes in Patients with Heart Failure with Secondary Mitral Regurgitation: The COAPT Trial. J Am Soc Echocardiogr. 2021;34(9):955-65.	Not a specified subgroup of interest. Does not report any additional outcomes that are not already covered by included studies.
Megaly M, Khalil C, Abraham B, Saad M, Tawadros M, Stanberry L, et al. Impact of Transcatheter Mitral Valve Repair on Left Ventricular Remodeling in Secondary Mitral Regurgitation: A Meta-Analysis. Structural Heart. 2018;2(6):541-7.	Does not include PICO specified outcomes.
Messika-Zeitoun D, Attias D, Piriou N, Iung B, Armoiry X, Trochu JN, et al. Impact of procedural success on clinical outcome after MitraClip: Results from the MITRA-FR trial. Arch Cardiovasc Dis. 2022.	Post hoc analysis of RCT; not a specified subgroup of interest. Does not report any additional outcomes that are not already covered by included studies.
Messika-Zeitoun D, Iung B, Armoiry X, Trochu JN, Donal E, Habib G, et al. Impact of Mitral Regurgitation Severity and Left Ventricular Remodeling on Outcome After MitraClip Implantation: Results From the Mitra-FR Trial. JACC Cardiovasc Imaging. 2021;14(4):742-52.	Does not include PICO specified outcomes.
Muller DWM, Farivar RS, Jansz P, Bae R, Walters D, Clarke A, et al. Transcatheter Mitral Valve Replacement for Patients With Symptomatic Mitral Regurgitation: A Global Feasibility Trial. J Am Coll Cardiol. 2017;69(4):381-91.	Incorrect intervention: transcatheter mitral valve replacement.

Munkholm-Larsen S, Wan B, Tian DH, Kearney K, Rahnavardi M, Dixen U, 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(6):473-8.	Does not report outcomes by PICO population (SMR).
Namazi F, Delgado V, Pio SM, Ajmone Marsan N, Asch FM, Medvedofsky D, et al. Prognostic implications of mitral valve geometry in patients with secondary mitral regurgitation: the COAPT trial. Eur Heart J Cardiovasc Imaging. 2022;23(11):1540-51.	Not a specified subgroup of interest. Does not report any additional outcomes that are not already covered by included studies.
Nappi F, Singh SSA, Bellomo F, Nappi P, Chello C, Iervolino A, et al. Exploring the Operative Strategy for Secondary Mitral Regurgitation: A Systematic Review. Biomed Res Int. 2021;2021:3466813.	Systematic review of included studies with no meta-analysis of results. Eligible studies separately considered for inclusion.
Oh NA, Kampaktsis PN, Gallo M, Guariento A, Weixler V, Staffa SJ, et al. An updated meta-analysis of MitraClip versus surgery for mitral regurgitation. Ann Cardiothorac Surg. 2021;10(1):1-14.	Does not report outcomes by PICO population (SMR).
Okuno T, Praz F, Kassar M, Biaggi P, Mihalj M, Kulling M, et al. Surgical versus transcatheter repair for secondary mitral regurgitation: A propensity score-matched cohorts comparison. Journal of Thoracic and Cardiovascular Surgery. 2021.	Observational study. RCT evidence available for all outcomes of interest.
Ondrus T, Bartunek J, Vanderheyden M, Stockman B, Kotrc M, Van Praet F, et al. Minimally invasive mitral valve repair for functional mitral regurgitation in severe heart failure: MitraClip versus minimally invasive surgical approach. Interact Cardiovasc Thorac Surg. 2016;23(5):784-9.	Observational study. RCT evidence available for all outcomes of interest.
Ondrus T, Penicka M, Kotrc M, Vanderheyden M, Bartunek J. MitraClip: catheter-based treatment of mitral regurgitation. Cor et vasa. 2017;59(1):e85?e91.	Observational study. RCT evidence available for all outcomes of interest.
Ostovar R, Claus T, Hartrumpf M, Kuehnel RU, Braun C, Butter C, et al. MitraClip for High-Risk Patients with Significant Mitral Insufficiency: Shall We Unreservedly Recommend It? Thorac Cardiovasc Surg. 2018;66(7):537-44.	Incorrect comparator: surgical MV replacement after TEER vs surgical repair / replacement initial intervention.
Outcomes with percutaneous mitral repair. Ann. 2020.	Duplicate
Paranskaya L, D'Ancona G, Bozdag-Turan I, Akin I, Kische S, Turan GR, et al. Percutaneous vs surgical repair of mitral valve regurgitation: single institution early and midterm outcomes. Can J Cardiol. 2013;29(4):452-9.	Does not report outcomes by PICO population (SMR).
Percutaneous interventions for mitral regurgitation - technology Note. Health Technology Assessment (HTA) Database. 2013.	Does not report outcomes by PICO population (SMR).
Pernia-Orena I, Sanchez-Silos FM, Alados-Arboledas P, Hervas-Sotomayor DI, Arias-Dachary J, Fernandez-Carbonell A, et al. Comparing mitral valve repair and the MitraClip device in the treatment of severe mitral regurgitation. Cirugia Cardiovascular. 2017;24(2):71-7.	Non-English papers excluded in PICO
Philip F, Athappan G, Tuzcu EM, Svensson LG, Kapadia SR. MitraClip for severe symptomatic mitral regurgitation in patients at high surgical risk: a comprehensive systematic review. Catheter Cardiovasc Interv. 2014;84(4):581-90.	Does not report outcomes by PICO population (SMR).

Rezapour A, Azari S, Arabloo J, Pourasghari H, Behzadifar M, Alipour V, et al. Cost-effectiveness analysis of mitral valve repair with the MitraClip delivery system for patients with mitral regurgitation: a systematic review. Heart Fail Rev. 2021;26(3):587-601.	US focussed systematic review of cost effectiveness studies. Population not restricted to secondary MR. UK based cost effectiveness studies available.
Sakamaki H, Nakao K, Matsumoto T, Inoue S. Cost-effectiveness analysis of percutaneous mitral valve repair with the MitraClip delivery system for patients with mitral regurgitation in Japan. J Med Econ. 2019;22(12):1312-20.	Non-UK cost effectiveness study. UK based cost effectiveness studies available.
Samad Z, Shaw LK, Phelan M, Ersboll M, Risum N, Al-Khalidi HR, et al. Management and outcomes in patients with moderate or severe functional mitral regurgitation and severe left ventricular dysfunction. Eur Heart J. 2015;36(40):2733-41.	Observational study. RCT evidence available for all outcomes of interest.
Sawalha K, Gupta K, Kadado AJ, Abozenah M, Battisha A, Salerno C, et al. In-hospital outcomes of transcatheter versus surgical mitral valve repair in patients with chronic liver disease. Int J Clin Pract. 2021;75(10):e14660.	Does not report outcomes by PICO population (SMR).
Saxon JT, Cohen DJ, Chhatriwalla AK, Kotinkaduwa LN, Kar S, Lim DS, et al. Impact of COPD on Outcomes After MitraClip for Secondary Mitral Regurgitation: The COAPT Trial. JACC Cardiovasc Interv. 2020;13(23):2795-803.	Not a specified subgroup of interest. Does not report any additional outcomes that are not already covered by included studies.
Sazzad F, Hon JKF, Ramanathan K, Nah JH, Ong ZX, Ti LK, et al. Design Variation, Implantation, and Outcome of Transcatheter Mitral Valve Prosthesis: A Comprehensive Review. Front Cardiovasc Med. 2021;8:782278.	Incorrect intervention: transcatheter mitral valve replacement.
Scotti A, Massussi M, Latib A, Munafo A, Colombo A, Taramasso M, et al. Meta-Analysis of Relation Between Left Ventricular Dysfunction and Outcomes After Transcatheter Mitral Edge-to-Edge Repair. Am J Cardiol. 2022;175:88-96.	Includes observational studies. RCT evidence available for all outcomes of interest.
Shahim B, Ben-Yehuda O, Chen S, Redfors B, Madhavan MV, Kar S, et al. Impact of Diabetes on Outcomes After Transcatheter Mitral Valve Repair in Heart Failure: COAPT Trial. JACC Heart Fail. 2021;9(8):559-67.	Not a specified subgroup of interest. Does not report any additional outcomes that are not already covered by included studies.
Shi W, Zhang W, Zhang D, Ye G, Ding C. Mortality and Clinical Predictors After Percutaneous Mitral Valve Repair for Secondary Mitral Regurgitation: A Systematic Review and Meta-Regression Analysis. Front. 2022;9:918712.	Non-comparison studies included. RCT evidence available for all outcomes of interest.
Song C, Madhavan MV, Lindenfeld J, Abraham WT, Kar S, Lim DS, et al. Age-Related Outcomes After Transcatheter Mitral Valve Repair in Patients With Heart Failure: Analysis From COAPT. JACC Cardiovasc Interv. 2022;15(4):397-407.	Not a specified subgroup of interest. Does not report any additional outcomes that are not already covered by included studies.
Swaans MJ, Bakker AL, Alipour A, Post MC, Kelder JC, de Kroon TL, et al. Survival of transcatheter mitral valve repair compared with surgical and conservative treatment in high-surgical-risk patients. JACC Cardiovasc Interv. 2014;7(8):875-81.	Observational study. RCT evidence available for all outcomes of interest.
Takagi H, Ando T, Umemoto T, Group A. A review of comparative studies of MitraClip versus surgical repair for mitral regurgitation. Int J Cardiol. 2017;228:289-94.	Does not report outcomes by PICO population (SMR).

Tan MK, Jarral OA, Thong EH, Kidher E, Uppal R, Punjabi PP, et al. Quality of life after mitral valve intervention. Interact Cardiovasc Thorac Surg. 2017;24(2):265-72.	Does not report outcomes by PICO population (SMR).
Taramasso M, Denti P, Buzzatti N, De Bonis M, La Canna G, Colombo A, 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. Eur J Cardiothorac Surg. 2012;42(6):920-6.	Observational study. RCT evidence available for all outcomes of interest.
Toyama K, Rader F, Ayabe K, Kar S, Trento A, Nishioka T, et al. Mitral annular motion in patients after transcatheter MitraClip and mitral valve surgery. Echocardiography. 2017;34(3):334-9.	Does not include PICO specified outcomes.
Ullah W, Sattar Y, Mukhtar M, Abdullah HM, Figueredo VM, Haas DC, et al. Corrigendum to "Outcomes of open mitral valve replacement versus Transcatheter mitral valve repair; insight from the National Inpatient Sample Database" [IJC Heart Vasculat. 28 (2020) 100540]. Int J Cardiol Heart Vasc. 2022;40:100945.	Does not report outcomes by PICO population (SMR).
Ullah W, Sattar Y, Mukhtar M, Abdullah HM, Figueredo VM, Haas DC, et al. Outcomes of open mitral valve replacement versus Transcatheter mitral valve repair; insight from the National Inpatient Sample Database. Int J Cardiol Heart Vasc. 2020;28:100540.	Does not report outcomes by PICO population (SMR).
Ussia GP, Cammalleri V, Sarkar K, Scandura S, Imme S, Pistritto AM, et al. Quality of life following percutaneous mitral valve repair with the MitraClip System. Int J Cardiol. 2012;155(2):194-200.	Non-comparative study. RCT evidence available for all outcomes of interest.
Vakil K, Roukoz H, Sarraf M, Krishnan B, Reisman M, Levy WC, et al. Safety and efficacy of the MitraClip R system for severe mitral regurgitation: a systematic review. Catheter Cardiovasc Interv. 2014;84(1):129-36.	Does not report outcomes by PICO population (SMR).
Vallakati A, Hasan AK, Boudoulas KD. Transcatheter Mitral Valve Repair in Patients with Heart Failure: A Meta-Analysis. Cardiology. 2021;146(1):42-8.	Includes observational studies. RCT evidence available for all outcomes of interest.
Velazquez EJ, Samad Z, Al-Khalidi HR, Sangli C, Grayburn PA, Massaro JM, et al. The MitraClip and survival in patients with mitral regurgitation at high risk for surgery: A propensity-matched comparison. Am Heart J. 2015;170(5):1050-9.e3.	Does not report outcomes by PICO population (SMR).
Wan B, Rahnavardi M, Tian DH, Phan K, Munkholm-Larsen S, Bannon PG, et al. A meta-analysis of MitraClip system versus surgery for treatment of severe mitral regurgitation. Ann Cardiothorac Surg. 2013;2(6):683-92.	Does not report outcomes by PICO population (SMR).
Wang TKM, Chatfield A, Wang MTM, Ruygrok P. Comparison of percutaneous MitraClip versus mitral valve surgery for severe mitral regurgitation: a meta-analysis: MitraClip and mitral valve surgery meta-analysis. AsiaIntervention. 2020;6(2):77-84.	Does not report outcomes by PICO population (SMR).
Wang TKM, Wang MTM, Ruygrok P. Comparison of mitraclip and mitral valve surgery for severe mitral regurgitation: A meta-analysis. J Am Coll Cardiol. 2016;67(13 SUPPL. 1):334.	Does not report outcomes by PICO population (SMR).
Watkins AR, Fialka N, El-Andari R, Kang JJH, Bozso SJ, Moon MC, et al. Mortality and morbidity of surgical and transcatheter mitral valve repair in octogenarians: A systematic review. J Card Surg. 2022;37(9):2752-60.	Not a specified subgroup of interest. Does not report any additional outcomes that are not already covered by included studies.

Whitlow PL, Feldman T, Pedersen WR, Lim DS, Kipperman R, Smalling R, 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. J Am Coll Cardiol. 2012;59(2):130-9.	Observational study. RCT evidence available for all outcomes of interest.
Willits I, Keltie K, de Belder M, Henderson R, Linker N, Patrick H, et al. Safety, effectiveness and costs of percutaneous mitral valve repair: A real-world prospective study. PLoS ONE. 2021;16(5):e0251463.	Does not report outcomes by PICO population (SMR). UK based cost effectiveness studies available based on RCT of secondary MR patients.
Yuan H, Wei T, Wu Z, Lu T, Chen J, Zeng Y, et al. Comparison of Transcatheter Mitral-Valve Repair and Surgical Mitral-Valve Repair in Elderly Patients with Mitral Regurgitation. Heart Surg Forum. 2021;24(1):E108-E15.	Does not report outcomes by PICO population (SMR).

