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MOHAMMED T. ANSARI, MBBS, MMEDSC, MPHIL,[1] NADERA AHMADZAI, MD, MPH, MSC,[1] KATHRYN COYLE, BSCPHARM, MSC,[2] DOUG COYLE, MA, MSC, PHD,[3] DAVID MOHER, PHD[1]

1. Ottawa Hospital Research Institute, Ottawa, Ontario
2. Brunel University London, Uxbridge, Middlesex, England, United Kingdom
3. Department of Epidemiology and Community Medicine, University of Ottawa, Ottawa, Ontario

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ABSTRACT

Background

Many of the 500,000 North American patients with chronic mitral regurgitation may be poor candidates for mitral valve surgery.

Objective

The objective of this study was to investigate the comparative effectiveness, harms, and cost-effectiveness of percutaneous mitral valve repair using mitral valve clips in candidates at prohibitive risk for surgery.

Data Sources

We searched articles in MEDLINE, Embase, and the Cochrane Library published from 1994 to February 2014 for evidence of effectiveness and harms; for economic literature we also searched NHS EED and Tufts CEA registry. Grey literature was also searched.

Review Methods

Primary studies were sought from existing systematic reviews that had employed reliable search and screening methods. Newer studies were sought by searching the period subsequent to the last search date of the review. Two reviewers screened records and assessed study validity. We used the Cochrane risk of bias tool for randomized, generic assessment for non-randomized studies, and the Phillips checklist for economic studies.

Results

Ten studies including 1 randomized trial were included. The majority of the direct comparative evidence compared the mitral valve clip repair with surgery in patients not particularly at prohibitive surgical risk. Irrespective of degenerative or functional chronic mitral regurgitation etiology, evidence of effectiveness and harms is inconclusive and of very low quality. Very-low-quality evidence indicates that percutaneous mitral valve clip repair may provide a survival advantage, at least during the first 1 to 2 years, particularly in medically managed chronic functional mitral regurgitation. Because of limitations in the design of studies, the cost-effectiveness of mitral valve clips in patients at prohibitive risk for surgery also could not be established.

Limitations

Because of serious concerns of risk of bias, indirectness, and imprecision, evidence is of very low quality.

Conclusions

No meaningful conclusions can be drawn about the comparative effectiveness, harms, and cost-effectiveness of mitral valve clips in the population with chronic mitral regurgitation who are at prohibitive risk for surgery.

PLAIN LANGUAGE SUMMARY

Chronic mitral regurgitation is a long-standing abnormal leakage of blood back into 1 of the heart chambers as the heart attempts to pump blood to the rest of the body. It occurs because the mitral valve is either anatomically distorted or functionally abnormal. Severe chronic mitral regurgitation is debilitating and requires corrective cardiac surgery. But many of the 500,000 patients in North America who have chronic mitral regurgitation are elderly and for various reasons are at prohibitive risk for surgery. For such patients, an approach has been proposed that involves a catheter puncturing the skin of the groin and travelling all the way to the affected valve to deploy a device that clips and repairs the valve leaflets (a mitral valve clip). This investigation sought to compare the effectiveness and cost-effectiveness of mitral valve clips with current standards of care in patients at high or prohibitive risk for surgery. To address this uncertainty, we searched, critically appraised, and collated existing research evidence.

We found sparse, very-low-quality evidence related to mitral valve clips. Most of the evidence was in populations not particularly at high risk for surgery. Important limitations in the design, conduct, and size of the studies precluded definitive conclusions about the relative effectiveness, harms, and cost-effectiveness of mitral valve clips when compared with conservative management in patients at prohibitive risk for surgery.

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LIST OF ABBREVIATIONS

ACCESS-EU	ACCESS-Europe
AMSTAR	Assessment of Multiple Systematic Reviews
CI	Confidence interval
COAPT	Cardiovascular Outcomes Assessment of the MitraClip Therapy Percutaneous Therapy for High Surgical Risk Patients
DARE	Database of Abstracts of Reviews of Effect
EuroSCORE	European System for Cardiac Operative Risk Evaluation
EVEREST	Endovascular Valve Edge-to-Edge Repair Study
FDA	US Food and Drug Administration
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HRS	High Risk Study
HTA	Health technology assessment
LV	Left ventricular
MR	Mitral regurgitation
NICE	National Institute for Health and Care Excellence
NYHA	New York Heart Association
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses
RCT	Randomized controlled trial
REALISM	Real World Expanded Multi-center Study of the MitraClip System
RESHAPE-HF	Randomized Study of the MitraClip Device in Heart Failure Patients With Clinically Significant Functional Mitral Regurgitation
SAE	Serious adverse event
SR	Systematic review
STS	Society of Thoracic Surgeons
TRAMI	Transcatheter mitral valve interventions
TRIP	Turning Research Into Practice
WHO	World Health Organization

BACKGROUND

Objective of Analysis

This evidence-based analysis aims to collate extant evidence regarding mitral valve clips with a view to minimizing bias to answer the following research questions:

- For symptomatic patients at high or prohibitive surgical risk, what are the comparative effectiveness, harms, and cost-effectiveness of percutaneous mitral valve repair using mitral valve clips?
- What are the important population effect modifiers?

Clinical Need and Target Population

Description of Condition

Mitral regurgitation (MR) is an abnormal backflow of blood into the left atrium during cardiac systole that is normally prevented by the bicuspid mitral valve. It is caused by a mitral apparatus dysfunction with potential for hemodynamic compromise. (1) The mitral apparatus is a 3-dimensional functional valvular unit that comprises the left atrial wall, mitral annulus, 2 mitral valve anteromedial and posterolateral leaflets, subvalvular chordae tendineae, papillary muscles, and adjacent left ventricular wall. (1)

Mitral regurgitation can be acute or chronic. Acute MR is a medical and surgical emergency and is invariably treated surgically. (2) For chronic MR, repair or replacement of the mitral valve is the current standard of care when patients become symptomatic with severe MR, dilated ventricles, new-onset atrial fibrillation, or pulmonary hypertension. (2) However, to prevent downstream complications, mitral valve repair or replacement may also be considered prophylactically in select asymptomatic patients. For example, in patients with flail leaflets (see below), early mitral valve surgery in asymptomatic patients was found to be more beneficial than watchful waiting. (3) In fact, it has been estimated that flail mitral valve leaflets will invariably require surgery within 10 years of diagnosis. (4)

Chronic MR is etiologically heterogeneous. The 2 most common categories are *degenerative* (myxomatous/fibroelastic deficiency causing flail leaflets or floppy valve leading to ineffective coaptation) and *functional*. (5) In functional MR, the mitral apparatus is structurally normal but its geometry is distorted. This may occur with left ventricular dilatation, ventricular remodelling, or dyssynchronous contraction of the left and right ventricles as observed post–myocardial infarction or in cardiomyopathy. (6) Surgical treatment of functional MR is less well established. (7)

Surgical correction of MR may employ valve repair or replacement (with or without preservation of the mitral apparatus). Surgical mitral valve repair is the treatment of choice in most cases because it preserves the mitral apparatus and competence, and does not require the lifelong anticoagulation needed if the valve were replaced with a prosthetic device. (8) Similar rates of reoperation (a postsurgical complication) have been observed following both valve repair and replacement, that is, about 20% over 19 years. (9) Despite the availability of the valvular repair option, the risk of undertaking the surgery may be too high or prohibitive; the Society of Thoracic Surgeons (STS) states that the risk of mortality is ≥ 8%. (10) In general this translates into a subgroup of symptomatic patients who are elderly, are frail, have several comorbidities, and have a history of previous cardiac procedures and/or hemodynamic instability. One meta-

analysis has reported a pooled 5-year survival rate of 23% (95% confidence interval [CI], 12%–39%) in octogenarians undergoing surgical mitral valve repair. (11) As per another categorization, the risk of surgery is highest in those with a left ventricular (LV) ejection fraction < 0.6, an LV end-systolic dimension > 40 mm, or New York Heart Association (NYHA) class III or IV symptoms. (2)

As alternatives to surgery, various mitral valve repair procedures that employ a percutaneous approach are under investigation, such as edge-to-edge leaflet repair and indirect and direct annuloplasties. (5) In theory, percutaneous mitral valve repair would decrease the short-term risk of operative mortality and morbidity while increasing survival rates and quality of life.