Appendix E Evidence table

For abbreviations see list after table

Study details	Population	Interventions	Study outcomes	Appraisal and funding
Bertaina M, Galluzzo A, D'Ascenzo F, Conrotto F, Grosso Marra W, Frea S, et al. Prognostic impact of MitraClip in patients with left ventricular dysfunction and functional mitral valve regurgitation: A comprehensive meta-analysis of RCTs and adjusted observational studies. Int J Cardiol. 2019;290:70-6. **Study location** International **Study type** Systematic review and meta-analysis **Study aim** To perform a meta-analysis of all RCTs and adjusted observational studies to evaluate the presence of a real independent prognostic effect of percutaneous mitral valve repair (PMVR) when	**Inclusion criteria** Randomised controlled trials (RCTs) or observational studies with multivariate analysis of patients with left ventricular dysfunction and functional mitral valve regurgitation (FMR) **Exclusion criteria** Non-human studies, articles not written in English, duplicate reporting, studies with <40 patients in each subgroup and those enrolling >30% of primary mitral regurgitation **Total sample size** 8 studies (2 RCTs & 6 observational studies[29]) n= 2,255 (all studies) n=918 (RCTs only) **No. of participants in each treatment group** PMVR: n=1,207 all studies n=454 RCTs only	**Interventions** PMVR (MitraClip) **Comparators** OMT	Results for pooled RCTs only **Critical outcomes** **Number of hospital admissions due to heart failure** Median follow-up of 438 days (IQR 360 to 625)[33] (2 RCTs): • Unadj OR 0.67 (95% confidence interval (CI) 0.27 to 1.65), p=0.38, I^2=87% • Adj OR[34] 0.77 (95% CI 0.37 to 1.62), p=0.49, I^2=91% **Survival** *All-cause mortality* 1 month (2 RCTs): • Unadj OR 1.74 (95% CI 0.67 to 4.52), p=0.25, I^2=0% • Adj OR 1.74 (95% CI 0.67 to 4.50), p=0.25, I^2=0% 1 year (2 RCTs): • Unadj OR 0.90 (95% CI 0.66 to 1.24), p=0.53, I^2=0% • Adj OR 0.91 (95% CI 0.68 to 1.22), p=0.53, I^2=8% Median follow-up of 438 days (IQR 360 to 625)[35] (2 RCTs):	This study was appraised using the AMSTAR 2 checklist for systematic reviews. 1. YES 2. NO 3. YES 4. NO 5. YES 6. YES 7. NO 8. NO 9. NO 10. YES 11. YES 12. YES 13. YES 14. YES 15. NO 16. NO **Other comments:** This systematic review pooled data from RCTs and observational studies with multivariate analysis. Only the results for the meta-analyses of RCTs have been extracted as combining observational results with the randomised results will introduce

[29] Only the results for the meta-analyses of RCTs have been extracted as combining observational results with the randomised results will introduce bias reducing the reliability of the randomised evidence.
[33] Mean follow-up for all studies including observational studies. Mean follow-up for RCTs only was not reported for this outcome.
[34] Adjusted for confounders. Confounding factors not reported.
[35] Mean follow-up for all studies including observational studies. Mean follow-up for RCTs only was not reported for this outcome.

compared with medical therapy alone **Study dates** Search date not reported	Optimal medical therapy (OMT): n=1,048 all studies; n=464 RCTs only **Baseline characteristics** <u>All patients (n=2,255)</u> Age (mean): 71.3 years Male: 74.8% BMI (mean): 23.9 Logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE)[30] (mean): 21 Society of Thoracic Surgery (STS)[31] score (mean):10.4 Hypertension: 46% Hyperlipidaemia: 40.8% Diabetes: 41.8% Atrial fibrillation (AF): 45.9% Chronic obstructive pulmonary disease (COPD): 40.1% Chronic kidney disease (CKD): 47.7% Ischemic heart disease: 65.0% FMR: 95.1% New York Heart Association (NYHA)[32] class III-IV: 85.3%		• Unadj OR 0.77 (95% CI 0.40 to 1.49), p=0.44, I^2=77% • Adj OR 0.80 (95% CI 0.46 to 1.42), p=0.45, I^2=76% *Cardiovascular mortality* Median follow-up of 438 days (IQR 360 to 625) (2 RCTs): • Unadj OR 0.77 (95% CI 0.40 to 1.49), p=0.44, I^2=77% • Adj OR 0.78 (95% CI 0.43 to 1.42), p=0.41, I^2=77% **Subgroups** Not reported for pooled RCT results	bias reducing the reliability of the randomised evidence. The search strategy was not comprehensive. Very few search terms were used and only the databases PubMed, Cochrane and Google Scholar were searched. The searches only retrieved 130 hits and according to the PRISMA flowchart only 7 full papers were screened. The literature search date was not reported. The most recent included study was published in 2018. Limited information was provided on the included studies. Limited information was reported on the population, intervention, comparator and research design for each study. Meta-analyses were performed according to a random effects model. Unadjusted and adjusted results were reported with little difference observed between the results with the exception of hospitalisations due to heart failure. The paper did not report on the factors included in the multivariate analysis, only stating that they were confounders. Meta-

[30] The Logistic EuroSCORE is a validated risk prediction model which allows the calculation of the risk of death after a heart operation. The patient's EuroSCORE is the probability (expressed as a percentage) of the patient dying during or shortly after the proposed surgery.
[31] The STS score is a validated risk prediction model for open surgery based on data from the STS National Adult Cardiac Surgery Database. In general, an STS predicted risk of surgical mortality of 4%-8% is considered intermediate risk and 8% or greater is considered high risk.
[32] The New York Heart Association (NYHA) functional classification is a widely used tool for risk stratification on the basis of severity of symptoms and limitation of physical activity. It places patients in one of four categories: Class I — no limitation of physical activity. Ordinary physical activity does not cause undue fatigue, breathlessness, or palpitations; Class II — slight limitation of physical activity. Comfortable at rest but ordinary physical activity results in undue breathlessness, fatigue, or palpitations; Class III — marked limitation of physical activity. Comfortable at rest but less than ordinary physical activity results in undue breathlessness, fatigue, or palpitations; Class IV — unable to carry out any physical activity without discomfort. Symptoms at rest can be present. If any physical activity is undertaken discomfort is increased.

	Ejection fraction (mean): 26% For baseline characteristics for the individual RCTs see Obadia et al 2018 & Stone et al 2018			regression was performed to assess the impact of age, NYHA class, comorbidities and cardiomyopathy aetiology and echocardiographic data but not for the RCTs alone, only for the RCTs pooled with the observational studies. The authors stated that they used modified Meta-analysis of Observational Studies in Epidemiology (MOOSE) criteria to assess the quality of the included studies, but they did not mention the use of a quality checklist specific to RCTs and therefore may not have assessed biases specific to RCTs such as allocation concealment. There was no assessment of publication bias (small study bias). Publication bias may lead to significant or large effects being more likely to be reported particularly in small studies. **Source of funding:** No funding was received. One of the authors was a consultant for Abbott Vascular and received research grants from Abbott Vascular
Cohen DJ, Wang K, Magnuson E, Smith R, Petrie MC, Buch MH, et al. Cost-effectiveness of transcatheter edge-to-edge repair in secondary mitral regurgitation. Heart. 2022;108(9):717-24. **Study location** UK perspective	**Inclusion criteria** People with symptomatic heart failure, left ventricular ejection fraction (LVEF) 20% to 50% and severe (3+ or 4+) secondary mitral regurgitation **Exclusion criteria** None reported **Total sample size**	**Interventions** Mitral valve TEER (MitraClip) plus GDMT. See Stone et al 2018 for further details **Comparators** GDMT alone. See Stone et al 2018 for further details	**Important outcomes** **Cost effectiveness** *Lifetime incremental cost effectiveness ratios (ICERs)* Cost per life-year gained: • £17,140 per life-year • 76% probability <£20,000 per life-year • 96% probability <£30,000 per life-year Cost per quality-adjusted life-year	This study was appraised using the Joanna Briggs checklist for economic evaluations. 1. YES 2. NO 3. YES 4. YES 5. YES 6. YES 7. YES 8. YES 9. YES

Study type Cost effectiveness study **Study aim** To determine whether mitral valve transcatheter edge to edge repair (TEER) in secondary mitral regurgitation is cost effective from a UK National Health Service (NHS) perspective **Study dates** COAPT trial recruitment period: 27 December 2012 to 23 June 2017 Costs assigned in 2019	n=614 (COAPT trial) **No. of participants in each treatment group** Mitral valve TEER plus guideline directed medical therapy (GDMT): n=302 GDMT alone: n=312 **Baseline characteristics** Median age: 74 years See Stone et al 2018 for further details		(QALY) gained: • £23,270 per QALY • 18% probability <£20,000 per QALY • 89% probability <£30,000 per QALY **Subgroups** Baseline mitral regurgitation 3+ (n=320): • £25,453 per QALY • 14% probability <£20,000 per QALY • 69% probability <£30,000 per QALY 4+ (n=293): • £20,301 per QALY • 47% probability <£20,000 per QALY • 90% probability <£30,000 per QALY New York Heart Association (NYHA) class: I or II (n=240) • £24,603 per QALY • 23% probability <£20,000 per QALY • 68% probability <£30,000 per QALY III (n=322) • £25, 345 per QALY • 15% probability <£20,000 per QALY • 68% probability <£30,000 per QALY IV (n=51) • £22,819 per QALY • 32% probability <£20,000 per QALY • 70% probability <£30,000 per QALY Baseline left ventricular ejection fraction (LVEF) <30% (n=274): • £15,482 per QALY • 91% probability <£20,000 per QALY • 100% probability <£30,000 per QALY	10. YES 11. NO **Other comments:** This cost effectiveness analysis is conducted from a UK NHS perspective over a lifetime timeframe and is based on effectiveness and resource utilisation individual patient data from the COAPT trial (Stone et al 2018). Survival and QoL (measured by SF-36) individual patient trial data up to 2 years were included. Individual responses were converted to utility weights for the UK population and QALYs were calculated as the time-weighted average of utility values. Utilities after the trial period were estimated from a linear regression model adjusted for age, sex, baseline utility, treatment group, stroke and left ventricular assist device or cardiac transplantation. Costs were assessed in 2019 GBP using resource utilisation trial data from baseline to 2 years and unit costs appropriate to the NHS. Future healthcare costs were estimated on the basis of a linear regression model derived from observed costs in the second year after randomisation. Future costs and health benefits were discounted at 3.5% per year. Results should be treated with caution due to uncertainties around modelled lifetime estimates based on 2-year trial data. Confidence

			≥30% (n=301): • £41,650 per QALY • 3% probability <£20,000 per QALY • 24% probability <£30,000 per QALY	intervals were not reported for the ICER estimates. The COAPT trial was conducted in the USA and therefore results, particularly costs based on resource allocation data derived from a different healthcare setting, may not be applicable to the UK. **Source of funding:** The study was funded by Abbott. The funding agreement stipulated that the academic investigators had full access to the study data, performed all analyses, and had the right to publish the results regardless of the findings
Giustino G, Lindenfeld J, Abraham WT, Kar S, Lim DS, Grayburn PA, et al. NYHA Functional Classification and Outcomes After Transcatheter Mitral Valve Repair in Heart Failure: The COAPT Trial. JACC Cardiovasc Interv. 2020;13(20):2317-28. **Study location** United States and Canada (78 centres) **Study type** RCT- subgroup study **Study aim**	This paper reports a pre-planned subgroup analysis from an RCT. See Stone 2018 for the trial inclusion/ exclusion criteria and baseline characteristics **Total sample size** n=613 **No. of participants in each treatment group** Device (TEER): n=302 • NYHA II: n=130 • NYHA III: n=154 • NYHA IV: n=18 Control (GDMT): n=311 • NYHA II: n=110	This paper reports a planned subgroup analysis from an RCT. The intervention group received transcatheter mitral-valve repair using MitraClip plus guideline directed medical therapy (TEER). The comparator group received guideline directed medical therapy (GDMT). **See Stone et al 2018 for further details**	All patient data are presented by baseline NYHA classification. **Critical outcomes** TEER v GDMT **Number of hospital admissions due to heart failure** *All hospitalisations for heart failure* 24 months, n (%)[37]: • NYHA II: 40 (33.0) v 51 (51.3); HR 0.57 (95% CI 0.38 to 0.86); NNT=5.5 • NYHA III: 49 (35.9) v 84 (55.6); HR 0.53 (95% CI 0.37 to 0.76); NNT=5.1 • NYHA IV: 6 (40.9) v 22 (78.3); HR 0.34 (95% CI 0.14 to 0.86); NNT=2.7 p=0.55 for interaction	This study was appraised using the JBI checklist for RCTs. 1. YES 2. YES 3. YES 4. NO 5. NO 6. UNCLEAR 7. YES 8. YES 9. YES 10. YES 11. YES 12. YES 13. YES **Other comments:** This is a pre-planned subgroup analysis of outcomes reported in the RCT (see Stone et al 2018 for main trial results and study appraisal).

[37] Percentages are estimated using the Kaplan-Meier time-to-event methodology.

Pre-planned subgroup analysis study, examining 24- month outcomes by NYHA classification at baseline **Study dates** 27 December 2012 to 23 June 2017	• NYHA III: n=168 • NYHA IV: n=33 Note: The RCT only enrolled patients that were NYHA II, II, and IVa (class IV ambulatory)[36]		**Survival** *Death from any cause* 24 months, n (%): • NYHA II: 31 (24.4) v 42 (40.8); HR 0.55 (95% CI 0.35 to 0.88); NNT=6.1 • NYHA III: 44 (29.4) v 64 (41.2); HR 0.71 (95% CI 0.48 to 1.04); NNT=8.5 • NYHA IV: 8 (44.4) v 19 (61.2); HR 0.64 (95% CI 0.28 to 1.46); NNT=6.0 p=0.74 for interaction *Death related to heart failure* 24 months, n (%): • NYHA II: 9 (8.0) v 18 (19.8); HR 0.37 (95% CI 0.17 to 0.83) • NYHA III/IV: 21 (14.4) v 45 (26.9); HR 0.50 (95% CI 0.30 to 0.84) **NYHA grade** *NYHA Class II at baseline* Baseline, n (%); TEER=130, GDMT=110 • NYHA II: 130 (100.0) v 110 (100.0); p=0.36 30 days, n (%); TEER=125, GDMT=101 • NYHA I: 32 (25.6) v 10 (9.8) • NYHA II: 75 (60.0) v 68 (67.6) • NYHA III: 17 (13.6) v 16 (15.7) • NYHA IV: 1 (0.8) v 7 (6.9) p=0.003 12 months, n (%); TEER=107, GDMT=87 • NYHA I: 24 (22.4) v 11 (12.6)	**Source of funding:** See Stone et al (2018)

[36] The New York Heart Association (NYHA) functional classification is a widely used tool for risk stratification on the basis of severity of symptoms and limitation of physical activity. It places patients in one of four categories: Class I — no limitation of physical activity. Ordinary physical activity does not cause undue fatigue, breathlessness, or palpitations; Class II — slight limitation of physical activity. Comfortable at rest but ordinary physical activity results in undue breathlessness, fatigue, or palpitations; Class III — marked limitation of physical activity. Comfortable at rest but less than ordinary physical activity results in undue breathlessness, fatigue, or palpitations; Class IV — unable to carry out any physical activity without discomfort. Symptoms at rest can be present. If any physical activity is undertaken discomfort is increased.

			• NYHA II: 65 (60.7) v 49 (56.3) • NYHA III: 12 (11.2) v 15 (17.2) • NYHA IV: 6 (5.6) v 12 (13.8) p=0.06 24 months, n (%); TEER=88, GDMT=74 • NYHA I: 19 (21.6) v 8 (10.8) • NYHA II: 42 (47.7) v 28 (37.8) • NYHA III: 16 (18.2) v 19 (25.7) • NYHA IV: 11 (12.5) v 19 (25.7) p=0.04 *NYHA Class III / IV at baseline* Baseline, n (%); TEER=172, GDMT=201 • NYHA III: 154 (89.5) v 168 (83.6) • NYHA IV: 18 (10.5) v 33 (16.4) p=0.10 30 days, n (%); TEER=158, GDMT=177 • NYHA I: 12 (7.6) v 4 (2.3) • NYHA II: 97 (61.4) v 51 (28.8) • NYHA III: 38 (24.1) v 100 (56.5) • NYHA IV: 11 (7.0) v 22 (12.4) p <0.0001 12 months, n (%); TEER=129, GDMT=142 • NYHA I: 16 (12.4) v 7 (4.9) • NYHA II: 66 (51.2) v 47 (33.1) • NYHA III: 30 (23.3) v 50 (35.2) • NYHA IV: 17 (13.2) v 38 (26.8) p=0.0003 24 months, n (%); TEER=118, GDMT=130 • NYHA I: 12 (10.2) v 4 (3.1) • NYHA II: 49 (41.5) v 41 (31.5) • NYHA III: 28 (23.7) v 34 (26.2) • NYHA IV: 29 (24.6) v 51 (39.2) p=0.01	

			Important outcomes **Health related quality of life (HRQL)** *KCCQ*[38,39]*,* mean (sd) *NYHA Class II at baseline*: • baseline: 66.8 (17.5) v 67.5 (20.6); p=0.78 • 30 days: 77.3 (18.1) v 67.4 (24.1); p=0.0005 • 1 year: 72.0 (25.5) v 59.8 (30.9); p=0.003 • 2 years: 68.2 (30.2) v 49.0 (35.0); p=0.0003 • Paired change from baseline to 12 months: 0.8 (31.5) v -20.0 (33.2); p <0.0001 *NYHA Class III or IV at baseline*: • baseline: 43.0 (20.9) v 42.9 (19.9); p=0.99 • 30 days: 64.9 (23.1) v 46.4 (22.3); p <0.0001 • 1 year: 61.7 (30.3) v 43.3 (31.3); p <0.0001 • 2 years: 55.4 (34.4) v 35.8 (33.4); p <0.0001 • Paired change from baseline to 12 months: 12.8 (36.5) v -7.4 (34.2); p <0.0001 **Pre discharge grading of mitral regurgitation** Data were available for 260 TEER patients only; (NYHA Class II: n=130,	

[38] The Kansas City Cardiomyopathy Questionnaire (KCCQ) is a 23-item self-administered questionnaire developed to independently measure the patient's perception of their health status, which includes heart failure symptoms, impact on physical and social function, and how their heart failure impacts their quality of life (QoL) within a 2-week recall period. KCCQ responses are provided along a rating scale continuum (0 to 100) and frequently summarized in 25-point ranges: 0 to 24: very poor to poor; 25 to 49: poor to fair; 50 to 74: fair to good; and 75 to 100: good to excellent.

[39] Subjects who experienced a heart failure-related death prior to follow-up (or were unable to walk due to cardiac reasons) were assigned a score of 0 for the KCCQ score.

			NYHA Class III: n=154, NYHA Class IV: n=18) *NYHA Class II at baseline* • None, n (%): 2 (1.7) • Grade 1+, n (%): 96 (82.8) • Grade 2+, n (%): 13 (11.2) • Grade 3+, n (%): 3 (2.6) • Grade 4+, n (%): 2 (1.7) *NYHA Class III at baseline* • None, n (%): 1 (0.8) • Grade 1+, n (%): 103 (80.5) • Grade 2+, n (%): 18 (14.1) • Grade 3+, n (%): 4 (3.1) • Grade 4+, n (%): 2 (1.6) *NYHA Class IV at baseline* • None, n (%): 0 (0) • Grade 1+, n (%): 12 (75.0) • Grade 2+, n (%): 2 (12.5) • Grade 3+, n (%): 2 (12.5) • Grade 4+, n (%): 0 (0) **Duration/durability of mitral regurgitation reduction** *Mitral regurgitation severity at follow-up* *NYHA Class II at baseline* Baseline, n (%); TEER=130, GDMT=130 • 3+: 75 (57.7) v 66 (60.0) • 4+: 55 (42.3) v 44 (40.0) p=0.72 30 days, n (%); TEER=120, GDMT=88 • 0: 1 (0.8) v 1 (1.1) • 1+: 93 (77.5) v 9 (10.2) • 2+: 19 (15.8) v 23 (26.1) • 3+: 5 (4.2) v 32 (36.4) • 4+: 2 (1.7) v 23 (26.1)	

			p <0.0001 12 months, n (%); TEER=98, GDMT=70 • 0: 0 (0) v 1 (1.4) • 1+: 69 (70.4) v 9 (12.9) • 2+: 25 (25.5) v 24 (34.3) • 3+: 3 (3.1) v 22 (31.4) • 4+: 1 (1.0) v 14 (20.0) p <0.0001 24 months, n (%); TEER=76, GDMT=50 • 0: 1 (1.3) v 1 (2.0) • 1+: 61 (80.3) v 6 (12.0) • 2+: 13 (17.1) v 14 (28.0) • 3+: 0 (0) v 15 (30.0) • 4+: 1 (1.3) v 14 (28.0) p <0.0001 *NYHA Class III / IV at baseline* Baseline, n (%); TEER=172, GDMT=201 • 3+: 73 (42.4) v 105 (52.5) • 4+: 99 (57.6) v 95 (47.5) p=0.053 30 days, n (%); TEER=153, GDMT=168 • 0: 1 (0.7) v 1 (0.6) • 1+: 104 (68.0) v 10 (6.0) • 2+: 35 (22.9) v 44 (26.2) • 3+: 11 (7.2) v 63 (37.5) • 4+: 2 (1.3) v 50 (29.8) p <0.0001 12 months, n (%); TEER=112, GDMT=104 • 0: 1 (0.9) v 1 (1.0) • 1+: 75 (67.0) v 9 (8.7) • 2+: 29 (25.9) v 38 (36.5) • 3+: 6 (5.4) v 37 (35.6) • 4+: 1 (0.9) v 19 (18.3) p <0.0001	

			24 months, n (%); TEER=86, GDMT=73 • 0: 1 (1.2) v 1 (1.4) • 1+: 64 (74.4) v 15 (20.5) • 2+: 21 (24.4) v 20 (27.4) • 3+: 0 (0) v 27 (37.0) • 4+: 0 (0) v 10 (13.7) p <0.0001 *Unplanned mitral valve intervention* 24 months, n (%)[40]: • NYHA II: 1 (0.9) v 6 (8.1); HR 0.12 (95% CI 0.01 to 0.97) • NYHA III/IV: 9 (6.2) v 11 (8.4); HR 0.89 (95% CI 0.37 to 2.15) p=0.09 for interaction **Functional outcomes** *6 min walk test*[41,42] metres, mean (sd) *NYHA Class II at baseline* • baseline: 313.7 (112.7) v 294.3 (111.4); p=0.18 • 30 days: 319.6 (125.1) v 277.9 (139.6); p=0.02 • 1 year: 296.2 (155.3) v 246.9 (175.2); p=0.04 • 2 years: 243.8 (182.1) v 221.4 (186.4); p=0.44 • Paired change from baseline to 12 months: -88.3 (161.3) v -97.4 (175.4); p=0.64 *NYHA Class III or IV at baseline*: • baseline: 199.4 (108.1) v 201.5 (117.8); p=0.86	

[40] Percentages are estimated using the Kaplan-Meier time-to-event methodology.
[41] The six-minute walk distance test is usually performed on a treadmill and is the distance in metres that the patient can walk in 6 minutes.
[42] Subjects who experienced a heart failure-related death prior to follow-up (or were unable to walk due to cardiac reasons) were assigned a score of 0 for the 6-min walk test.

			• 30 days: 244.0 (131.5) v 183.5 (121.4); p <0.0001 • 1 year: 223.2 (151.4) v 153.5 (151.4); p=0.0002 • 2 years: 166.6 (161.1) v 115.5 (154.4); p=0.01 • Paired change from baseline to 12 months: -33.3 (147.0) v -86.4 (160.5); p=0.005 **Safety** **Procedural complications** *Adverse event rates* *Stroke* 24 months, n (%)[43] • NYHA Class II at baseline: 5 (4.2) v 5 (6.3); HR 0.77 (95% CI 0.22 to 2.66) • NYHA Class III/IV at baseline: 6 (4.3) v 10 (6.6); HR 0.66 (95% CI 0.24 to 1.81) *Myocardial Infarction (MI)* 24 months, n (%) • NYHA Class II at baseline: 5 (4.2) v 5 (6.3); HR 0.77 (95% CI 0.22 to 2.66) • NYHA Class III/IV at baseline: 7 (4.6) v 11 (7.7); HR 0.70 (95% CI 0.27 to 1.80) p=0.90 for interaction	
Iung B, Armoiry X, Vahanian A, Boutitie F, Mewton N, Trochu JN, et al. Percutaneous repair or medical treatment for	Adults with heart failure and severe secondary mitral regurgitation	**Interventions** PMVR (MitraClip) plus OMT **Comparators** OMT alone	Median follow-up was 23.9 months (IQR 11.4 to 24.6) for PMVR patients (n=149) and 23.5 months (IQR 12.0 to 24.6) for OMT patients (n=140)	This study was appraised using the JBI checklist for RCTs.

[43] Percentages are estimated using the Kaplan-Meier time-to-event methodology.

secondary mitral regurgitation: outcomes at 2 years. Eur J Heart Fail. 2019;21(12):1619-27. **Study location** France (37 centres) **Study type** RCT (MITRA-FR trial) **Study aim** To report the 24-month outcomes from the MITRA-FR trial **Study dates** December 2013 to March 2017	This paper reports the 24-month results of the MITRA-FR trial. See Obadia et al 2018 for the trial inclusion/ exclusion criteria and baseline characteristics **Total sample size** n=304 **No. of participants in each treatment group** PMVR: n=152 OMT n=152		No p-values reported **Critical outcomes** **Number of hospital admissions due to heart failure** *Unplanned hospitalisation for heart failure* From baseline to 24 months, n (rate per 100 patient-years): • PMVR (n=152 patient-years): 85 (55.9) • OMT (n=156 patient-years): 94 (62.3) • HR 0.97 (95% CI 0.72 to 1.30) From 12 to 24 months, n (rate per 100 patient-years): • PMVR (n=59 patient-years): 11 (18.6) • OMT (n=56 patient-years): 22 (39.3) • HR 0.47 (95% CI 0.22 to 0.98) **Survival** *Death from any cause* From baseline to 24 months, n (rate per 100 patient-years): • PMVR (n=230 patient-years): 53 (23.1) • OMT (n=229 patient-years): 52 (22.8) • HR 1.02 (95% CI 0.70 to 1.50) From 12 to 24 months, n (rate per 100 patient-years): • PMVR (n=103 patient-years): 16 (15.5) • OMT (n=99 patient-years): 18 (18.2) • HR 0.86 (95% CI 0.44 to 1.69) *Cardiovascular death*	See Obadia et al 2018 for ratings and comments relating to the design and conduct of this RCT **Other comments:** See Obadia et al 2018 **Source of funding:** See Obadia et al 2018

			From baseline to 24 months, n (rate per 100 patient-years): • PMVR (n=230 patient-years): 47 (20.5) • OMT (n=229 patient-years): 48 (21.1) • HR 0.99 (95% CI 0.66 to 1.48) From 12 to 24 months, n (rate per 100 patient-years): • PMVR (n=103 patient-years): 14 (13.6) • OMT (n=99 patient-years): 17 (17.2) • HR 0.80 (95% CI 0.39 to 1.63) **NYHA grade** The paper reported that there was no significant difference between groups at 24 months (PMVR n=90; OMT n=87) **Important outcomes** **Functional outcomes** *6-minute walk test distance (metres)* Median (IQR) Baseline: • PMVR (n=120): 307 (212 to 387) • OMT (n=103): 335 (210 to 410) 24 months: • PMVR (n=66): 335 (280 to 462) • OMT (n=54): 398 (280 to 462[44]) Change between baseline and 24 months: • PMVR (n=59): 15 (-18 to 67) • OMT (n=42): 22 (-6 to 94)	

[44] Likely to be incorrectly reported as the IQR is the same as reported for the PMVR group.

			Safety *Prespecified serious adverse events* From baseline to 24 months, n (rate per 100 patient-years) • All serious adverse events: 129 (84.9) v 128 (82.1) • Heart transplantation or mechanical cardiac assistance: 7 (4.6) v 9 (5.8) • Ischemic or haemorrhagic stroke: 7 (4.6) v 3 (1.9) • Myocardial infarction: 0 (0) v 3 (1.9) • Need for renal-replacement therapy: 6 (3.9) v 2 (1.3) • Severe haemorrhage: 13 (8.6) v 6 (3.8) • Infections: 32 (21.1) v 30 (19.2) From 12 to 24 months, n (rate per 100 patient-years) • All serious adverse events: 4 (6.8) v 7 (12.5) • Heart transplantation or mechanical cardiac assistance: 1 (1.7) v 0 (0) • Ischemic or haemorrhagic stroke: 0 (0) v 2 (3.6) • Myocardial infarction: 0 (0) v 1 (1.8) • Need for renal-replacement therapy: 1 (1.7) v 1 (1.8) • Severe haemorrhage: 2 (3.4) v 0 (0) • Infections: 4 (6.8) v 3 (5.4) **Subgroups** Not reported	
Lodhi MU, Usman MS, Siddiqi TJ, Khan MS, Khan MAA, Khan SU, et al. Percutaneous Mitral Valve Repair versus Optimal	**Inclusion criteria** RCTs and non-randomised studies of adult patients where at least 70% of the	**Interventions** PMVR **Comparators** OMT	Results for pooled RCTs only **Critical outcomes**	This study was appraised using the AMSTAR 2 checklist for systematic reviews. 1. YES 2. NO

Medical Therapy in Patients with Functional Mitral Regurgitation: A Systematic Review and Meta-Analysis. J. 2019;2019:2753146. **Study location** International **Study type** Systematic review and meta-analysis **Study aim** To compare PMVR with optimal medical therapy in patients with heart failure and severe FMR **Study dates** Literature search date: 25 September 2018	patients had heart failure complicated by FMR **Exclusion criteria** None reported **Total sample size** 8 studies (2 RCTs & 6 observational studies[45]) n=3,009 (all studies) n=918 (RCTs only) **No. of participants in each treatment group** PMVR: n=1,689 all studies n=454 RCTs only OMT: n=1,320 all studies n=464 RCTs only **Baseline characteristics** All patients (n=3,009) Age (mean): 72 years Male: 62% LVEF (mean): 33% NYHA class III or IV: 69% Coronary artery disease: 53% AF: 48% For baseline characteristics for the individual RCTs see Obadia et al 2018 & Stone et al 2018		**Number of hospital admissions due to heart failure** *Incidence of heart failure hospitalisations* Mean follow-up of 1.64 years[46] (2 RCTs): • HR 0.76 (95% CI 0.36 to 1.63), p=0.48, I^2=92% **Survival** *All-cause mortality* 30 days (2 RCTs): • OR 1.74 (95% CI 0.67 to 4.52), p=0.25, I^2=0% • RR 1.72 (95% CI 0.66 to 4.36), p=0.26, I^2=0% 12 months (2 RCTs): • OR 0.87 (95% CI 0.59 to 1.29), p=0.50, I^2=32% • RR 0.90 (95% CI 0.66 to 1.23), p=0.51, I^2=33.3% *Cardiovascular mortality* Mean follow-up of 1.54 years[47] (2 RCTs): • OR 0.75 (95% CI 0.40 to 1.43), p=0.39, I^2=73% • RR 0.81 (95% CI 0.50 to 1.31), p=0.38, I^2=71.5% **Subgroups** Not reported	3. NO 4. YES 5. YES 6. UNCLEAR 7. YES 8. NO 9. YES 10. NO 11. YES 12. YES 13. YES 14. YES 15. YES 16. YES **Other comments:** This systematic review pooled data from RCTs and observational studies. Only the results for the meta-analyses of RCTs have been extracted as combining observational results with the randomised results will introduce bias reducing the reliability of the randomised evidence. The paper states that two reviewers independently screened search hits and assessed risk of bias, and a third reviewer was consulted to resolve any discrepancies. However, the paper does not state whether two independent reviewers were also used for data extraction. Limited information was reported on the intervention, comparator and research design for each study.

[45] Only the results for the meta-analyses of RCTs have been extracted as combining observational results with the randomised results will introduce bias reducing the reliability of the randomised evidence.
[46] Mean follow-up for all studies including observational studies. Mean follow-up for RCTs only was not reported for this outcome.
[47] Mean follow-up for all studies including observational studies. Mean follow-up for RCTs only was not reported for this outcome.