Prevalence and Incidence

With prevalence rates as high as 9% in the elderly population aged ≥ 75 years, MR is the most common valvular abnormality observed in population-based studies. (12) About 50% of cases of isolated chronic MR may be of the severe symptomatic grade 3+/4+ variety, of which 49% may be at prohibitive risk for surgery. (13) By another estimation, many of the 500,000 North American patients with chronic MR may be poor candidates for mitral valve surgery. (14)

Technology/Technique

The mitral valve clip is one percutaneous mitral valve repair option, first used in humans in 2003. (15) The mitral valve clip system consists of the clip device, a delivery system, and a catheter guide through which the delivery system is introduced trans-septally into the left atrium toward the mitral valve through a femoral venous approach. Mitral valve clips have been implanted in more than 10,000 patients. (7) The clip device is conceptually based upon the commonly employed surgical edge-to-edge Alfieri technique of suturing the opposing leaflets in the middle, thereby creating 2 orifices for blood flow across the mitral opening. (16;17)

Regulatory Status

In October 2013, the US Food and Drug Administration (FDA) approved mitral valve clips for use in patients with symptomatic MR (≥ 3+) of degenerative etiology who are at prohibitive risk for mitral valve surgery. (18) Clinical studies that supported this approval were these:

- Endovascular Valve Edge-to-Edge Repair Study (EVEREST) I, a feasibility study
- EVEREST II, a randomized controlled trial (RCT)
- EVEREST II High Risk Registry study, a single arm-registry study
- Real World Expanded Multi-center Study of the MitraClip System (REALISM) High Risk and REALISM Non-High Risk, continued access registry studies

In Europe, since the CE Marking approval in 2008, the device has been used in German and Italian centres primarily in patients with functional MR with low ejection fractions, and it has shown favourable acute and short-term outcomes based on longitudinal follow-up registry data (transcatheter mitral valve interventions [TRAMI] and ACCESS-Europe [ACCESS-EU] registries). (19;20) The Cardiovascular Outcomes Assessment of the MitraClip Therapy Percutaneous Therapy for High Surgical Risk Patients (COAPT) and the Randomized Study of the MitraClip Device in Heart Failure Patients With Clinically Significant Functional Mitral Regurgitation (RESHAPE-HF) are ongoing studies in high-risk patients with functional MR. (21)

There is only one mitral valve clip device approved for use in Canada for significant symptomatic degenerative mitral regurgitation (MR ≥ 3+) in patients who have been determined to be too high risk for mitral valve surgery by a heart team, including a cardiac surgeon, and in whom existing co-morbidities would not preclude the expected benefit from correction of the mitral regurgitation. The MitraClip system (licence number 93117) was approved on April 17, 2014, by Health Canada.

EVIDENCE-BASED ANALYSIS

Research Questions

- For symptomatic patients at high or prohibitive surgical risk, what are the comparative effectiveness, harms, and cost-effectiveness of percutaneous mitral valve repair using a mitral valve clip?
- What are the important population effect modifiers?

Research Methods

The methodological approach to evidence searching and synthesis conformed to the Cochrane Collaboration's methods guidance and followed an a priori protocol. As a priority, evidence was sought from the most recent and relevant existing systematic reviews (SRs) and health technology assessments (HTAs) if the documents included a broad and transparently reported search strategy, an appraisal of the validity of included studies, and a synthesis of the primary evidence aimed at minimizing bias. The search strategy had to report databases searched, search end dates, and screened identified studies using predefined eligibility criteria in order for the review to qualify as an SR and be assessed further for methodological rigour. If the evidence synthesis of available SRs/HTAs did not incorporate the risk of bias, but the searching and screening of literature were judged to be well conducted (i.e., reporting having searched at least 2 databases with 1 being MEDLINE; search end dates; and more than 1 reviewer screening), we used the most recent SR to identify relevant primary studies. Subsequent bibliographical searches updated the original review search, followed by a de novo evidence synthesis of originally included and newly identified studies.

Literature Search

A literature search was performed on January 26, 2014, using Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, and Embase using the OVID platform, for studies published within the past 10 years. (Appendix 1 provides details of the literature search strategies). We also searched the Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effect (DARE) on Wiley, NHS EED, and Tufts CEA registry. A focused grey literature search was undertaken using the Turning Research Into Practice (TRIP) database and the World Health Organization (WHO) Trial Registry, which also searches www.clinicaltrials.gov. A subsequent search to identify primary studies was performed on February 7, 2014. We applied a filter to identify SRs and HTAs and a separate filter for economic studies. While screening titles or abstracts, a single reviewer included eligible records; a second reviewer rescreened excluded records as an additional consideration. Full texts of included records were obtained and screened by 2 reviewers. Discrepancies were resolved by consensus or by involving a third team member. Systematic reviews were screened in reverse chronological order to identify 1 or 2 reviews with reliable search or methodological quality. Further, we screened primary literature to update the searches of identified reviews—searches overlapped by 6 months. Economic literature was searched and screened separately. Along with our a priori outcomes of interest, record eligibility criteria are reported below. Note, we did not exclude studies by outcomes.

Inclusion Criteria

- Population: symptomatic patients (NYHA class III or IV) with moderate or severe MR (3+ or 4+) of chronic functional or degenerative etiology who are at high or prohibitive risk for

surgical mitral valve repair or replacement (i.e., those who have a high risk based on STS score, or elderly with patients who have undergone previous cardiac surgery)
- Intervention: mitral valve clip
- Comparator: current standards of care—that is, surgical mitral valve repair or replacement or conservative medical treatment
- Study designs and other criteria: SRs, HTAs, RCTs, comparative observational studies (including registry data), and full economic evaluations (i.e., cost-effectiveness analyses, cost-utility analyses, and cost-benefit analyses) reported in the English language

Exclusion Criteria

- Studies involving populations with rheumatic heart disease, NYHA class I or II symptoms, and acute MR

Outcomes of Interest

- Procedure-related adverse events (30-day mortality, 30-day stroke, cardiac perforation, blood transfusion requirement)
- 1-year all-cause mortality
- NYHA class at 12 months
- Quality of life
- Readmission rates during the first 12 months
- Recurrent (grade 3+ or 4+) MR at 12 months
- Total serious adverse events (SAEs)
- Ventricular remodelling (absolute end-systolic volume or change in end-systolic volume at 12 months)
- Incremental cost-effectiveness

Risk of Bias Assessment

Primary study risk of bias was judged using the Cochrane risk of bias tool for RCTs. Generic assessment was employed to judge the risk of selection bias, confounding, and information bias (for a hypothetical target trial) for observational studies, and Phillips checklist was used to evaluate the methodological rigour of primary economic evaluations. For outcomes that were to be graded, publication bias was planned to be investigated when there were ≥ 10 studies contributing data for an outcome, studies were of unequal sizes, there were no important clinical and methodological differences between smaller and larger studies, and quantitative results were reported with accompanying measures of dispersion.