				Meta-analyses were performed according to a random effects model. Unadjusted results were presented. Multivariate analyses were not performed. Leave-one-out sensitivity analyses were conducted for all. outcomes to assess if any single study disproportionately influenced the results. A funnel plot and Eggers regression test were performed and both suggested the presence of publication bias. The authors reported that the funnel plot results suggested that missing studies would have been of small size and could have possibly shown increased mortality with PMVR. **Source of funding:** Not reported
Obadia JF, Messika-Zeitoun D, Leurent G, Iung B, Bonnet G, Piriou N, et al. Percutaneous Repair or Medical Treatment for Secondary Mitral Regurgitation. N Engl J Med. 2018;379(24):2297-306. **Study location** France (37 centres) **Study type** RCT (MITRA-FR trial) **Study aim** To evaluate the clinical efficacy and safety of percutaneous mitral-valve	**Inclusion criteria** • Age >18 years old • Severe secondary MR characterised, according to the European guidelines and recommendations, by a regurgitant volume>30 mL/beat or an effective regurgitant orifice>20mm² • New York Heart Association Class ≥II • Minimum of one hospitalisation for heart failure within 12 months preceding randomisation.	**Interventions** PMVR through MitraClip system plus OMT **Comparators** OMT alone	PMVR v OMT **Critical outcomes** **Number of hospital admissions due to heart failure** *Number of patients who had an unplanned hospitalisation for heart failure* 12 months, n (%): • 74 (48.7) v 72 (47.4) • HR 1.13 (95% CI 0.81 to 1.56), p-value NR **Survival** *Death from any cause* 30 days, n (%): • 5 (3.3) v 4 (2.6) 12 months, n (%): • 37 (24.3) v 34 (22.4)	This study was appraised using the JBI checklist for RCTs. 1. YES 2. YES 3. NO 4. NO 5. NO 6. UNCLEAR 7. YES 8. NO 9. YES 10. YES 11. YES 12. NO 13. YES **Other comments:** The demographic and clinical characteristics, and medical therapy of the two groups were broadly similar at baseline, with the

repair in addition to medical treatment in patients with heart failure and severe secondary mitral regurgitation **Study dates** December 2013 to March 2017	• LVEF between 15% and 40% • Optimal standard of care therapy for heart failure according to investigator • Affiliation to a health insurance system or a similar system **Exclusion criteria** • Eligible for a mitral surgery intervention according to the Heart Team • MI or coronary bypass grafting surgery, cardiac resynchronisation therapy, cardioversion or transcatheter aortic valve implantation within 3 months prior to randomisation. • Need for any cardiovascular surgery • Coronary angioplasty within one month prior to randomisation. • Previous surgical mitral valve repair • Renal replacement therapy • Active infection requiring current antibiotic therapy • Severe hepatic insufficiency. • Stroke within 3 months prior to randomisation.		• HR 1.11 (95% CI 0.69 to 1.77), p-value NR *Cardiovascular death* 12 months, n (%): • 33 (21.7) v 31 (20.4) • HR 1.09 (95% CI 0.67 to 1.78), p-value NR **NYHA grade** The paper reported that there was no significant difference between groups at 12 months (PMVR n=114; OMT n=112) **Important outcomes** **Health related quality of life** *EQ5D global score*[48] Mean (sd) Baseline: • PMVR (n=143): 51.5 (91.2) • OMT (n=128): 53.2 (16.6) 12 months: • PMVR (n=93): 60.8 (20.3) • OMT (n=87): 58.6 (18.2) **Pre discharge grading of mitral regurgitation** *Reduction of mitral regurgitation of at least one grade at the time of discharge, n (%)* PMVR (n=123): 117 (95.1%) *Reduction of mitral regurgitation to 2+ (mild to moderate) or lower at the time of discharge, n (%)*	exception of proportion of males and history of ischaemic cardiomyopathy, myocardial infarction and diabetes, which were more common in the intervention group. Given the nature of the intervention, it was not possible to blind participants and those delivering the intervention to treatment allocation. The paper does not report whether outcome assessors were blinded. The trial had a high attrition rate which differed between the two groups (28% PMVR group & 9% in OMT group). Reasons included patient cross over (8 PMVR v 2 OMT); not meeting prespecified criteria or had a protocol deviation (13 v 12); device procedure failure (6); and underwent device implantation more than 21 days after randomisation (21). However, an ITT analysis was performed and a comparison with results from a per protocol analysis showed no significant difference. A large amount of follow-up data on echocardiographic, functional and QoL outcomes were missing and the impact of this on results was not explored. No p-values other than that for the primary outcome were reported. The authors stated that this was because no adjustment was made for multiple testing. However, confidence intervals were reported for survival

[48] The EQ5D is a measure of quality of life based on 5 dimensions: activities, anxiety, mobility, pain and self-care. A higher score indicates a better quality of life with a visual acuity scale ranging from 0 (worst imaginable health) to 100 (best imaginable health).

	• Concurrent medical condition with a life expectancy of less than 12 months. • Uncontrolled arterial hypertension • Hypersensitivity to nitinol • Pregnancy • Patient deemed to be not suitable for technical MitraClip implantation according to expert proctoring by Abbott **Total sample size** n=304 **No. of participants in each treatment group** PMVR: n=152 OMT n=152 **Baseline characteristics** PMVR v medical therapy Age (years), mean (sd): 70.1 (10.1) v 70.6 (9) Male, n (%): 120 (78.9) v 107 (70.4) Medical and surgical history: • Ischaemic cardiomyopathy: 95/152 (62.5%) v 85/151 (56.3%) • Non-ischaemic cardiomyopathy: 57/152 (37.5%) v 66/151 (43.7%)		PMVR (n=123): 113 (91.9%) *Reduction of mitral regurgitation to 0+ (none or trace) to 1+ (mild) at the time of discharge, n (%)* PMVR (n=123): 93 (75.6%) **Functional outcomes** *6-minute walk test distance (metres)* Mean (sd) Baseline: • PMVR (n=120): 301 (126) • OMT (n=103): 319 (127) 12 months: • PMVR (n=82): 339 (151) • OMT (n=77): 363 (157) Change between baseline and 12 months, median (IQR): • PMVR (n=73): 25 (-40 to 71) • OMT (n=57): 19 (-27 to 75) **Safety** **Procedural complications, n (%)** PMVR (n=144) • Total complications: 21 (14.6) • Device implantation failure: 6 (4.2) • Haemorrhage resulting in transfusion or vascular complication resulting in surgical intervention: 5 (3.5) • Atrial septum lesion or atrial septal defect: 4 (2.8) • Cardiogenic shock resulting in intravenous inotropic support: 4 (2.8) • Cardiac embolism, including gas embolism and stroke: 2 (1.4) • Tamponade: 2 (1.4)	and hospital admission outcomes. The NYHA class results were only presented as graphs and could not be extracted. The trial is only powered to detect a large treatment effect (an event rate of 50% in the control group and 33% in the intervention group). **Source of funding:** Primary funding was provided by the French Ministry of Health and Research National Program. Abbott Vascular, the manufacturer of the trial device, provided the devices as well as support for investigators' meetings. They also proctored the procedures for implantation of the device. The paper stated that Abbott Vascular did not have a role in the design of the trial; the selection of participating trial centres; the monitoring or oversight of the centres; the enrolment or care of the patients; the collection, storage, analysis, or interpretation of the data; the writing of the manuscript; or the decision to submit the manuscript for publication. However, three patients were excluded prior to randomisation due to a proctoring decision by Abbott

	• Previous myocardial infarction: 75/152 (49.3%) v 52/152 (34.2%) • Previous coronary revascularisation: 71/152 (46.7%) v 64/151 (42.4%) • Atrial fibrillation: 49/142 (34.5%) v 48/147 (32.7%) • Diabetes: 50/152 (32.9%) v 39/152 (25.7%) • Renal insufficiency: 22/152 (14.5%) v 19/152 (12.5%) NYHA II, n (%): 56 (36.8) v 44 (28.9) NYHA III, n (%): 82 (53.9) v 96 (63.2) NYHA IV, n (%): 14 (9.2) v 12 (7.9) EuroSCORE II, median (IQR): 6.6 (3.5 to 11.9) v 5.9 (3.4 to 10.4) LVEF %, mean (sd): 33.3 (6.5) v 32.9 (6.7) LV end-diastolic volume (ml/m^2), mean (sd): 136.2 (37.4) v 134.5 (33.1) Effective regurgitant orifice area (mm^2), mean (sd): 31 (10) v 31 (11) Regurgitant volume (ml), mean (sd): 45 (13) v 45 (14)		• Urgent conversion to heart surgery: 0 (0) *Prespecified serious adverse events at 1 year,* n (%) • All serious adverse events: 125 (82.2) v 121 (79.6) • Heart transplantation or mechanical cardiac assistance: 6 (3.9) v 9 (5.9) • Ischaemic or haemorrhagic stroke: 7 (4.6) v 1 (0.7) • Myocardial infarction: 0 (0) v 2 (1.3) • Need for renal-replacement therapy: 5 (3.3) v 1 (0.7) • Severe haemorrhage: 11 (7.2) v 6 (3.9) • Infections: 28 (18.4) v 27 (17.8) **Subgroups** Not reported	
Shore J, Russell J, Frankenstein L, Candolfi P, Green M. An analysis of the cost-effectiveness of transcatheter mitral valve repair for people with	**Inclusion criteria** People with secondary mitral valve regurgitation at high risk of surgical mortality or deemed inoperable	**Interventions** Transcatheter mitral valve repair (MitraClip) plus GDMT. See Stone et al 2018 for further details	**Important outcomes** **Cost effectiveness** *ICERs* • £30,057 per QALY (lifetime time horizon)	This study was appraised using the Joanna Briggs checklist for economic evaluations. 1. YES 2. NO 3. YES

secondary mitral valve regurgitation in the UK. J Med Econ. 2020;23(12):1425-34. **Study location** UK perspective **Study type** Cost effectiveness study **Study aim** To present an economic model structure suitable for comparing interventions used in functional mitral or tricuspid regurgitation, and assess the cost-effectiveness of transcatheter mitral valve repair plus GDMT compared with GDMT alone in people with functional mitral regurgitation **Study dates** COAPT trial recruitment period: 27 December 2012 to 23 June 2017 Costs assigned in 2017/18	**Exclusion criteria** None reported **Total sample size** n=614 (COAPT trial) **No. of participants in each treatment group** Transcatheter mitral valve repair plus GDMT n=302 GDMT alone n=312 **Baseline characteristics** Mean age: 72 years Male: 64% See Stone et al 2018 for further details	**Comparators** GDMT alone. See Stone et al 2018 for further details	• £37,440 per QALY (10-year time horizon) • £63,608 per QALY (5-year time horizon) **Subgroups** Not reported	4. YES 5. YES 6. YES 7. YES 8. YES 9. YES 10. YES 11. NO **Other comments:** This cost effectiveness analysis is conducted from a UK NHS perspective over a lifetime timeframe and is based on an economic model of extrapolated survival data and NYHA classifications to describe disease severity (partitioned survival model combined with a “proportion in state” model). Clinical inputs were mostly derived from the COAPT trial (Stone et al 2018). Individual data on quality of life was not used in the model. Instead, quality of life was assumed to be captured within the NYHA classes and sensitivity analyses were performed which showed that these utility estimates were not a key driver of the ICER. Utilities for each NYHA class were calculated using UK population norms combined with a disutility by NYHA class. Costs were assessed in 2017/18 GBP mostly using resource utilisation data from COAPT, EVEREST I/II and ACCESS-Europe trials. Background medication costs were based on NICE guidelines and the number of out-patient and GP

				visits were taken from a study by Biermann et al. based in Germany. Future costs and health benefits were discounted at 3.5% per year. Results should be treated with caution due to uncertainties around modelled lifetime estimates based on short-term trial data. Confidence intervals were not reported for the ICER estimates. Although the costings were in GBP, model inputs were derived from non-UK trials (mostly the COAPT trial which was based in the USA) and therefore results, particularly costs based on resource allocation data derived from a different healthcare setting, may not be applicable to the UK. **Source of funding:** Edwards Lifesciences funded the development of the economic model and manuscript
Stone GW, Lindenfeld J, Abraham WT, Kar S, Lim DS, Mishell JM, et al. Transcatheter Mitral-Valve Repair in Patients with Heart Failure. N Engl J Med. 2018;379(24):2307-18. **Study location** United States and Canada (78 centres) **Study type** RCT	**Inclusion criteria** • Symptomatic SMR (≥3+) due to cardiomyopathy of either ischemic or nonischaemic aetiology • Subject has been adequately treated per applicable standards, including for coronary artery disease, LV dysfunction, MR, and HF • Subject has had at least 1 hospitalisation for HF in the 12 months prior to registration and/or a	**Interventions** TEER: Transcatheter mitral-valve repair using MitraClip plus medical therapy (device group) **Comparators** GDMT: guideline directed medical therapy (control group)	TEER v GDMT The median (IQR) for follow-up was 22.7 months (12.4 to 24.0) v 16.5 months (10.1 to 24.0). **Critical outcomes** **Number of hospital admissions due to heart failure** *All hospitalisations for heart failure* 24 months, number of events/total no of patient-years (rate per 100 patient-years): • 160 /446.5 (35.8) v 283/416.8 (67.9)	This study was appraised using the JBI checklist for RCTs. 1. YES 2. YES 3. YES 4. NO 5. NO 6. UNCLEAR 7. YES 8. YES 9. YES 10. YES 11. YES 12. YES 13. YES

Study aim To evaluate the safety and effectiveness of the MitraClip for treatment of clinically significant SMR in symptomatic heart failure patients despite maximally tolerated GDMT (and CRT and revascularisation where appropriate). **Study dates** 27 December 2012 to 23 June 2017	corrected[49] BNP ≥300pg/mL or a corrected NT-proBNP ≥1500pg/mL • NYHA functional class II, III, or ambulatory IV • Local heart team has determined that MV surgery will not be offered as a treatment option even if subject is randomised to control group • LVEF ≥20% and ≤50% • LVESD ≤70mm • The primary regurgitant jet is noncommissural and, in the opinion of the MitraClip implanting investigator, can be successfully treated by the MitraClip (if a secondary jet exists, it must be considered clinically insignificant) • CK-MB obtained within prior 14 days at local laboratory < upper limit of normal • Transseptal catheterization and femoral vein access is feasible per the MitraClip implanting investigator • Age 18y or older		• HR 0.53 (95% CI 0.40 to 0.70), p <0.001 • NNT: 3.1 (95% CI 1.9 to 7.9) **Survival** *Death from any cause* 30 days, n (%) • 7 (2.3) v 3 (1.0) • HR 2.43 (95% CI 0.63 to 9.40), p=0.20 12 months, n (%)[54] • 57 (19.1) v 70 (23.2) • HR 0.81 (95% CI 0.57 to 1.15), p <0.001 for noninferiority[55] • NNT: 5.9 (95% CI 3.9 to 11.7) 24 months, n (%): • 80 (29.1) v 121 (46.1) • HR 0.62 (95% CI 0.46 to 0.82), p <0.001 *Death related to heart failure* 30 days, n (%): • 7 (2.3) v 2 (0.6) • HR 3.64 (95% CI 0.76 to 17.53), p=0.11 24 months, n (%): • 28 (12.0) v 61 (25.9) • HR 0.43 (95% CI 0.27 to 0.67), p <0.001 **NYHA grade** 30 days, n (%); TEER=283, GDMT=281	**Other comments:** This was a prospective, randomised, open-label, multicentre RCT evaluating the safety and effectiveness of MitraClip compared to maximally tolerated GDMT. Enrolled patients were randomised in a 1:1 ratio to receive TEER + GDMT or GDMT alone using computer-generated blocks of random size. Randomisation was stratified by site and cardiomyopathy aetiology (ischaemic v nonischaemic). The demographic and clinical characteristics, and medical therapy of the two groups were broadly similar at baseline. Given the nature of the intervention, it was not possible to blind participants and those delivering the intervention to treatment allocation. The paper does not report whether outcome assessors were blinded. The outcomes were objective or used standardised assessment measures. Statistical comparison between the groups was not reported for safety outcomes. Results only presented graphically were not extracted.