Synthesis of Evidence

Given the heterogeneity in comparative evidence, no meta-analysis could be performed. For the synthesis of the economic literature, we first identified common methodological issues within studies. Each study was assessed through a 3-step process: initial assessment for validity, assessment of the overall study quality (use of the Phillips checklist), and assessment of the study's quality and pertinence to the decision question. The focus was on the validity of evidence addressing cost-effectiveness of percutaneous mitral valve repair using a mitral valve clip when compared with the current standards of care. We also attempted to identify optimal patient subpopulations. Exploration of effect modification, especially by MR etiology, was planned but was not possible because of few studies contributing evidence.

Quality of Evidence

Using GRADEprofiler (version 3.6), the quality of the body of evidence for each a priori important outcome was judged according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group criteria as high, moderate, low, or very low. (22)

Study design was the first consideration; the starting assumption was that RCTs are high quality, whereas observational studies are low quality because of concerns about residual and unmeasured confounding, even when some adjustments for confounding were made. Five additional factors—risk of bias, inconsistency, indirectness, imprecision, and publication bias—were then taken into account. Limitations in these areas resulted in downgrading the quality of evidence. None of the 3 optional domains that may raise the quality of evidence could be invoked.

As stated by the GRADE Working Group, the final quality score can be interpreted using the following definitions:

High	High confidence in the effect estimate—the true effect lies close to the estimate of the effect
Moderate	Moderate confidence in the effect estimate—the true effect is likely to be close to the estimate of the effect, but may be substantially different
Low	Low confidence in the effect estimate—the true effect may be substantially different from the estimate of the effect
Very Low	Very low confidence in the effect estimate—the true effect is likely to be substantially different from the estimate of the effect

Results of Evidence-Based Analysis

Search Yield

The database search yielded 737 citations (with duplicates removed). Of these, 683 articles were excluded based on information in the title and abstract. The full texts of 54 potentially relevant articles (13 reviews, and 41 primary studies) were obtained for further assessment. In total, 17 records were included (2 reviews (23;24) and 15 primary studies (7;25-38)). Figure 1 shows the breakdown of when and for what reason citations were excluded from the analysis.

Study Selection

We screened the literature obtained using 3 separate search strategies. Strategies retrieved the following:

a. SRs addressing effectiveness and harms of mitral valve clips
b. Economic literature (primary or secondary studies) from Embase and MEDLINE, NHS EED, and Tufts CEA registry
c. New primary studies of effectiveness and harms of mitral valve clips from searches that updated the SRs identified in strategy *a* (above)

Records Addressing Effectiveness and Harms of Mitral Valve Clips

For effectiveness and harms of mitral valve clips, we identified 70 potential SRs from electronic searches and grey literature. Additionally, 1 SR that was not captured in the literature search was nominated by 1 of the reviewers. (23) Of these, 13 passed the title and abstract screening. (23;24;39-49) We screened the full-text reviews in reverse chronological order (latest to earliest) and stopped as soon as we identified a recent and relevant SR with adequate quality based on a priori–stipulated criteria. We included 2 SRs published in 2013 and 2014. (23;24) These SRs were deemed to have employed reliable search strategies (i.e., at least 2 databases [1 of which was MEDLINE] were searched, end dates and key search terms were reported), but their evidence synthesis was not judged to have been undertaken with a view to minimizing bias. Assessment of Multiple Systematic Reviews (AMSTAR) scores for the 2 reviews were 4 and 7, respectively, out of a total of 11. As such, we used the 2 SRs to identify 36 relevant primary included studies.

We added new evidence to the 36 SR-identified studies by searching MEDLINE, Embase, and the Cochrane Library for primary studies of effectiveness and harms, with an overlap of 3 months from the earlier of the 2 last search dates of the reviews; that is, our start search period was January 2013. (23) Our updating searches (see strategy *c* in "Study Selection," above) retrieved 476 new records. We additionally brought in 9 records previously flagged as potentially relevant primary studies while screening the economic literature (see strategy *b* in "Study Selection," above). (27;36;50-56) After de-duplication, a total of 484 records formed the database of potential records of primary studies of the effectiveness and harms of mitral valve clips. Of the 484 records, 36 passed to full-text screening on a title and abstract screening. Following our full-text screening, 13 were records were included. (25-37)

Records Addressing Economic Evaluation of Mitral Valve Clips

For the economic evaluation of mitral valve clips, searches retrieved 141 records (see strategy *b* in "Study Selection," above). In total, 136 of 141 were excluded based on the title and abstract screening, with 2 studies finally included after the full-text screening. (7;38) The reference lists of the included economic studies were hand searched, but no additional citations were identified; however, 3 previous technology appraisals from the perspectives of Australia, New Zealand, and the United Kingdom were flagged to inform the discussion. (57-59) Figure 1 presents the flow diagram for the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA). Further details of the screening process are reported in Appendix 5. Appendix 4 presents the list of the included and excluded studies.

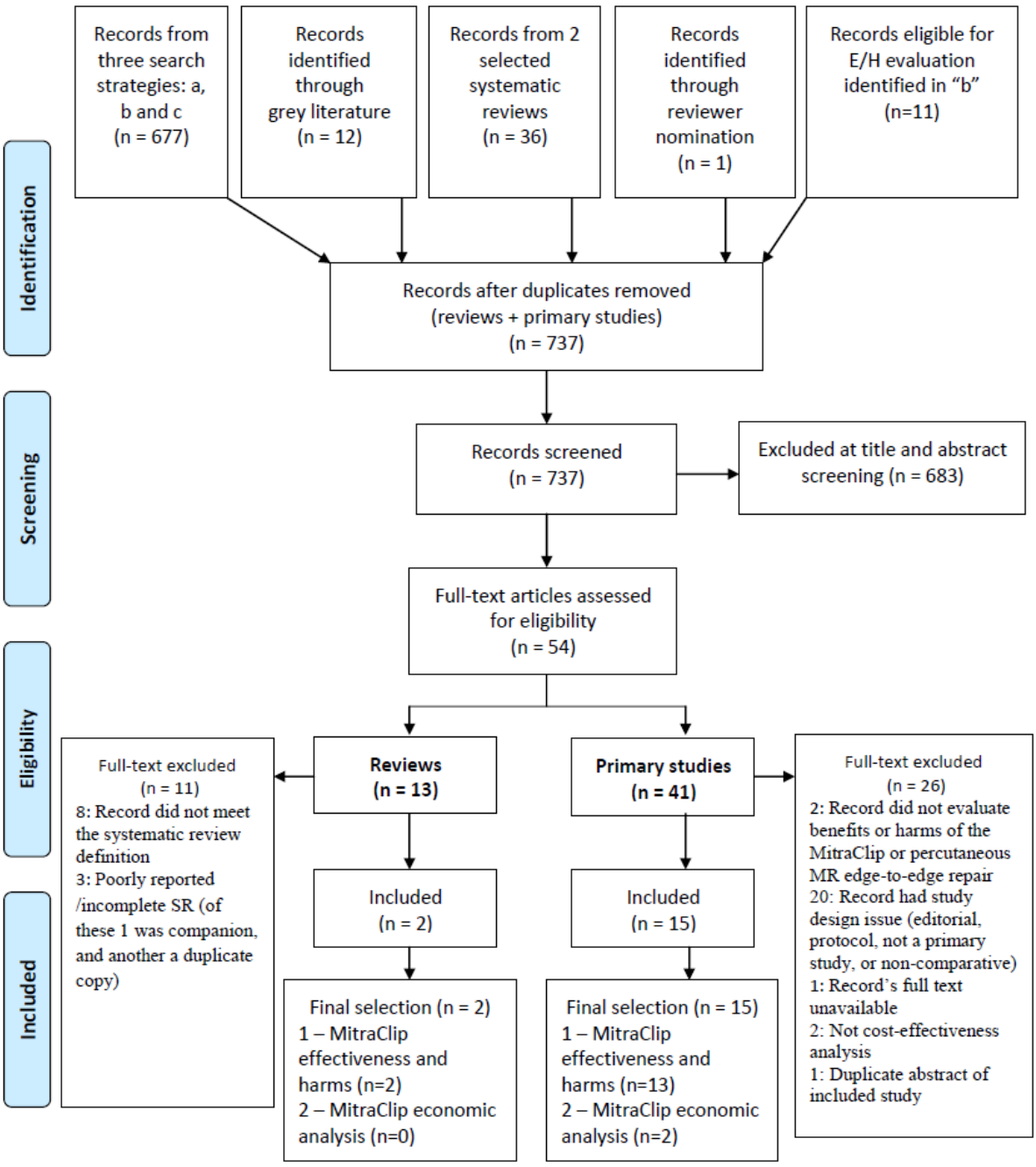

Figure 1: PRISMA Flow Diagram for the Effectiveness and Harms of Mitral Valve Clip, and Economic Review

Abbreviations: E/H, effectiveness and harms; MR, mitral regurgitation; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses; SR, systematic review.
Search strategies: (a) SRs addressing effectiveness and harms of mitral valve clips; (b) economic literature (primary or secondary studies) from Embase and MEDLINE, NH SEED, and Tufts CEA registry; (c) new primary studies of effectiveness and harms of mitral valve clips from searches that updated SRs identified in "a" above.

Summary of Included Studies and Methodological Rigour

For each included study, the study design was identified and is summarized below in Table 1.

Table 1: Included Studies According to Study Design

Study Design	Number of Eligible Studies	Cost-Effectiveness Studies
Randomized controlled trial	1	1
Comparative cohort design	4	1
Interrupted time series	1	0
Uncontrolled before-after study	2	0
Total	**8**	**2**

A total of 8 studies reported as 13 records were included as effectiveness and harms evidence. We identified 1 of the 5 records of the EVEREST II trial as the primary study, (25) with the remaining as its companion reports. (34;36;37;60) Seven of 8 studies were observational study designs: 4 were comparative cohort studies, (26;27;29;30) 2 were predicted-versus-observed mortality before-after studies, (31;32) and 1 was an interrupted time series. (28)

Table 2 summarizes the characteristics of these studies. Detailed evidence tables are reported in Appendix 3. Detailed risk of bias assessments of individual studies are presented in Appendix 2. Five of 7 observational studies were judged to be at high risk of bias because of important concerns about confounding or attrition/selection bias. (26-30) Conradi et al's cohort study, however, was considered to be at low risk of bias for the outcome of mortality at 6 months because the reported estimate of effect adjusted for important confounders; these data, though, did not contribute to our prespecified analysis of 1-year mortality. (27) The remaining 2 non-randomized studies of observational design were deemed to have an unclear risk of bias because of insufficiently reported information. (31;32) The randomized study was assessed either as low or high risk of bias for the various outcomes of interest. Outcome-specific risk-of-bias assessments are reported in Appendix 2. Two of 8 studies were judged to have good applicability to our population of interest; that is, they involved patients at high or prohibitive risk of surgical mortality. (27;31)

Details on the 2 included studies in the economic evaluation of mitral valve clips are presented in the section "Cost-Effectiveness of Mitral Valve Clips." Published as an abstract, the cost-effectiveness analysis based on the EVEREST II trial data by Reynolds et al was judged to be of low quality.(38) Mealing et al's cost-effectiveness decision-analytic model with data from the EVEREST II High Risk Study (HRS) was considered of moderate validity because it met many of the criteria of the Phillips checklist, but it lacked in key areas such as the quality of the source of efficacy data and assumptions regarding effectiveness of the treatment and comparator within the model. (7) Detailed Phillips checklist assessments are reported in Appendix 2.

Post Hoc Changes or Decisions

Table 2: Characteristics of Included Primary Studies

Authors, Year	Industry Funding	Study Design	Applicability to Population at Prohibitive Risk for Surgery	Intervention	Comparator (If Applicable)	Maximum Duration for the Study
Mauri et al, 2013 (25) Conradi et al, 2013 (26) Conradi et al, 2013 (28) Paranskaya et al, 2013 (29) Ajello et al, 2013 (30) Schau et al, 2013 (31) Buzzatti et al, 2013 (32) Whitlow et al, 2012 (27)	Yes (n = 3) (25-27) No (n = 0) NR (n = 5) (28-32)	RCT: n = 1 (25) Comparative observational: n = 7 (26-32), particularly: cohort: n = 4 (26;27;29;30); before-after time series n = 1 (28); prognostic modelling based on baseline characteristics: n = 2 (31;32)	High: n = 1 (27) Low: n = 2 (25;29) Mix of low–high: n = 2 (26;30) Unclear: n = 3 (28;31;32)	Mitral valve clip	Surgery: n = 3 (25;26;29) Surgery or conservative treatment: n = 1 (30) Conservative treatment/standard care: n = 1 (27) n/a: n = 3 (28;31;32)	4 y: n = 2 (25;28) 2 y: n = 2 (28;32) About 1 y: n = 3 (27;29;30) 6 mo: n = 1 (26) NR: n = 1 (31)

Abbreviations: n/a, not applicable; NR, not reported; RCT, randomized controlled trial.

We had planned to include comparative study designs, that is, at least 2 intervention and comparator independent groups. In a post hoc decision, we included specific before-after designs because they compared observed outcomes against a virtual counterfactual (i.e., predicted outcomes) originating in validated risk prediction models. (31;32) We also included an interrupted time series because it investigated the impact of the mitral valve clip program on surgical mitral valve activity—a design that is acceptable for causal inference, especially for program-directed interventions. (28) Also, for prespecified effectiveness outcomes that were planned for specific time points, we extracted and synthesized longer-term data when reported (e.g., planned outcome of 1-year all-cause mortality, as well as post hoc synthesis for all-cause mortality at 4 years, when reported). Lastly, we synthesized evidence on important investigator-defined adverse events as reported across the studies that were not prespecified in the protocol.