[49] Corrected refers to a 4% reduction in the BNP or NT-proBNP cutoff for every increase in 1 kg/m^2 in body mass index above a reference of 20 kg/m^2.
[54] Percentages are estimated using the Kaplan-Meier time-to-event methodology.
[55] The primary analysis used a Cox regression model and tested for non-inferiority with a margin of 1.5. Statistical significance in non-inferiority trials is set as a one-sided p-value < 0.025. If a new treatment is shown to be non-inferior to standard treatment, it means that the new treatment is not worse than the standard treatment by the predetermined non-inferior margin (1.5).

	• Subject / guardian agrees to all provisions of the protocol, including the possibility of randomisation to the Control group and returning for all required post procedure follow-up visits, and has provided written informed consent **Exclusion criteria** (all must be absent) • Untreated, clinically significant coronary artery disease requiring revascularization • CABG, PCI, or TAVR within the prior 30 days • Aortic or tricuspid valve disease requiring surgery or transcatheter intervention • COPD requiring continuous home oxygen therapy or chronic outpatient steroid use • Cerebrovascular accident within prior 30 days • Carotid surgery or stenting within prior 30 days • ACC/AHA stage D HF[50] • Estimated PAP >70mmHg assessed by site, based on echocardiography or		• NYHA I: 44 (15.5) v 14 (5.0) • NYHA II: 172 (60.8) v 120 (42.7) • NYHA III: 55 (19.4) v 117 (41.6) • NYHA IV: 10 (3.5) v 27 (9.6) p <0.001 6 months, n (%); TEER=263, GDMT=261 • NYHA I: 51 (19.4) v 14 (5.4) • NYHA II: 139 (52.9) v 117 (44.8) • NYHA III: 56 (21.3) v 100 (38.3) • NYHA IV: 7 (2.7) v 7 (2.7) p <0.001 12 months, n (%); TEER=237, GDMT=232 • NYHA I: 40 (16.9) v 18 (7.8) • NYHA II: 131 (55.3) v 97 (41.8) • NYHA III: 42 (17.7) v 65 (28.0) • NYHA IV: 6 (2.5) v 11 (4.7) p <0.001 18 months, n (%); TEER=183, GDMT=183 • NYHA I: 23 (12.6) v 15 (8.2) • NYHA II: 98 (53.6) v 70 (38.3) • NYHA III: 37 (20.2) v 36 (20.2) • NYHA IV: 2 (1.1) v 8 (4.4) p <0.001 24 months, n (%); TEER=157, GDMT=153 • NYHA I: 19 (12.1) v 8 (5.2) • NYHA II: 67 (42.7) v 43 (28.1) • NYHA III: 34 (21.7) v 36 (23.5) • NYHA IV: 9 (5.7) v 5 (3.3) p <0.001	The trial had data available for 97.7% of patients in the TEER group at 12 months, 94.7% at 24 months vs 94.2% at 12 months and 89.9% at 24 months in the GDMT group. Nine individuals in the TEER group did not receive the intervention; one patient in the control group received the intervention. During the 24 months of follow up 19 patients in the TEER group withdrew and 5 were lost to follow up; in the GDMT group, 44 withdrew and 3 were lost to follow-up. Reasons for withdrawal were not explored. All analyses were conducted as ITT. Furthermore, the primary endpoints were analysed and compared using ITT, 'as-treated' and 'per-protocol' and showed no significant difference in the findings. Data were also analysed using a multiple imputation model to account for missing data; no significant difference was made to the findings. The trial was powered to find the following differences of interest (assuming 7.5% attrition in each group) These were pre-decided and published in a peer-reviewed protocol paper: • Number of hospital admissions due to heart failure: 30% relative risk reduction (0.42/patient-year v 0.6/patient-year)

[50] The American College of Cardiology (ACC) and the American Heart Association (AHA) heart failure classification system that compliments the NYHA classification system by identifying a patient class that is not present in the NYHA Classification – those patients who don't have heart failure, but are at high risk for developing the condition. ACC/AHA Class D HF is defined as refractory heart failure requiring specialized interventions.

	right heart catheterization, unless active vasodilator therapy in the catheterization lab is able to reduce the PVR <3 Wood units or between 3 and 4.5 Wood units with v wave less that twice the mean of the PCWP • Hypertrophic cardiomyopathy, restrictive cardiomyopathy, constrictive pericarditis, or any other structural heart disease causing HF other than dilated cardiomyopathy of either ischaemic or nonischaemic aetiology • Infiltrative cardiomyopathies (eg amyloidosis, hemochromatosis, sarcoidosis) • Hemodynamic instability requiring inotropic support or mechanical heart assistance • Physical evidence of right-sided congestive HF with echocardiographic evidence of moderate or severe right ventricular dysfunction		**Important outcomes** **Health related quality of life (HRQL)** *KCCQ* 12 months, mean (sd); TEER=237, GDMT=228: • 66.4 (28.6) v 49.6 (32.0) • Mean change (sd) Change from baseline to 12 months: 12.2 (30.3) v -3.2 (30.0) • Adjusted mean change (se)[56], baseline to mean 12 months: 12.5 (1.8) v -3.6 (1.9), p <0.001 **Pre discharge grading of mitral regurgitation** Data were available for 260 TEER patients; 30 day follow-up data, as specified in the trial protocol, are used for comparison in the GDMT group (n=257). *TEER*, n (%) • Grade 1+ or lower: 214 (82.3) • Grade 2+: 33 (12.7) • Grade 3+: 9 (3.5) • Grade 4: 4 (1.5) *GDMT*, n=257 • Grade 1+ or lower: 21 (8.2) • Grade 2+: 67 (26.1) • Grade 3+: 96 (37.4) • Grade 4: 73 (28.4) **Duration/durability of mitral regurgitation reduction** *Mitral regurgitation severity at follow-up* 30 days**,** n (%); TEER=273, GDMT=257 • 0: 2 (0.7) v 2 (0.8) • 1+: 197 (72.2) v 19 (7.4)	• All-cause mortality: noninferiority against a relative HR=1.5 • HRQL: 8 points difference in mean change • Pre-discharge grading of mitral regurgitation: • Duration/durability of MR reduction: >20% difference • Functional Outcomes: 30m difference in mean walk distance • Safety: performance goal of freedom from device-related complications >88% **Source of funding:** The primary funder (sponsor) of the COAPT trial was Abbott, Inc, the manufacturer of the trial device. The protocol was designed by the principal investigators and sponsor in accordance with the principles of the Mitral Valve Academic Research Consortium. The sponsor participated in site selection, management and data analysis.

[56] Adjusted mean using least squares mean method uses a linear model to calculate the mean and correct for unbalanced design with an interaction. The COAPT trial used a ANCOVA model with baseline score and treatment effect as covariates.

	• Implant of CRT or CRT-D within the last 30 days • Mitral valve orifice area <4.0cm^2 (assessed TTE at each enrolment site) • Leaflet anatomy which may preclude MitraClip implantation, proper MitraClip positioning on the leaflets, or sufficient reduction in MR by the MitraClip support or intra-aortic balloon pump or other hemodynamic support device • Need for emergent or urgent surgery for any reason or any planned cardiac surgery within the next 12 months • Life expectancy <12 months due to noncardiac conditions • Modified Rankin Scale ≥4 disability[51] • Status 1[52] heart transplant or prior orthotopic heart transplantation • Prior mitral valve leaflet surgery or any currently implanted prosthetic mitral valve, or any prior transcatheter mitral valve procedure • Echocardiographic evidence of intracardiac		• 2+: 54 (19.8) v 67 (26.1) • 3+: 16 (5.9) v 96 (37.4) • 4+: 4 (1.5) v 73 (28.4) p <0.001 6 months, n (%); TEER=240, GDMT=218 • 0: 1 (0.4) v 1 (0.5) • 1+: 159 (66.3) v 19 (8.7) • 2+: 65 (27.1) v 63 (28.9) • 3+: 11 (4.6) v 92 (42.2) • 4+: 4 (1.7) v 43 (19.7) p <0.001 12 months, n (%); TEER=210, GDMT=175 • 0: 1 (0.5) v 2 (1.1) • 1+: 144 (68.6) v 18 (10.3) • 2+: 54 (25.7) v 62 (35.4) • 3+: 9 (4.3) v 60 (34.3) • 4+: 2 (1.0) v 33 (18.9) p <0.001 18 months, n (%); TEER=141, GDMT=114 • 0: 1 (0.7) v 1 (0.9) • 1+: 105 (74.5) v 13 (11.4) • 2+: 28 (19.9) v 32 (28.1) • 3+: 6 (4.3) v 47 (41.2) • 4+: 1 (0.7) v 21 (18.4) p <0.001 24 months, n (%); TEER=114, GDMT=76 • 0: 1 (0.9) v 2 (2.6) • 1+: 87 (76.3) v 10 (13.2) • 2+: 25 (21.9) v 21 (27.6) • 3+: 0 (0) v 31 (40.8)	

[51] The Modified Rankin Scale (mRS) assesses disability in patients who have suffered a stroke and is compared over time to check for recovery and degree of continued disability. A score of 0 is no disability, 5 is disability requiring constant care for all needs; 6 is death.
[52] Individuals on the heart transplant waiting list will be categorised based on clinical need on a scale of 1-6. Patients who are categorized as Status 1 and 2 have top priority in receiving heart transplants. They are often severely ill, may be on advanced life support, and are not expected to survive more than a month.

	mass, thrombus, or vegetation • Active endocarditis or active rheumatic heart disease or leaflets degenerated from rheumatic disease • Active infections requiring antibiotic therapy • TEER is contraindicated or high risk • Known hypersensitivity or contraindication to procedural medications which cannot be adequately managed medically • Pregnant or planning pregnancy within next 12 months • Currently participating in an investigational drug or another device study that has not reached its primary end point • Subject belongs to a vulnerable population or has any disorder that compromises his/her ability to give written informed consent and/or to comply with study procedures		• 4+: 1 (0.9) v 12 (15.8) p <0.001 *Unplanned mitral-valve intervention* 24 months, n (%): • 10 (4.0) v 15 (9.0) • HR 0.61 (95% CI 0.27 to 1.36); p=0.23 **Functional outcomes** *6-minute walk test* 12 months, meters; mean (sd); TEER=230, GDMT=237: • 256.7 (157.7) v 188.8 (166.7) • Mean change (sd) from baseline to 12 months: -4.6 (134.8) v -57.6 (152.5) • Adjusted mean change[57] (se), baseline to 12 months: -2.2 (9.1) v -60.0 (9.0), p <0.001 **Safety** **Procedural complications** *Freedom from device related complications (TEER group only)*[58] % free from complications at 12 months[59] (95% CI lower estimate) • 96.9 (94.7) • p <0.001 for comparison with goal of 80.0% *Adverse event rates*	

[57] Adjusted mean using least squares mean method uses a linear model to calculate the mean and correct for unbalanced design with an interaction. The COAPT trial used a ANCOVA model with baseline score and treatment effect as covariates.
[58] A device related complication was defined as any occurrence of single-leaflet device attachment, embolization of the device, endocarditis that led to surgery, mitral stenosis (as confirmed by the echocardiographic core laboratory) that led to mitral-valve surgery, implantation of a left ventricular assist device, heart transplantation, or any other device-related event that led to nonelective cardiovascular surgery.
[59] Percentages are estimated using the Kaplan-Meier time-to-event methodology.

	Total sample size n=614 **No. of participants in each treatment group** Device: n=302 Control: n=312 **Baseline characteristics** Device vs Control Age years, mean (sd): 71.7 (11.8) v 72.8 (10.5) Male, n (%): 201 (66.6) v 192 (61.5) Medical and surgical history, n (%): • Diabetes: 106 (35.1) v 123 (39.4) • Hypertension: 243 (80.5) v 251 (80.4) • Hypercholesterolemia 166 (55.0) v 163 (52.2) • Previous MI: 156 (51.7) v 160 (51.3) • Previous PCI: 130 (43.0) v 153 (49.0) • Previous coronary-artery bypass grafting: 121 (40.1) v 126 (40.4) • Previous stroke or TIA: 56 (18.5) v 49 (15.7) • Peripheral vascular disease: 52 (17.2) v 57 (18.3)		30 days, n (%)[60]: • Stroke: 2 (0.7) v 0 (0) • MI: 3 (1.0) v 0 (0) 24 months, n (%): • Stroke: 11 (4.4) v 11 (5.1); HR 0.96 (95% CI 0.42 to 2.22); p=0.93 • MI: 12 (4.7) v 14 (6.5); HR 0.82 (95% CI 0.38 to 1.78); p=0.62 **Subgroups** Subgroup: severe, MR grade 4+ **Critical outcomes** **Number of hospital admissions due to heart failure** *All hospitalisations for heart failure* 24 months, number of events / total number of patient-years (annualised rate[61]); TEER, n=154; GDMT, n=139: • 97/219.5 (44.6) v 146/182.4 (80.1) • HR 0.57 (95% CI 0.40 to 0.80) Subgroup: NYHA Class IV **Critical outcomes** **Number of hospital admissions due to heart failure** *All hospitalisations for heart failure* 24 months, number of events / total number of patient-years (annualised rate[62]); Device (TEER), n=18; Control (GDMT), n=33: • 20/24.0 (83.4) v 40/35.4 (113.0)	

[60] Percentages are estimated using the Kaplan-Meier time-to-event methodology.
[61] Death per 100 patient-years of all hospitalisations for heart failure within 24 months of follow-up across subgroups.
[62] Death per 100 patient-years of all hospitalisations for heart failure within 24 months of follow-up across subgroups.

	• COPD: 71 (23.5) v 72 (23.1) • History of AF or flutter: 173 (57.3) v 166 (53.2) BMI, mean (sd): 27.0 (5.8) v 27.1 (5.9) Creatinine, clearance mL/min; mean (sd): 50.9 (28.5) v 47.8 (25.0) Anaemia, n (%): 180 (59.8) v 192 (62.7) STS risk score[53], mean (sd): 7.8 (5.5) v 8.5 (6.2) Ischemic cardiomyopathy, n (%): 184 (60.9) v 189 (60.6) NYHA I , n (%): 1 (0.3) v 0 (0) NYHA II, n (%): 129 (42.7) v 110 (35.4) NYHA III, n (%): 154 (51.0) v 168 (54.0) NYHA IV, n (%): 18 (6.0) v 33 (10.6) Severity of MR: Grade 3+, n (%): 148 (49.0) v 172 (55.3) Grade 4+, n (%): 154 (51.0) v 139 (44.7) Hospitalisation for HF within previous year, n (%): 176 (58.3) v 175 (56.1) LVEF %, mean (sd): 31.3 (9.1) v 31.3 (9.6) LVESD mm; mean (sd): 135.5 (56.1) v 134.3 (60.3) LV end-diastolic volume, ml; mean (sd): 194.4 (69.2) v 191.0 (72.9)		• HR 0.77 (95% CI 0.34 to 1.75)	

[53] The STS risk score is a validated risk prediction model for open surgery based on data from the STS National Adult Cardiac Surgery Database. In general, an STS predicted risk of surgical mortality of 4%-8% is considered intermediate risk and 8% or greater is considered high risk.