Comparative Effectiveness and Harms

Appendix 2 includes the assessment of the risk of bias for individual outcomes based on the Cochrane risk of bias tool for randomized studies, and based on design-specific key features such as selection, information, and confounding biases for observational studies. Detailed GRADE tables are also reported in Appendix 2.

Mortality

Evidence for mortality is summarized in Table 3.

Table 3: Summary of Evidence for Mortality

No. of Studies	Total No. of Patients	Study Design	Applicability
6 (25;27;29-32)	1,030 (sample size range: 50–279)	• 1 randomized controlled trial • 3 cohort • 2 before-after with predicted-versus-observed outcome comparison	Only 2 cohort studies were considered to be in patients at high risk for surgery (27;31)

Four of 6 studies were judged to be at high overall risk of bias for this outcome measured at 1 year; 3 studies also reported longer-term data (2–4 years). (25;27;29;30) Two studies published as abstracts were rated as having an unclear risk of bias because of a lack of detailed information about the study conduct. (31;32) Methodological and clinical diversity across studies precluded quantitative synthesis. Overall, studies were underpowered, yielding fragile estimates even when they were reported as significant. Because studies were clinically and methodologically quite heterogeneous, yet more or less equally at risk of bias, we judged the quality of evidence for each individually. Across studies, findings were inconsistent, possibly due to clinical and methodological differences between them (Table 4). Mortality effect estimates were inconclusive when mitral valve clips were compared with surgery. However, very low quality of evidence (or reviewers' confidence) signals that compared with conservative medical treatment, mitral valve clips might reduce 1- to 2-year mortality in those with chronic functional MR, a population often at high risk for surgery.

Table 4: Comparative Evidence for the Outcome of Mortality (≥ 1 Year's Duration)

Study and Design, Funding	Population	Total Sample Size	Comparator	Risk of Bias	Mortality (1 y Unless Specified and Highlighted)	Quality of Evidence[a]
EVEREST II RCT, (25) Abbott Vascular	• MR etiology: mixed (majority degenerative) • Surgical risk: low • NYHA III/IV = 50% • MR status: 3+/4+ • EF > 25%	279	Surgery	High 21% of patients receiving a mitral valve clip had subsequent surgery Attrition bias 4-y data	16 events RR, 1.08 (95% CI, 0.39–3.02) ARD = 4 more per 1,000 (from 34 fewer to 113 more)	Very low
					4-y mortality: 41 events RR, 0.98 (95% CI, 0.54–1.77) ARD = 4 more per 1,000 (from 82 fewer to 137 more)	Very low
Paranskaya et al, Germany, cohort, (29) NR	• MR etiology: mixed (majority degenerative) • Surgical risk: low • NYHA III/IV = 92% • MR status: 3+/4+ • EF > 45%	50	Surgery	High Prognostic imbalance and variable duration of follow-up	2 events with mitral valve clips (not estimable)	Very low
Ajello et al, Italy, cohort, as abstract only, (30) NR	• MR etiology: functional • Surgical risk: mixed • NYHA III/IV = 62% • MR status: 3+/4+ (92%) • EF mean = 27%	160	Surgery and conservative management equally distributed	High Selection bias (subset of data from the 2 groups were analyzed) and confounding	**Favours mitral valve clips** Actuarial survival = 88.9 ± 3.5% vs 69.5 ± 7.3% (*P* = 0.002)	Very low
					2-y mortality**:** **Favours mitral valve clips** Actuarial survival = 80.2 ± 5.2% vs 57.0 ± 8.1% (*P* = 0.002)	Very low

Study and Design, Funding	Population	Total Sample Size	Comparator	Risk of Bias	Mortality (1 y Unless Specified and Highlighted)	Quality of Evidence[a]
Buzzatti et al, before-after (predicted vs observed mortality), abstract only, (32) NR	• MR etiology: mixed (70% functional) • Surgical risk: unclear • NYHA III/IV = 78% • MR status: 3+/4+ (NR) • EF mean = 36%	135	SHFM risk prediction (assumed a proxy for conservative management)	Unclear Some concerns about completeness of data and validity of SHFM risk prediction	**Favours mitral valve clips for functional MR[b]** RD, 9.1% (95% CI, 3.1–15.1) Degenerative MR, RD = 11.1% (95% CI, −19.7 to 41.9)	Very low
					2-y mortality**:** **Favours mitral valve clips for functional MR[b]** RD, 12.1% (95% CI, 3.1–15.1) Degenerative MR, RD, 22.2% (95% CI, −24.8 to 69.2)	Very low
EVEREST II HRS, cohort, (27) Abbott Vascular	• MR etiology: mixed (58% functional) • Surgical risk: high (some uncertainty) • NYHA III/IV ≥ 80% • MR status: 3+/4+ • EF mean = 54% (excluded < 20%)	114	Conservative management and surgery (14%)	High Selection bias (post hoc control group) and confounding by indication	**Favours mitral valve clips** 35 events RR, 0.55 (95% CI, 0.32–0.94)	Very low
Schau and Neuss et al, Germany, before-after (predicted vs observed mortality), abstract only, (31;61) NR	• MR etiology: mixed (73% functional) • Surgical risk: high • NYHA III/IV • MR status: 3+/4+ • EF: NR **Duration of follow-up NR** but probably > 6 mo	155	SHFM risk prediction (assumed a proxy for conservative management)	Unclear Some concerns about completeness of data and validity of SHFM risk prediction	Qualitative results showing no difference in predicted vs observed survival rate	Very low

Abbreviations**:** ARD, absolute risk difference; CI, confidence interval; EVEREST, Endovascular Valve Edge-to-Edge Repair Study; EF, ejection fraction; HRS, High Risk Study; MR, mitral regurgitation; NR, not reported; NYHA, New York Heart Association; RD, risk difference; RR, relative risk; SHFM, Seattle Heart Failure Model.

[a]Quality of evidence (or reviewers' confidence in estimates of effect) was graded as per the guidelines of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group. Randomized trial evidence was provisionally assigned quality that was downgraded because of very serious concerns about the validity of evidence, its applicability to medically manage patients with chronic MR at prohibitive risk, and the fragility of estimates of effect given event rate, sample size, and the width of CI (optimal information size criteria). Observational evidence was provisionally assigned an initial rating of low that was further downgraded because of our very serious concerns about its validity, applicability to the population and comparator of interest, and/or optimal information size criteria. No upgrading criteria were met for observational studies.

[b]Confidence intervals estimated from *P* values.

Quality of Life

Quality of life data were rarely reported across studies. The EVEREST II RCT judged to be at high risk of bias for this outcome included patients deemed to be good surgical candidates. Quality of life was measured with the Short-Form Health Survey. (25) At 1 year no significant differences were noted in physical and mental domains between the mitral valve clip and surgery treatment arms, although the outcomes showed significant improvement from baseline in both groups of about 4 to 5 points on a scale of 100 (Table 5).

Table 5: Mitral Valve Clip Versus Mitral Valve Surgery for Mitral Regurgitation—Quality of Life at 12 Months

Quality Assessment							No. of Patients		Effect		Quality
No. of Studies	Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Mitral Valve Clip	Surgery	Relative (95% CI)	Absolute	
Quality of life (physical component)[a]											
1 (25)	Randomized trial	Very serious[b]	No serious inconsistency	Very serious[c]	No serious imprecision	None	132	60	–	MD 0 higher (3.1 lower to 3.1 higher)	⊕OOO VERY LOW
Quality of life (mental component)[a]											
1 (25)	Randomized trial	Very serious[b]	No serious inconsistency	Very serious[c]	No serious imprecision	None	133	60	–	MD 1.9 higher (−1.2 lower to 5.0 higher)	⊕OOO VERY LOW

Abbreviations: CI, confidence interval; MD, mean difference.
[a]Follow-up mean 1 y; measured with Short Form Health Survey; range of scores: 0–100, with better indicated by higher values.
[b]High risk of detection bias, attrition bias, and confounding.
[c]Low applicability because good surgical candidates.

Patients in NYHA Class III/IV

One-Year Follow-Up

Table 6: Summary of Evidence for Patients in NYHA Class III/IV at 1 Year

No. of Studies	Total No. of Patients	Study Design	Applicability
2 (25;29)	329 (sample size range: 50–279)	• 1 randomized controlled trial • 1 cohort	Low applicability based on surgical mortality risk

Abbreviations: NYHA, New York Heart Association.

A summary of the evidence for patients in NYHA class III/IV at 1 year is presented in Table 6. Both of the 2 contributing studies were judged to be at high risk of bias for this outcome given various concerns about selection/attrition bias and confounding. (25;29) Patients in NYHA class III/IV were comparable in proportions at baseline for the mitral valve clip and surgery arms. At 1-year follow-up, a total of 15 patients across both studies were in NYHA class III/IV—sparse data yielding very fragile comparative estimates. We judged the evidence to be grossly underpowered and biased for any meaningful causal inference but formally rated our confidence for the RCT evidence (Table 7). Note that about 50% of the trial population was in NYHA class III/IV at baseline. In the cohort study, 46 of 50 patients were in NYHA class III/IV at baseline but only 3 remained in, or later progressed to, this functional category.

Table 7: Mitral Valve Clip Versus Mitral Valve Surgery for Mitral Regurgitation—1 Year, NYHA Class III/IV

Quality Assessment							No. of Patients		Effect		Quality
No. of Studies	Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Mitral Valve Clip	Surgery	Relative (95% CI)	Absolute	
1 (25)	Randomized trial	Very serious[a]	No serious inconsistency	Very serious[b]	Serious[c]	None	3/151 (2%)	9/67 (13.4%)	RR, 0.15 (0.04–0.53)	114 fewer per 1,000 (from 63 fewer to 129 fewer)	⊕OOO VERY LOW

Abbreviations: CI, confidence interval; RR, relative risk.
[a]Important concerns about attrition bias and confounding.
[b]Low applicability because of good surgical candidates.
[c]Sparse events and small sample size (optimal information size criteria not met).

Follow-Up Greater Than 1 Year

One RCT (N = 279) and 1 cohort study (N = 252) published as an abstract reported patients in class III/IV for a follow-up duration of more than 1 year. (25;30) The RCT evidence was judged at high risk of bias because of concerns about substantial attrition and confounding. Observational evidence was critically biased, with twice as long a follow-up duration for the surgical group compared with the intervention group.(30) In the RCT, no significant differences were observed for patients otherwise at low risk for surgery between the mitral valve clip and surgery arms (crude relative risk [RR], 0.91; 95% CI, 0.24–3.50) (Table 8).

Table 8: Mitral Valve Clip Versus Mitral Valve Surgery for Mitral Regurgitation—4 Years, NYHA Class III/IV

Quality Assessment							No. of Patients		Effect		Quality
No. of Studies	Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Mitral Valve Clip	Surgery	Relative (95% CI)	Absolute	
1 (25)	Randomized trial	Very serious[a]	No serious inconsistency	Very serious[b]	Serious[c]	None	6/105 (6%)	3/48 (6%)	RR, 0.91 (0.24–3.50)	6 fewer per 1,000 (from 47 fewer to 156 more)	⊕OOO VERY LOW

Abbreviations: CI, confidence interval; NYHA, New York Heart Association; RR, relative risk.
[a]Important concerns about attrition bias and confounding.
[b]Low applicability because of good surgical candidates.
[c]Wide confidence intervals and sparse events (optimal information size criteria not met).

Readmission Rates

We found no evidence addressing the outcome of readmission rates for the 12-month duration or beyond.

Recurrent Mitral Regurgitation 3+/4+

Table 9: Summary of Evidence for Recurrent Mitral Regurgitation 3+/4+

No. of Studies	Total No. of Patients	Study Design	Applicability
2 (25;29)	329 (sample size range: 50–279)	• 1 randomized controlled trial • 1 cohort	Low applicability based on surgical mortality risk

The evidence for recurrent MR 3+/4+ is summarized in Table 9. Both contributing studies were judged to be at high risk of bias for this outcome because of various concerns about selection/attrition bias or confounding. (25;29) Of the 50 patients with MR 3+/4+ at baseline, only 1 patient remained with, or progressed to, MR of grade 3+ after 12 months in the cohort study (surgery group). In the RCT, 94% of patients had MR 3+/4+ at baseline. The evidence from a single RCT (EVEREST II) yielded very low confidence in effect estimates for this outcome (Table 10).

For a duration of greater than 1 year, 1 observational study was critically biased, with twice as long a follow-up duration for the surgical group compared with the intervention group. (30) Four-year follow-up evidence from the EVEREST II trial did not meaningfully change from 1-year data (RR, 0.88; 95% CI, 0.54–1.45). This longer-term estimate, however, was further impacted by a higher risk for attrition (25%) bias.

Table 10: Mitral Valve Clip Versus Mitral Valve Surgery for Mitral Regurgitation—Recurrent Mitral Regurgitation 3+/4+ at 1 Year

Quality Assessment							No. of Patients		Effect		Quality
No. of Studies	Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Mitral Valve Clip	Surgery	Relative (95% CI)	Absolute	
1 (25)	Randomized trial	Serious[a]	No serious inconsistency	Very serious[b]	Very serious[c]	None	38/181 (21%)	18/89 (20.2%)	RR, 1.04 (0.63–1.71)	8 more per 1,000 (from 75 fewer to 144 more)	⊕OOO VERY LOW

Abbreviations: CI, confidence interval; RR, relative risk.
[a]At high risk of confounding bias.
[b]Low applicability because of good surgical candidates.
[c]Wide CI and few events.

Ventricular Remodelling (End-Systolic Volume)

Table 11: Summary of Evidence for Ventricular Remodelling (End-Systolic Volume)

No. of Studies	Total No. of Patients	Study Design	Applicability
2 (25;29)	329 (sample size range: 50–279)	• 1 randomized controlled trial • 1 cohort	Low applicability based on surgical mortality risk

Although both contributing studies were at high risk of bias, we graded the 1-year evidence of change in end-systolic volume over time from the RCT in 279 patients, the other being a grossly underpowered observational study (Tables 11 and 12). (25) In both groups, however, end-systolic volume decreased by about 5 mL from baseline.

Four years of data from the RCT were reported as post-treatment mean difference and were impacted by further attrition of patients, rendering the estimate relatively imprecise (mean difference, 5.52 mL; 95% CI, 3.87–14.91).