	Effective regurgitant orifice area, cm^2; mean (sd): 0.41 (0.15) v 0.40 (0.15) Right ventricular systolic pressure, mmHg; mean (sd): 44.0 (13.4) v 44.6 (14.0) KCCQ Summary Score, mean (sd): 54.2 (22.7) v 52.9 (23.3) 6-minute walk test distance, metres; mean (sd): 261.3 (125.3) v 246.4 (127.1)			
Zimarino M, Ricci F, Capodanno D, De Innocentiis C, Verrengia E, Swaans MJ, et al. Left Ventricular Size Predicts Clinical Benefit After Percutaneous Mitral Valve Repair for Secondary Mitral Regurgitation: A Systematic Review and Meta-Regression Analysis. Cardiovasc Revasc Med. 2020;21(7):857-64. **Study location** International **Study type** Systematic review and meta-analysis **Study aim** To compare the outcome of PMVR with OMT versus OMT alone in patients with secondary mitral	**Inclusion criteria** RCTs or non-randomised longitudinal observational studies with follow-up ≥12 months and reporting all-cause mortality data in patients with moderately severe or severe predominantly (enrolment >60%) secondary mitral regurgitation **Exclusion criteria** Studies reporting only composite endpoints, without specific data on all-cause death; Observational studies that did not include accepted statistical techniques for adjustment; Non-English language literature. **Total sample size**	**Interventions** PMVR (MitraClip) plus OMT **Comparators** OMT alone	Results for pooled RCTs only Mean follow-up of 24 (+/- 15) months[64] (2 RCTs) **Critical outcomes** **Survival** *All-cause mortality* • HR 0.80 (95% CI 0.46 to 1.42), p=0.45, I^2=76% *Cardiovascular mortality* • HR 0.78 (95% CI 0.43 to 1.42), p=0.41, I^2=77% **Subgroups** Not reported	This study was appraised using the AMSTAR 2 checklist for systematic reviews. 1. YES 2. NO 3. YES 4. YES 5. YES 6. YES 7. YES 8. NO 9. YES 10. YES 11. YES 12. YES 13. NO 14. YES 15. YES 16. NO **Other comments:** This systematic review pooled data from RCTs and observational studies. Only the results for the meta-analyses of RCTs have been extracted as combining

[64] Mean follow-up for all studies including observational studies. Mean follow-up for RCTs only was not reported for these outcomes.

regurgitation and to assess the role of potential effect modifiers **Study dates** Literature search dates: 1 January 2000 to 30 September 2018	9 studies (2 RCTs & 7 non-randomised observational studies[63]) n=3,118 (all studies) n=918 (RCTs only) **No. of participants in each treatment group** PMVR (n=1,775 all studies; n=454 RCTs only) OMT (n=1,343 all studies; n=464 RCTs only) **Baseline characteristics** All patients (n=3,118) for PMVR v OMT Age: 73.2 v 71.8 years Male: 65 vs 61% Diabetes: 29.8 v 32.7% CKD: 28.8 v 23.1% COPD: 17.1 18.1% AF: 50.5 v 45.2% Previous MI: 47.3 v 39.0% NYHA III-IV: 73.8 v 61.4% SMR: 82.3 v 87.4% For baseline characteristics for the individual RCTs see Obadia et al 2018 & Stone et al 2018			observational results with the randomised results will introduce bias reducing the reliability of the randomised evidence. Meta-analyses were performed according to a random effects model and fixed-effect model. Results for the random effects model were reported due to significant heterogeneity observed between the studies. In order to explore potential sources of heterogeneity, leave-one-out sensitivity analyses and explorative meta-regression analysis were conducted. Limited information was reported on the intervention, comparator and research design for each study. Publication bias (small study effect) was assessed by a funnel plot and the Eggers regression test and both suggested no significant bias for all outcomes. **Source of funding:** No funding was received. Several of the authors declared conflicts of interest.

Abbreviations

ACC: American College of Cardiology; AF: Atrial fibrillation; AHA: American Heart Association; AMSTAR 2: assessing the methodological quality of systematic reviews; aOR: adjusted odds ratio; BMI: body mass index; BNP: brain natriuretic peptide; CABG: coronary artery bypass grafting; CI: confidence interval; CKD: Chronic kidney disease; CK-MB: creatine kinase-MB; COAPT: Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation Trial; COPD: chronic obstructive pulmonary disease; CRT: cardiac resynchronisation therapy (pace-maker); CRT-D: cardiac resynchronisation therapy defibrillator (pace-maker with built in defibrillator); EuroSCORE: European system for cardiac operative risk evaluation; EVEREST II: Endovascular Valve Edge-to-Edge Repair Study; FMR: functional mitral valve regurgitation; GBP: Great British Pound (£); GDMT: guideline directed medical

[63] Only the results for the meta-analyses of RCTs have been extracted as combining observational results with the randomised results will introduce bias reducing the reliability of the randomised evidence.

therapy; HF: heart failure; HR: hazard ratio; HRQL: health related quality-of-life; ICER: incremental cost effectiveness ratio; IQR: interquartile range; ITT: intention-to-treat; KCCQ: The Kansas City Cardiomyopathy Questionnaire; LV: left ventricle; LVEF: left ventricular ejection fraction; LVESD: left ventricle end-systolic diameter; m: metres; MI: myocardial infarction; MITRA-FR: Multicentre Study of Percutaneous Mitral Valve Repair MitraClip Device in Patients with Severe Secondary Mitral Regurgitation; MOOSE: Meta-analysis of Observational Studies in Epidemiology; MR: mitral regurgitation; n: number; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; NNT: number needed to treat; NR: not reported; NT-proBNP: N-terminal pro b-type natriuretic peptide; NYHA: New York Heart Association; OMT: optimal medical therapy; OR: odds ratio; PAP: pulmonary artery pressure; PCI: percutaneous coronary intervention; PCWP: pulmonary capillary wedge pressure; PMVR: percutaneous mitral valve repair; PRISMA: preferred reporting items for systematic reviews & meta-analyses; PVR: pulmonary vascular resistance; QALY: quality-adjusted life-year; QoL: quality of life; RCT: randomised controlled trial; RR: relative risk; sd: standard deviation; se: standard error; SMR: secondary mitral regurgitation; SRMA: systematic review and meta-analysis; STS: Society of Thoracic Surgeons; TAVR: transcatheter aortic valve replacement; TEER: transcatheter edge to edge repair; TIA: transient ischaemic attack; TTE: transthoracic echocardiography; UK: United Kingdom; US / USA: United States of America; v: versus

Appendix F Quality appraisal checklists

AMSTAR 2 critical appraisal checklist for systematic reviews

1. Did the research questions and inclusion criteria for the review include the components of PICO?
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?
3. Did the review authors explain their selection of the study designs for inclusion in the review?
4. Did the review authors use a comprehensive literature search strategy?
5. Did the review authors perform study selection in duplicate?
6. Did the review authors perform data extraction in duplicate?
7. Did the review authors provide a list of excluded studies and justify the exclusions?
8. Did the review authors describe the included studies in adequate detail?
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?
10. Did the review authors report on the sources of funding for the studies included in the review?
11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?

JBI critical appraisal checklist for RCTs

1. Was true randomisation used for assignment of participants to treatment groups?
2. Was allocation to treatment groups concealed?
3. Were treatment groups similar at the baseline?
4. Were participants blinded to treatment assignment?
5. Were those delivering treatment blind to treatment assignment?

6. Were outcomes assessors blind to treatment assignment?
7. Were treatment groups treated identically other than the intervention of interest?
8. Was follow-up complete and if not, were differences between groups in terms of their follow-up adequately described and analysed?
9. Were participants analysed in the groups to which they were randomised?
10. Were outcomes measured in the same way for treatment groups?
11. Were outcomes measured in a reliable way?
12. Was appropriate statistical analysis used?
13. Was the trial design appropriate, and any deviations from the standard RCT design (individual randomisations, parallel groups) accounted for in the conduct and analysis of the trial

JBI critical appraisal checklist for economic evaluations

1. Is there a well-defined question/objective?
2. Is there a comprehensive description of alternatives?
3. Are all important and relevant costs and outcomes for each alternative identified?
4. Has clinical effectiveness been established?
5. Are costs and outcomes measured accurately?
6. Are costs and outcomes valued credibly?
7. Are costs and outcomes adjusted for differential timing?
8. Is there any incremental analysis of costs and consequences?
9. Were sensitivity analysis conducted to investigate uncertainty in estimates of costs or outcomes?
10. Do study results include all issues of concern to users?
11. Are the results generalizable to the setting of interest in the review?

Appendix G GRADE profiles

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	TEER	Optimised medical management	Result		
Number of hospital admissions due to heart failure (2 SRMAs & 2 RCTs)									
Unplanned hospitalisations for heart failure at 12 months (n, %; HR)									
1 RCT Obadia et al 2018	Serious limitations[1]	No serious indirectness	Not applicable	Serious imprecision[2]	152	152	PMVR: 74 (48.7) OMT: 72 (47.4) HR 1.13 (95% CI 0.81 to 1.56)	Critical	Low
Hospital admissions due to heart failure at median follow-up of 438 (IQR 360 to 625) days[65] (OR)									
1 SRMA Bertaina et al 2019	Very serious limitations[3]	No serious indirectness	Very serious inconsistency[4]	Not calculable	454	464	Unadj OR 0.67 (95% confidence interval (CI) 0.27 to 1.65), p=0.38, I^2=87%, 2 RCTs Adj OR[66] 0.77 (95% CI 0.37 to 1.62), p=0.49, I^2=91%, 2 RCTs	Critical	Very low
Hospital admissions due to heart failure at a mean follow-up of 1.64 years[67] (HR)									
1 SRMA Lodhi et al 2019	Serious limitations[5]	No serious indirectness	Very serious inconsistency[4]	Very serious imprecision[6]	454	464	HR 0.76 (95% CI 0.36 to 1.63), p=0.48, I^2=92%, 2 RCTs	Critical	Very low
Unplanned hospitalisations for heart failure from 12 to 24 months (n, rate per 100 patient-years; HR)									
1 RCT Iung et al 2019	Serious limitations[1]	No serious indirectness	Not applicable	Serious imprecision[7]	59 patient-years	56 patient-years	PMVR: 11 (18.6) OMT: 22 (39.3) HR 0.47 (95% CI 0.22 to 0.98)	Critical	Low
Unplanned hospitalisations for heart failure at 24 months (n, rate per 100 patient-years; HR)									
1 RCT Iung et al 2019	Serious limitations[1]	No serious indirectness	Not applicable	Very serious imprecision[6]	152 patient-years	156 patient-years	PMVR: 85 (55.9) OMT: 94 (62.3) HR 0.97 (95% CI 0.72 to 1.30)	Critical	Very low
All hospitalisations for heart failure at 24 months (events, rate per 100 patient-years; HR; NNT)									

[65] Mean follow-up for all studies including observational studies. Mean follow-up for RCTs only was not reported for this outcome.
[66] Adjusted for confounders. Confounding factors not reported.
[67] Mean follow-up for all studies including observational studies. Mean follow-up for RCTs only was not reported for this outcome.

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	TEER	Optimised medical management	Result		
1 RCT Stone et al 2018	No serious limitations	No serious indirectness	Not applicable	No serious imprecision	446.5 patient-years	416.8 patient-years	TEER: 160 (35.8) GDMT: 283 (67.9) HR 0.53 (95% CI 0.40 to 0.70), p <0.001 NNT: 3.1 (95% CI 1.9 to 7.9)	Critical	High
Survival (3 SMRAs & 2 RCTs)									
All-cause mortality at 30 days (OR)									
1 SRMA Bertaina et al 2019	Very serious limitations[3]	No serious indirectness	No serious inconsistency	Not calculable	454	464	Unadj OR 1.74 (95% CI 0.67 to 4.52), p=0.25, I^2=0%, 2 RCTs Adj OR 1.74 (95% CI 0.67 to 4.50), p=0.25, I^2=0%, 2 RCTs	Critical	Low
All-cause mortality at 30 days (OR)									
1 SRMA Lodhi et al 2019	Serious limitations[5]	No serious indirectness	No serious inconsistency	Not calculable	454	464	OR 1.74 (95% CI 0.67 to 4.52), p=0.25, I^2=0%, 2 RCTs	Critical	Moderate
All-cause mortality at 30 days (RR)									
1 SRMA Lodhi et al 2019	Serious limitations[5]	No serious indirectness	No serious inconsistency	Very serious imprecision[6]	454	464	RR 1.72 (95% CI 0.66 to 4.36), p=0.26, I^2=0%, 2 RCTs	Critical	Very low
All-cause mortality at 12 months (OR)									
1 SRMA Bertaina et al 2019	Very serious limitations[3]	No serious indirectness	No serious inconsistency	Not calculable	454	464	Unadj OR 0.90 (95% CI 0.66 to 1.24), p=0.53, I^2=0%, 2 RCTs Adj OR 0.91 (95% CI 0.68 to 1.22), p=0.53, I^2=8%, 2 RCTs	Critical	Low
All-cause mortality at 12 months (OR)									
1 SRMA Lodhi et al 2019	Serious limitations[5]	No serious indirectness	No serious inconsistency	Not calculable	454	464	OR 0.87 (95% CI 0.59 to 1.29), p=0.50, I^2=32%, 2 RCTs	Critical	Moderate
All-cause mortality at 12 months (RR)									

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	TEER	Optimised medical management	Result		
1 SRMA Lodhi et al 2019	Serious limitations[5]	No serious indirectness	No serious inconsistency	Serious imprecision[7]	454	464	RR 0.90 (95% CI 0.66 to 1.23), p=0.51, I^2=33.3%	Critical	Low
All-cause mortality at median follow-up of 438 (IQR 360 to 625) days[68] (OR)									
1 SRMA Bertaina et al 2019	Very serious limitations[3]	No serious indirectness	Very serious inconsistency[4]	Not calculable	454	464	Unadj OR 0.77 (95% CI 0.40 to 1.49), p=0.44, I^2=77%, 2 RCTs Adj OR 0.80 (95% CI 0.46 to 1.42), p=0.45, I^2=76%, 2 RCTs	Critical	Very low
Death from any cause from 12 to 24 months (n, rate per 100 patient-years; HR)									
1 RCT Iung et al 2019	Serious limitations[1]	No serious indirectness	Not applicable	Very serious imprecision[6]	103 patient-years	99 patient-years	PMVR: 16 (15.5) OMT: 18 (18.2) HR 0.86 (95% CI 0.44 to 1.69)	Critical	Very low
All-cause mortality at mean follow-up of 24 (+/- 15) months[69] (HR)									
1 SRMA Zimarino et al 2020	Serious limitations[5]	No serious indirectness	Very serious inconsistency[4]	Very serious imprecision[6]	454	464	HR 0.80 (95% CI 0.46 to 1.42), p=0.45, I^2=76%, 2 RCTs	Critical	Very low
Death from any cause at 24 months (n, rate per 100 patient-years; HR)									
1 RCT Iung et al 2019	Serious limitations[1]	No serious indirectness	Not applicable	Very serious imprecision[6]	230 patient-years	229 patient-years	PMVR: 53 (23.1) OMT: 52 (22.8) HR 1.02 (95% CI 0.70 to 1.50)	Critical	Very low
Death from any cause at 24 months (n; HR)									
1 RCT Stone et al 2018	No serious limitations	No serious indirectness	Not applicable	Serious imprecision[7]	302	312	TEER: 80 GDMT: 121 HR 0.62 (95% CI 0.46 to 0.82), p <0.001	Critical	Moderate
Cardiovascular mortality at median follow-up of 438 (IQR 360 to 625) days[70] (OR)									
1 SRMA	Very serious limitations[3]	No serious indirectness	Very serious inconsistency[4]	Not calculable	454	464	Unadj OR 0.77 (95% CI 0.40 to 1.49), p=0.44, I^2=77%, 2 RCTs	Critical	Very low

[68] Mean follow-up for all studies including observational studies. Mean follow-up for RCTs only was not reported for this outcome.
[69] Mean follow-up for all studies including observational studies. Mean follow-up for RCTs only was not reported for this outcome.
[70] Mean follow-up for all studies including observational studies. Mean follow-up for RCTs only was not reported for this outcome.