Table 12: Mitral Valve Clip Versus Mitral Valve Surgery for Mitral Regurgitation—Change in End-Systolic Volume at 1 Year

Quality Assessment							No. of Patients		Effect		Quality
No. of Studies	Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Mitral Valve Clip	Surgery	Relative (95% CI)	Absolute (Change from Baseline, mL)	
1 (25)	Randomized trials	Very serious[a]	No serious inconsistency	Very serious[b]	No serious imprecision	None	144	66	–	MD, 0.10 higher (5.49 lower to 5.69 higher)	⊕OOO VERY LOW

Abbreviations: CI, confidence interval; MD, mean difference.
[a]Important concerns about attrition bias and confounding.
[b]Low applicability because of good surgical candidates.

Serious Adverse Events (Total)

Only 1 study reported an outcome of SAEs by the end of the first year of postintervention follow-up. The EVEREST II RCT registered 139 (unadjudicated) SAEs in 279 patients. (25) The evidence and grading of our confidence for it are reported in Table 13.

Table 13: Mitral Valve Clip Versus Mitral Valve Surgery for Mitral Regurgitation—Serious Adverse Events

Quality Assessment							No. of Patients		Effect		Quality
No. of Studies	Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Mitral Valve Clip	Surgery	Relative (95% CI)	Absolute	
1 (25)	Randomized trials	Very serious[a]	No serious inconsistency	Very serious[b]	Serious[c]	None	93/184 (50.5%)	46/95 (48.4%)	RR, 1.04 (0.81–1.34)	19 more per 1,000 (from 92 fewer to 165 more)	⊕OOO VERY LOW

Abbreviations: CI, confidence interval; RR, relative risk.
[a]High risk of detection and confounding.
[b]Low applicability because of good surgical candidates.
[c]Wide CI.

In 1 cohort study at high risk of bias, incidences of death (n = 12), stroke, major bleeding, myocardial infarction, or cardiac rehospitalization occurred in 50 patients who had a European System for Cardiac Operative Risk Evaluation (EuroSCORE) of < 20%, an LV ejection fraction ≥ 45%, and grade 3+/4+ MR (RR, 2.17; 95% CI, 0.75–6.28). (29)

Procedure-Related Adverse Events

30-Day Mortality

Table 14: Summary of Evidence for Procedure-Related Adverse Events (30-Day Mortality)

No. of Studies	Total No. of Patients	Study Design	Applicability
5 (25-29)	1,096 (sample size range: 50–446)	• 1 randomized controlled trial • 3 cohort • 1 before-after/interrupted time series	Only 1 cohort study was considered to be in patients at high risk for surgery (27)

The evidence for procedure-related adverse events is summarized in Table 14. Across 5 studies of various research designs, 4% of patients died within 30 days of either mitral valve clip therapy or the surgery/conservative management comparator (total deaths, 44; crude average, 4.6% with mitral valve clips vs 3.7% with surgery or conservative management). However, most of the comparator sample pertained to surgery. Only 1 study, the EVEREST II RCT, was judged at low risk of bias for this outcome. (25) Meta-analysis was not undertaken because of important clinical and methodological heterogeneity across the studies. No study had the power to detect a meaningful difference for this outcome; all effect estimates were imprecise. The quality of evidence was graded for the low risk of bias randomized trial (Table 15).

Table 15: Mitral Valve Clip Versus Mitral Valve Surgery for Mitral Regurgitation—30-Day Mortality

Quality Assessment							No. of Patients		Effect		Quality
No. of Studies	Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Mitral Valve Clip	Surgery	Relative (95% CI)	Absolute	
1 (25)	Randomized trials	No serious risk of bias	No serious inconsistency	Very serious[a]	Very serious[b]	None	2/180 (1.1%)	2/94 (2.1%)	RR, 0.52 (0.07–3.65)	10 fewer per 1,000 (from 20 fewer to 56 more)	⊕OOO VERY LOW

Abbreviations: CI, confidence interval; RR, relative risk.
[a]Low applicability because of good surgical candidates.
[b]Wide CI and few events.

30-Day Stroke and Cardiac Perforation

Seven strokes across 3 studies in 495 patients precluded any meaningful synthesis for this outcome. No data were available for the cardiac perforation outcome.

Periprocedural Blood Transfusion

Two studies showed consistent results for the periprocedural blood transfusion outcome, favouring mitral valve clips. Because of methodological diversity between them, no meta-analysis was conducted. We graded the quality of evidence for the low risk of bias RCT evidence (Table 16). (25) No significant interaction was noted between effect estimates in patients with or without atrial fibrillation (Breslow-Day test for homogeneity of odds ratio not significant; $P = 0.42$).

Table 16: Mitral Valve Clip Versus Mitral Valve Surgery for Mitral Regurgitation—Blood Transfusion by Day 30

Quality Assessment							No. of Patients		Effect		Quality
No. of Studies	Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Mitral Valve Clip	Surgery	Relative (95% CI)	Absolute	
1 (25)	Randomized trials	No serious risk of bias	No serious inconsistency	Very serious[a]	No serious imprecision	None	24/180 (13.3%)	42/94 (44.7%)	RR, 0.30 (0.24–0.37)	313 fewer per 1,000 (from 281 fewer to 340 fewer)	⊕⊕OO LOW

Abbreviation: CI, confidence interval; RR, relative risk.
[a]Low applicability because of good surgical candidates.

Other Important Adverse Events (Post Hoc)

Comparative data for postintervention cardiac surgery were reported in 3 studies, none in high surgical risk populations. (25;26;29) Of 455 patients, 11% had to undergo surgery again. The duration of follow-up varied from 6 months to 4 years. Two of the 3 studies were grossly underpowered. (29;62) The EVEREST II trial, with substantial risk of attrition bias at 4 years, showed results favouring the surgical approach (RR, 4.53; 95% CI, 1.68–12.20; control event rate, 5%). Twenty-five percent of patients who underwent mitral valve clip therapy had to later undergo open mitral valve surgery (20% within 1 year). This implies that having forgone the first-line surgery option, 1 in every 5 patients who undergo the mitral valve clip procedure will have to undergo subsequent surgery anyway, if the clip were to be used in candidates at low risk of surgical mortality (very low quality of evidence). Given the imprecision around the point estimate, this number could be as extreme (i.e., the 95% CI for number needed to harm equalling to 5) as every 27th patient or every second mitral valve clip patient undergoing a subsequent surgery.

The EVEREST trial, at unclear risk of selective outcome reporting bias and detection bias for this outcome, demonstrated about a 70% risk reduction in 30-day major adverse events with mitral valve clips when compared with surgery (RR, 0.31; 95% CI, 0.21–0.47; very low quality of evidence). However, excluding blood transfusion, with a total of only 18 major adverse events, the estimate became imprecise (RR, 0.52; 95% CI, 0.21–1.27).

Cost-Effectiveness of Mitral Valve Clips

Two economic evaluations were included (Tables 17 and 18). (7;38) The cost-effectiveness analysis based on the EVEREST II trial data (from good surgical candidates) by Reynolds et al was judged to have inadequately robust validity due to the fact that it was only published in abstract form with limited information. (38) Mealing et al's cost-effectiveness decision-analytic model with data from the EVEREST II HRS was considered of moderate/limited validity because it met many of the criteria of the Phillips checklist but lacked in key areas such as the quality of the source of efficacy data and assumptions regarding effectiveness of the treatment and comparator within the model. Detailed Phillips checklist assessments are reported in Appendix 2.