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	TEER	Optimised medical management	Result		
Bertaina et al 2019							Adj OR 0.78 (95% CI 0.43 to 1.42), p=0.41, I^2=77%, 2 RCTs		
Cardiovascular mortality at mean follow-up of 1.54 years[71] (OR)									
1 SRMA Lodhi et al 2019	Serious limitations[5]	No serious indirectness	Serious inconsistency[8]	Not calculable	454	464	OR 0.75 (95% CI 0.40 to 1.43), p=0.39, I^2=73%, 2 RCTs	Critical	Low
Cardiovascular mortality at mean follow-up of 1.54 years[72] (RR)									
1 SRMA Lodhi et al 2019	Serious limitations[5]	No serious indirectness	Serious inconsistency[8]	Very serious imprecision[6]	454	464	RR 0.81 (95% CI 0.50 to 1.31), p=0.38, I^2=71.5%, 2 RCTs	Critical	Very low
Cardiovascular mortality from 12 to 24 months (n, rate per 100 patient-years; HR)									
1 RCT Iung et al 2019	Serious limitations[1]	No serious indirectness	Not applicable	Very serious imprecision[6]	103 patient-years	99 patient-years	PMVR: 14 (13.6) OMT: 17 (17.2) HR 0.80 (95% CI 0.39 to 1.63)	Critical	Very low
Cardiovascular mortality at 2 years (n, rate per 100 patient-years; HR)									
1 RCT Iung et al 2019	Serious limitations[1]	No serious indirectness	Not applicable	Very serious imprecision[6]	230 patient-years	229 patient-years	PMVR: 47 (20.5) OMT: 48 (21.1) HR 0.99 (95% CI 0.66 to 1.48	Critical	Very low
Death related to heart failure at 24 months (n; HR)									
1 RCT Stone et al 2018	No serious limitations	No serious indirectness	Not applicable	No serious imprecision	302	312	TEER: 28 GDMT: 61 HR 0.43 (95% CI 0.27 to 0.67), p <0.001	Critical	High
Cardiovascular mortality at mean follow-up of 24 (+/- 15) months[73] (HR)									
1 SRMA Zimarino et al 2020	Serious limitations[5]	No serious indirectness	Very serious inconsistency[4]	Very serious imprecision[6]	454	464	HR 0.78 (95% CI 0.43 to 1.42), p=0.41, I^2=77%, 2 RCTs	Critical	Very low

[71] Mean follow-up for all studies including observational studies. Mean follow-up for RCTs only was not reported for this outcome.
[72] Mean follow-up for all studies including observational studies. Mean follow-up for RCTs only was not reported for this outcome.
[73] Mean follow-up for all studies including observational studies. Mean follow-up for RCTs only was not reported for this outcome.

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	TEER	Optimised medical management	Result		
NYHA grade[74] (2 RCTs)									
NYHA grade at 30 days (n, %)									
1 RCT Stone et al 2018	Serious limitations[10]	No serious indirectness	Not applicable	Not calculable	283	281	TEER v GDMT • NYHA I: 44 (15.5) v 14 (5.0) • NYHA II: 172 (60.8) v 120 (42.7) • NYHA III: 55 (19.4) v 117 (41.6) • NYHA IV: 10 (3.5) v 27 (9.6) p <0.001	Critical	Moderate
NYHA grade at 6 months (n, %)									
1 RCT Stone et al 2018	Serious limitations[10]	No serious indirectness	Not applicable	Not calculable	263	261	TEER v GDMT • NYHA I: 51 (19.4) v 14 (5.4) • NYHA II: 139 (52.9) v 117 (44.8) • NYHA III: 56 (21.3) v 100 (38.3) • NYHA IV: 7 (2.7) v 7 (2.7) p-value <0.001	Critical	Moderate
NYHA grade at 12 months (n, %)									
1 RCT Stone et al 2018	Serious limitations[10]	No serious indirectness	Not applicable	Not calculable	237	232	TEER v GDMT • NYHA I: 40 (16.9) v 18 (7.8) • NYHA II: 131 (55.3) v 97 (41.8) • NYHA III: 42 (17.7) v 65 (28.0) • NYHA IV: 6 (2.5) v 11 (4.7) p <0.001	Critical	Moderate
NYHA grade at 12 months									

[74] The New York Heart Association (NYHA) functional classification is a widely used tool for risk stratification on the basis of severity of symptoms and limitation of physical activity. It places patients in one of four categories: Class I — no limitation of physical activity. Ordinary physical activity does not cause undue fatigue, breathlessness, or palpitations; Class II — slight limitation of physical activity. Comfortable at rest but ordinary physical activity results in undue breathlessness, fatigue, or palpitations; Class III — marked limitation of physical activity. Comfortable at rest but less than ordinary physical activity results in undue breathlessness, fatigue, or palpitations; Class IV — unable to carry out any physical activity without discomfort. Symptoms at rest can be present. If any physical activity is undertaken discomfort is increased.

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	TEER	Optimised medical management	Result		
1 RCT Obadia et al 2018	Very serious limitations[9]	No serious indirectness	Not applicable	Not calculable	114	112	The paper reported that there was no significant difference between groups	Critical	Low
NYHA grade at 18 months (n, %)									
1 RCT Stone et al 2018	Serious limitations[10]	No serious indirectness	Not applicable	Not calculable	183	183	TEER v GDMT • NYHA I: 23 (12.6) v 15 (8.2) • NYHA II: 98 (53.6) v 70 (38.3) • NYHA III: 37 (20.2) v 36 (20.2) • NYHA IV: 2 (1.1) v 8 (4.4) p <0.001	Critical	Moderate
NYHA grade at 24 months									
1 RCT Iung et al 2019	Very serious limitations[9]	No serious indirectness	Not applicable	Not calculable	90	87	The paper reported that there was no significant difference between groups	Critical	Low
NYHA grade at 24 months (n, %)									
1 RCT Stone et al 2018	Serious limitations[10]	No serious indirectness	Not applicable	Not calculable	157	153	TEER v GDMT • NYHA I: 19 (12.1) v 8 (5.2) • NYHA II: 67 (42.7) v 43 (28.1) • NYHA III: 34 (21.7) v 36 (23.5) • NYHA IV: 9 (5.7) v 5 (3.3) p <0.001	Critical	Moderate
Health related quality of life (2 RCTs)									
Kansas City Cardiomyopathy Questionnaire (KCCQ) Score[75] at 12 months (mean, sd; benefit is indicated by higher result)									
1 RCT Stone et al 2018	Serious limitations[10]	No serious indirectness	Not applicable	Not calculable	237	228	TEER v GDMT 66.4 (28.6) v 49.6 (32.0)	Important	Moderate

[75] The Kansas City Cardiomyopathy Questionnaire (KCCQ) is a 23-item self-administered questionnaire developed to independently measure the patient's perception of their health status, which includes heart failure symptoms, impact on physical and social function, and how their heart failure impacts their quality of life (QoL) within a 2-week recall period. KCCQ responses are provided along a rating scale continuum (0 to 100) and frequently summarized in 25-point ranges: 0 to 24: very poor to poor; 25 to 49: poor to fair; 50 to 74: fair to good; and 75 to 100: good to excellent.

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	TEER	Optimised medical management	Result		
							Change from baseline to 12 months: 12.2 (30.3) v -3.2 (30.0) Adjusted mean change[76], baseline to mean 12 months: 12.5 (1.8) v -3.6 (1.9), p <0.001		
EQ5D global score[77] at 12 months (mean, sd; benefit is indicated by higher result)									
1 RCT Obadia et al 2018	Very serious limitations[11]	No serious indirectness	Not applicable	Not calculable	Baseline: 143 Follow-up: 93	Baseline: 128 Follow-up: 87	Baseline: • PMVR: 51.5 (91.2) • OMT: 53.2 (16.6) 12 months: • PMVR: 60.8 (20.3) • OMT: 58.6 (18.2)	Important	Low
Pre discharge grading of mitral regurgitation (2 RCTs)									
Reduction of mitral regurgitation of at least one grade at the time of discharge (n, %)									
1 RCT Obadia et al 2018	Very serious limitations[13]	Serious indirectness[14]	Not applicable	Not calculable	123		117 (95.1%)	Important	Very low
Reduction of mitral regurgitation to 2+ (mild to moderate) or lower at the time of discharge (n, %)									
1 RCT Obadia et al 2018	Very serious limitations[13]	Serious indirectness[14]	Not applicable	Not calculable	123		113 (91.9%)	Important	Very low
Reduction of mitral regurgitation to 0+ (none or trace) to 1+ (mild) at the time of discharge (n, %)									
1 RCT Obadia et al 2018	Very serious limitations[13]	Serious indirectness[14]	Not applicable	Not calculable	123		93 (75.6%)	Important	Very low
Pre discharge grading of mitral regurgitation (n, %) [0 none to trace, 1+ mild, 2+ mild-to-moderate, 3+ moderate-to-severe, 4+ severe]									
1 RCT	Serious limitations[10]	No serious indirectness	Not applicable	Not calculable	260	257	30 day follow-up data are used for comparison in the GDMT group, as per study protocol	Important	Moderate

[76] Adjusted mean using least squares mean method uses a linear model to calculate the mean and correct for unbalanced design with an interaction. The COAPT trial used a ANCOVA model with baseline score and treatment effect as covariates.
[77] The EQ5D is a measure of quality of life based on 5 dimensions: activities, anxiety, mobility, pain and self-care. A higher score indicates a better quality of life with a visual acuity scale ranging from 0 (worst imaginable health) to 100 (best imaginable health).

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	TEER	Optimised medical management	Result		
Stone et al 2018							TEER v GDMT • Grade 1+ or lower: 214 (82.3) v 21 (8.2) • Grade 2+: 33 (12.7) v 67 (26.1) • Grade 3+: 9 (3.5) v 96 (37.4) • Grade 4+: 4 (1.5) v 73 (28.4)		
Duration/durability of mitral regurgitation reduction (1 RCT)									
Mitral regurgitation severity at 30 days (n, %) [0 none or trace, 1+ mild, 2+ mild-to-moderate, 3+ moderate-to-severe, 4+ severe]									
1 RCT Stone et al 2018	Serious limitations[10]	No serious indirectness	Not applicable	Not calculable	273	257	TEER v GDMT • 0: 2 (0.7) v 2 (0.8) • 1+: 197 (72.2) v 19 (7.4) • 2+: 54 (19.8) v 67 (26.1) • 3+: 16 (5.9) v 96 (37.4) • 4+: 4 (1.5) v 73 (28.4) p <0.001	Important	Moderate
Mitral regurgitation severity at 6 months (n, %) [0 none or trace, 1+ mild, 2+ mild-to-moderate, 3+ moderate-to-severe, 4+ severe]									
1 RCT Stone et al 2018	Serious limitations[10]	No serious indirectness	Not applicable	Not calculable	240	218	TEER v GDMT • 0: 1 (0.4) v 1 (0.5) • 1+: 159 (66.3) v 19 (8.7) • 2+: 65 (27.1) v 63 (28.9) • 3+: 11 (4.6) v 92 (42.2) • 4+: 4 (1.7) v 43 (19.7) p <0.001	Important	Moderate
Mitral regurgitation severity at 12 months (n, %) [0 none or trace, 1+ mild, 2+ mild-to-moderate, 3+ moderate-to-severe, 4+ severe]									
1 RCT Stone et al 2018	Serious limitations[10]	No serious indirectness	Not applicable	Not calculable	210	175	TEER v GDMT • 0: 1 (0.5) v 2 (1.1) • 1+: 144 (68.6) v 18 (10.3) • 2+: 54 (25.7) v 62 (35.4) • 3+: 9 (4.3) v 60 (34.3) • 4+: 2 (1.0) v 33 (18.9) p <0.001	Important	Moderate
Mitral regurgitation severity at 18 months (n, %) [0 none or trace, 1+ mild, 2+ mild-to-moderate, 3+ moderate-to-severe, 4+ severe]									
1 RCT	Serious limitations[10]	No serious indirectness	Not applicable	Not calculable	141	114	TEER v GDMT • 0: 1 (0.7) v 1 (0.9)	Important	Moderate

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	TEER	Optimised medical management	Result		
Stone et al 2018							• 1+: 105 (74.5) v 13 (11.4) • 2+: 28 (19.9) v 32 (28.1) • 3+: 6 (4.3) v 47 (41.2) • 4+: 1 (0.7) v 21 (18.4) p <0.001		
Mitral regurgitation severity at 24 months (n, %) [0 none or trace, 1+ mild, 2+ mild-to-moderate, 3+ moderate-to-severe, 4+ severe]									
1 RCT Stone et al 2018	Serious limitations[10]	No serious indirectness	Not applicable	Not calculable	114	76	TEER v GDMT • 0: 1 (0.9) v 2 (2.6) • 1+: 87 (76.3) v 10 (13.2) • 2+: 25 (21.9) v 21 (27.6) • 3+: 0 (0) v 31 (40.8) • 4+: 1 (0.9) v 12 (15.8) p <0.001	Important	Moderate
Unplanned mitral-valve intervention at 24 months (n; HR)									
1 RCT Stone et al 2018	No serious limitations	No serious indirectness	Not applicable	Very serious imprecision[6]	302	312	TEER v GDMT 10 v 15 HR 0.61 (95% CI 0.27 to 1.36), p=0.23	Important	Low
Functional outcomes (2 RCTs)									
6-minute walk test distance (metres)[78] at 12 months (mean, sd & median, IQR; benefit is indicated by higher result)									
1 RCT Obadia et al 2018	Very serious limitations[11]	No serious indirectness	Not applicable	Not calculable	Baseline: 120 Follow-up: 82 Change: 73[79]	Baseline: 103 Follow-up: 77 Change: 57	Baseline, mean (sd): • PMVR: 301 (126) • OMT: 319 (127) 12 months, mean (sd): • PMVR: 339 (151) • OMT: 363 (157) Change between baseline and 12 months, median (IQR): • PMVR: 25 (-40 to 71) • OMT: 19 (-27 to 75)	Important	Low

[78] The six-minute walk distance test is usually performed on a treadmill and is the distance in metres that the patient can walk in 6 minutes.
[79] Number of patients for whom a change was measured.

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	TEER	Optimised medical management	Result		
6-minute walk test distance (metres) at 12 months (mean, sd; benefit is indicated by higher result)									
1 RCT Stone et al 2018	Serious limitations[10]	No serious indirectness	Not applicable	Not calculable	230	237	TEER v GDMT 256.7 (157.7) v 188.8 (166.7) Change from baseline to 12 months: -4.6 (134.8) v -57.6 (152.5) Adjusted mean change[80], baseline to 12 months: -2.2 (9.1) v -60.0 (9.0), p <0.001	Important	Moderate
6-minute walk test distance (metres) at 24 months (median, IQR; benefit is indicated by higher result)									
1 RCT Iung et al 2019	Very serious limitations[11]	No serious indirectness	Not applicable	Not calculable	Baseline: 120 Follow-up: 66 Change: 59[81]	Baseline: 103 Follow-up: 54 Change: 42	Baseline: • PMVR: 307 (212 to 387) • OMT: 335 (210 to 410) 24 months: • PMVR: 335 (280 to 462) • OMT: 398 (280 to 462[82]) Change between baseline and 24 months: • PMVR: 15 (-18 to 67) • OMT: 22 (-6 to 94)	Important	Low
Safety (2 RCTs)									
Procedural complications (n, %)									
1 RCT Obadia et al 2018	Serious limitations[15]	No serious indirectness	Not applicable	Not calculable	144	n/a	Total complications: 21 (14.6) • Device implantation failure: 6 (4.2) • Haemorrhage resulting in transfusion or vascular complication resulting in surgical intervention: 5 (3.5)	Important	Moderate

[80] Adjusted mean using least squares mean method uses a linear model to calculate the mean and correct for unbalanced design with an interaction. The COAPT trial used a ANCOVA model with baseline score and treatment effect as covariates.
[81] Number of patients for whom a change was measured.
[82] Likely to be incorrectly reported as the IQR is the same as reported for the PMVR group.

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	TEER	Optimised medical management	Result		
							• Atrial septum lesion or atrial septal defect: 4 (2.8) • Cardiogenic shock resulting in intravenous inotropic support: 4 (2.8) • Cardiac embolism, including gas embolism and stroke: 2 (1.4) • Tamponade: 2 (1.4) • Urgent conversion to heart surgery: 0 (0)		
Freedom from device related complications[83] at 12 months (% free from complications at 12 months[84] (95% CI lower estimate)									
1 RCT Stone et al 2018	Serious limitations[10]	No serious indirectness	Not applicable	Not calculable	302	n/a	96.9 (94.8) p <0.001 for comparison with goal of 80.0%	Important	Moderate
Adverse event rates at 30 days (n)									
1 RCT Stone et al 2018	Serious limitations[10]	No serious indirectness	Not applicable	Not calculable	302	312	TEER v GDMT • Stroke: 2 v 0 • Myocardial Infarction: 3 v 0	Important	Moderate
Adverse event rates at 24 months (n; HR)									
1 RCT Stone et al 2018	Serious limitations[10]	No serious indirectness	Not applicable	Very serious imprecision[6]	302	312	TEER v GDMT • Stroke: 11 v 11; HR 0.96 (95% CI 0.42 to 2.22); p=0.93 • Myocardial Infarction: 12 v 14; HR 0.82 (95% CI 0.38 to 1.78); p=0.62	Important	Very low
Prespecified serious adverse events at 12 months (n, %)									
1 RCT Obadia et al 2018	Very serious limitations[13]	No serious indirectness	Not applicable	Not calculable	152	152	PMVR v OMT All serious adverse events: 125 (82.2) v 121 (79.6)	Important	Low

[83] A device related complication was defined as any occurrence of single-leaflet device attachment, embolization of the device, endocarditis that led to surgery, mitral stenosis (as confirmed by the echocardiographic core laboratory) that led to mitral-valve surgery, implantation of a left ventricular assist device, heart transplantation, or any other device-related event that led to nonelective cardiovascular surgery.

[84] Percentages are estimated using the Kaplan-Meier time-to-event methodology.

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	TEER	Optimised medical management	Result		
							• Heart transplantation or mechanical cardiac assistance: 6 (3.9) v 9 (5.9) • Ischaemic or haemorrhagic stroke: 7 (4.6) v 1 (0.7) • Myocardial infarction: 0 (0) v 2 (1.3) • Need for renal-replacement therapy: 5 (3.3) v 1 (0.7) • Severe haemorrhage: 11 (7.2) v 6 (3.9) • Infections: 28 (18.4) v 27 (17.8)		
Prespecified serious adverse events from 12 to 24 months (n, rate per 100 patient-years)									
1 RCT Iung et al 2019	Very serious limitations[13]	No serious indirectness	Not applicable	Not calculable	152	152	PMVR v OMT All serious adverse events: 4 (6.8) v 7 (12.5) • Heart transplantation or mechanical cardiac assistance: 1 (1.7) v 0 (0) • Ischemic or haemorrhagic stroke: 0 (0) v 2 (3.6) • Myocardial infarction: 0 (0) v 1 (1.8) • Need for renal-replacement therapy: 1 (1.7) v 1 (1.8) • Severe haemorrhage: 2 (3.4) v 0 (0) Infections: 4 (6.8) v 3 (5.4)	Important	Low
Prespecified serious adverse events at 24 months (n, rate per 100 patient-years)									
1 RCT Iung et al 2019	Very serious limitations[13]	No serious indirectness	Not applicable	Not calculable	152	152	PMVR v OMT All serious adverse events: 129 (84.9) v 128 (82.1) • Heart transplantation or mechanical cardiac assistance: 7 (4.6) v 9 (5.8)	Important	Low

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	TEER	Optimised medical management	Result		
							• Ischemic or haemorrhagic stroke: 7 (4.6) v 3 (1.9) • Myocardial infarction: 0 (0) v 3 (1.9) • Need for renal-replacement therapy: 6 (3.9) v 2 (1.3) • Severe haemorrhage: 13 (8.6) v 6 (3.8) • Infections: 32 (21.1) v 30 (19.2)		

Abbreviations
CI: confidence interval; COAPT: Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation Trial; GDMT: guideline directed medical therapy; HR: hazard ratio; HRQL: health related quality-of-life; IQR: interquartile range; KCCQ: The Kansas City Cardiomyopathy Questionnaire; m: metres; MI: myocardial infarction; MR: mitral regurgitation; n: number; NNT: number needed to treat; NR: not reported; NYHA: New York Heart Association; OMT: optimal medical therapy; OR: odds ratio; PMVR: percutaneous mitral valve repair; RCT: randomised controlled trial; RR: relative risk; sd: standard deviation; SMR: secondary mitral regurgitation; SRMA: systematic review and meta-analysis; TEER: transcatheter edge to edge repair; v: versus

GRADE table footnotes
1 Risk of bias: serious limitations due to some unbalanced baseline characteristics between the groups and high attrition rate including cross-overs and exclusions which differed between the two groups.
2 Imprecision: serious imprecision due to wide 95% confidence intervals that cross the default minimal clinically important difference upper threshold
3 Risk of bias: very serious limitations due to limited literature search strategy, not utilising a quality checklist specific to RCTs, no assessment of publication bias, and one of the two included RCTs being of moderate risk of bias
4 Inconsistency: very serious inconsistency due to considerable heterogeneity.
5 Risk of bias: serious limitations due to one of the two included RCTs being of moderate risk of bias.
6 Imprecision: very serious imprecision due to very wide 95% confidence intervals that cross the default minimal clinically important difference lower and upper thresholds.
7 Imprecision: serious imprecision due to wide 95% confidence intervals that cross the default minimal clinically important difference lower threshold.
8 Inconsistency: serious inconsistency due to moderate heterogeneity.
9 Risk of bias: very serious limitations due to some unbalanced baseline characteristics between the groups, high attrition rate including cross-overs and exclusions which differed between the two groups and a lack of any statistical analysis or summary statistic.
10 Risk of bias: serious limitations due to lack of blinding.
11 Risk of bias: very serious limitations due to some unbalanced baseline characteristics between the groups, lack of blinding, no statistical significance test results reported, high attrition rate including cross-overs and exclusions which differed between the two groups and high proportion of missing data.
12 Risk of bias: serious limitations due to some unbalanced baseline characteristics between the groups and high attrition rate including cross-overs and exclusions which differed between the two groups.
13 Risk of bias: very serious limitations due to some unbalanced baseline characteristics between the groups, lack of blinding and high attrition rate including cross-overs and exclusions which differed between the two groups.
14 Indirectness: serious indirectness due to lack of a comparator.
15 Risk of bias: serious limitations due to lack of blinding and high attrition rate including cross-overs and exclusions.

Glossary

Adverse event	Any undesirable event experienced by a person while they are having a drug or any other treatment or intervention, regardless of whether or not the event is suspected to be related to or caused by the drug, treatment or intervention.
Baseline	The set of measurements at the beginning of a study (after any initial 'run-in' period with no intervention), with which subsequent results are compared.
Bias	Systematic (as opposed to random) deviation of the results of a study from the 'true' results, which is caused by the way the study is designed or conducted.
Blinding	A way to prevent researchers, doctors and patients in a clinical trial from knowing which study group each patient is in so they cannot influence the results. The best way to do this is by sorting patients into study groups randomly. The purpose of 'blinding' or 'masking' is to protect against bias.
Clinical importance	A benefit from treatment that relates to an important outcome such as length of life and is large enough to be important to patients and health professionals.
Confidence interval (CI)	A way of expressing how certain we are about the findings from a study, using statistics. It gives a range of results that is likely to include the 'true' value for the population. A wide confidence interval indicates a lack of certainty about the true effect of the test or treatment - often because a small group of patients has been studied. A narrow confidence interval indicates a more precise estimate (for example, if a large number of patients have been studied).
Control group	A group of people in a study who do not have the intervention or test being studied. Instead, they may have the standard intervention. The results for the control group are compared with those for a group having the intervention being tested. The aim is to check for any differences. Ideally, the people in the control group should be as similar as possible to those in the intervention group, to make it as easy as possible to detect any effects due to the intervention.
Cost effectiveness study	An analysis that assesses the cost of achieving a benefit by different means. The benefits are expressed in non-monetary terms related to health, such as life years

	gained (that is, the number of years by which life is extended as a result of the intervention). Options are often compared on the cost incurred to achieve 1 outcome (for example, cost per life year gained).
Discounting	Costs and perhaps benefits incurred today have a higher value than costs and benefits occurring in the future. Discounting health benefits reflects individual preference for benefits to be experienced in the present rather than the future. Discounting costs reflects individual preference for costs to be experienced in the future rather than the present.
GRADE (Grading of recommendations assessment, development and evaluation)	A systematic and explicit approach to grading the quality of evidence and the strength of recommendations developed by the GRADE working group.
Hazard ratio (HR)	The hazard or chance of an event occurring in the treatment arm of a study as a ratio of the chance of an event occurring in the control arm over time.
Incremental cost-effectiveness ratio (ICER)	The difference in the change in mean costs in the population of interest divided by the difference in the change in mean outcomes in the population of interest.
Intention-to-treat analysis (ITT)	An assessment of the people taking part in a trial, based on the group they were initially (and randomly) allocated to. This is regardless of whether or not they dropped out, fully adhered to the treatment or switched to an alternative treatment. ITT analyses are often used to assess clinical effectiveness because they mirror actual practice, when not everyone adheres to the treatment, and the treatment people have may be changed according to how their condition responds to it. Studies of drug treatments often use a modified ITT analysis, which includes only the people who have taken at least one dose of a study drug.
Meta-analysis	A method often used in systematic reviews to combine results from several studies of the same test, treatment or other intervention to estimate the overall effect of the treatment.
Minimal clinically important difference	The smallest change in a treatment outcome that people with the condition would identify as important (either beneficial or harmful), and that would lead a person or their clinician to consider a change in treatment.

Objective measure	A measurement that follows a standardised procedure which is less open to subjective interpretation by potentially biased observers and people in the study.
Odds ratio	Compares the odds of something happening in 1 group with the odds of it happening in another. An odds ratio of 1 shows that the odds of the event happening (for example, a person developing a disease or a treatment working) is the same for both groups. An odds ratio of greater than 1 means that the event is more likely in the first group than the second. An odds ratio of less than 1 means that the event is less likely in the first group than in the second group.
Per-protocol analysis	A comparison of treatment groups in a trial that includes only those patients who completed the treatment they were originally allocated to. If done alone, this analysis leads to bias.
PICO (population, intervention, comparison and outcome) framework	A structured approach for developing review questions that divides each question into 4 components: the population (the population being studied); the interventions (what is being done); the comparators (other main treatment options); and the outcomes (measures of how effective the interventions have been).
P-value (p)	The p value is a statistical measure that indicates whether or not an effect is statistically significant. For example, if a study comparing 2 treatments found that 1 seems to be more effective than the other, the p value is the probability of obtaining these results by chance. By convention, if the p value is below 0.05 (that is, there is less than a 5% probability that the results occurred by chance), it is considered that there probably is a real difference between treatments. If the p value is 0.001 or less (less than a 0.1% probability that the results occurred by chance), the result is seen as highly significant. If the p value shows that there is likely to be a difference between treatments, the confidence interval describes how big the difference in effect might be.
Quality-adjusted life year (QALY)	A measure of the state of health of a person or group in which the benefits, in terms of length of life, are adjusted to reflect the quality of life. One QALY is equal to 1 year of life in perfect health. QALYs are calculated by estimating the years of life remaining for a patient following a particular treatment or intervention and weighting each year with a quality-of-life score (on a 0 to 1 scale). It is often measured in terms of the person's

	ability to carry out the activities of daily life, and freedom from pain and mental disturbance.
Randomised controlled trial (RCT)	A study in which a number of similar people are randomly assigned to 2 (or more) groups to test a specific drug, treatment or other intervention. One group (the experimental group) has the intervention being tested, the other (the comparison or control group) has an alternative intervention, a dummy intervention (placebo) or no intervention at all. The groups are followed up to see how effective the experimental intervention was. Outcomes are measured at specific times and any difference in response between the groups is assessed statistically. This method is also used to reduce bias.
Standard deviation (SD)	A measure of the spread, scatter or variability of a set of measurements. Usually used with the mean (average) to describe numerical data.
Statistical significance	A statistically significant result is one that is assessed as being due to a true effect rather than random chance.
Systematic review	A study which involves systematically searching for evidence using pre-defined criteria. Relevant studies are selected and quality appraised. Evidence from multiple studies is extracted and reported and may be combined in a meta-analysis (see above).
Time horizon	The time period over which the main differences between interventions in effects and the use of resources in health and social care are expected to be experienced, taking into account the limitations of the supporting evidence.

References

Included studies

- Bertaina M, Galluzzo A, D'Ascenzo F, Conrotto F, Grosso Marra W, Frea S, et al. Prognostic impact of MitraClip in patients with left ventricular dysfunction and functional mitral valve regurgitation: A comprehensive meta-analysis of RCTs and adjusted observational studies. Int J Cardiol. 2019;290:70-6.
- Cohen DJ, Wang K, Magnuson E, Smith R, Petrie MC, Buch MH, et al. Cost-effectiveness of transcatheter edge-to-edge repair in secondary mitral regurgitation. Heart. 2022;108(9):717-24.
- Giustino G, Lindenfeld J, Abraham WT, Kar S, Lim DS, Grayburn PA, et al. NYHA functional classification and outcomes after transcatheter mitral valve repair in heart failure: The COAPT Trial. JACC Cardiovasc Interv. 2020;13(20):2317-28.
- Iung B, Armoiry X, Vahanian A, Boutitie F, Mewton N, Trochu JN, et al. Percutaneous repair or medical treatment for secondary mitral regurgitation: outcomes at 2 years. Eur J Heart Fail. 2019;21(12):1619-27.
- Lodhi MU, Usman MS, Siddiqi TJ, Khan MS, Khan MAA, Khan SU, et al. Percutaneous mitral valve repair versus optimal medical therapy in patients with functional mitral regurgitation: a systematic review and meta-analysis. J. 2019;2019:2753146.
- Obadia JF, Messika-Zeitoun D, Leurent G, Iung B, Bonnet G, Piriou N, et al. Percutaneous repair or medical treatment for secondary mitral regurgitation. N Engl J Med. 2018;379(24):2297-306.
- Shore J, Russell J, Frankenstein L, Candolfi P, Green M. An analysis of the cost-effectiveness of transcatheter mitral valve repair for people with secondary mitral valve regurgitation in the UK. J Med Econ. 2020;23(12):1425-34.
- Stone GW, Lindenfeld J, Abraham WT, Kar S, Lim DS, Mishell JM, et al. Transcatheter mitral-valve repair in patients with heart failure. N Engl J Med. 2018;379(24):2307-18.
- Zimarino M, Ricci F, Capodanno D, De Innocentiis C, Verrengia E, Swaans MJ, et al. Left ventricular size predicts clinical benefit after percutaneous mitral valve repair for secondary mitral regurgitation: a systematic review and meta-regression analysis. Cardiovasc Revasc Med. 2020;21(7):857-64.

NHS England
Wellington House
133-155 Waterloo Road
London
SE1 8UG