Table 17: Summary of Evidence for Cost-Effectiveness

No. of Studies	Study Design	Applicability
2 (7;38)	2 cost-utility analyses, 1 from a US perspective and 1 from a UK health care system perspective	Reynolds et al's study published only in abstract form was in patients eligible for surgery (funding not reported). Mealing et al's economic evaluation addressed high-risk patients ineligible for surgery. (Study was funded by industry.)

Table 18: Mitral Valve Clip Cost-Effectiveness Versus Conventional Surgery and Medical Management

Quality Assessment					Results		Quality
No. of Studies	**Design**	**Structural Concerns**	**Concerns with Data**	**Concerns with Consistency**	**Main Estimate**	**Sensitivity Analyses**	
1 (38)	Trial-based analysis of mitral valve clip versus surgery (1-y duration)	Serious	Serious	Serious	Mitral valve clip increased QALYs by 0.015 versus surgery and reduced costs by $2,200 USD per patient versus surgery Mitral valve clip dominated surgery being more efficacious and less costly	Results were sensitive to assumptions regarding the duration of the QOL benefit with mitral valve clips relative to surgery, the price of mitral valve clips, and the analyzed population. Using a European price of $26,200 USD per clip, the ICER was greater than $400,000 USD per QALY	Low
1 (7)	Markov model of the mitral valve clip versus medical management (5-y duration)	No serious structural concerns	Serious	Moderate	Mitral valve clips resulted in 1.22 incremental QALYs versus MM and incurred additional costs of £27,000 ICER for mitral valve clips versus MM = £22,153/QALY	Results were most sensitive to the time horizon, the utility decrement associated with NYHA II, and the cost of the mitral valve clip procedure; however, the ICER did not exceed £30,000 per QALY except with a time horizon of 2 y	Moderate

Abbreviations: ICER, incremental cost-effectiveness ratio; MM, medical management; NYHA, New York Heart Association; QALY, quality-adjusted life-year; QOL, quality of life.

The following is a brief summary of the methodological issues that should be considered when interpreting the results of these studies. The validity of the assessment of the Reynolds et al analysis is challenged by the fact that it was not published in full; therefore, an assessment of the quantification and valuation of resource usage and the estimation of treatment effect were not possible. (38) Specifically with respect to the effect of the interventions on quality of life, it is unclear how the effect of the treatments over the course of the year was derived from measurements at 1 month and 12 months. The clinical trial concluded that surgery was more effective in reducing MR than percutaneous repair, although there were fewer adverse events 30 days after the intervention within the percutaneous repair group. The significant difference between the 2 groups related primarily to variation in the need for blood transfusions within the first 30 days postsurgery. The better outcome with surgery and comparable quality of life at 12 months calls into question the face validity of the reported effectiveness within this analysis. A more detailed fully published report would be required to provide a more robust assessment.

The second study focused specifically on high-risk subjects who were not eligible for surgical management, and compared mitral valve clips with medical management from the perspective of the UK health care system. (7) A number of concerns regarding the medical management arm have been raised that may have biased the estimate of the relative effectiveness of mitral valve clips versus medical management.

The medical management arm of the trial was a historical matched cohort, rather than an arm of an RCT. Furthermore, 58% of those within the medical management arm did not meet the entry criteria for the trial, primarily due to anatomical factors prohibiting the insertion of the clip. Details were not provided regarding the nature of the medical management the patients received, and no outcomes apart from mortality were reported for this group. The potential lack of comparability of this arm with that of the mitral valve clip study patients brings into question the estimates of relative effectiveness used within the cost-effectiveness analysis. Due to the scarcity of data, assumptions related to medical management were required within the analysis, including the assumption that the mix of NYHA classification would remain constant over a 2-year period within this group and that the mortality estimates over the first year of treatment could be extrapolated out to 2, 5, and 10 years.

Additional concerns in the mitral valve clip group include the estimate of the effectiveness of the treatment, which may have been influenced by the fact that a portion of the improvement in NYHA status may have been due to attrition, rather than true improvement—1 in 4 patients died within the first year. Lastly, the presurgical costs were not included within the model, which may have led to an underestimation of the true cost of the mitral valve clip procedure. Together, the lack of comparability of the medical management arm and the treatment assumptions incorporated within the model may have biased the results in favour of mitral valve clips.

Three technology appraisals have been reported within this area. (57-59) The first, by the National Institute for Health and Care Excellence (NICE) in the United Kingdom, was conducted in 2009 and did not consider the cost-effectiveness of the procedure—a later 2010 version of this had already been excluded in our regular screen. (45) The other 2, conducted by the Australian Medical Service Advisory Committee and the New Zealand National Health Committee, did consider cost-effectiveness and both agencies recommended against public funding of mitral valve clips given their expense and the lack of cost-effectiveness. (57;58) Relative to surgical intervention, these appraisals cited evidence of inferior efficacy of mitral valve clips and a lack of evidence supporting improved safety. This brings into question the conclusions of the Reynold et al abstract, which assumed a greater safety profile of mitral valve clips. With respect to high-risk patients not eligible for surgery, they concluded that more data

were required to inform this decision, although mitral valve clips may have a role for these patients.

CONCLUSIONS

- Evidence was generally inadequate to explore subgroup effect modification, including differences in estimates of effectiveness and harms by MR etiology
- The majority of the direct comparative evidence compares percutaneous mitral valve clip repair with surgery in patients not particularly at prohibitive surgical risk
- In low-surgical-risk populations with chronic MR, important limitations in design, power, and generalizability of evidence preclude definitive conclusions about the relative benefit or harms of the mitral valve clip procedure when compared with surgery
- Within the intervention arm, however, mitral valve clips did meaningfully improve MR, New York Heart Association (NYHA) functional class, and quality of life (by 4 or 5 points on a scale of 100) from baseline values
- Very low quality of evidence indicates that percutaneous mitral valve clip repair may provide a survival advantage, at least during the first 1 to 2 years, especially in medically managed chronic functional MR
- Across the studies, when compared with surgery, the mitral valve clip repair was not found to be definitively harmful. However, 20% to 25% of patients who received a mitral valve clip subsequently underwent valve surgery because of clip failure
- As such, there is an unmet need for the use of this emerging technology in patients with chronic MR who are at prohibitive surgical risk who are either in poor functional status or at risk of progression toward it, despite drug therapy. The true advantage may be greater in patients with functional MR, but our confidence for this hypothesis is very low. However, the cost-effectiveness of mitral valve clips in patients at prohibitive risk for surgery could not be established
- Future studies should investigate the pragmatic clinical scenario of treating patients with MR who are at prohibitive surgical risk, versus conservative management, while controlling for important confounding biases and adjusting for participant attrition

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Editorial Staff
Susan Harrison

Medical Information Services
Becky Skidmore, BA (H), MLS
Raymond Daniel, BA, Dipl. LIT

Clinical Experts
Thierry Mesana, MD, PhD
Eric Cohen, MD, FRCPC

APPENDICES

Appendix 1: Literature Search Strategies

Effectiveness and Harms Reviews
Multifile
Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>, Embase <1980 to 2014 Week 04>

Search Strategy, January 26, 2014:
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1 (Mitraclip* or Mitralclip* or (mitra adj clip*) or (mitral adj clip*)).tw. (738)
2 (Alfieri and (technique? or surger* or surgical* or repair*)).tw. (163)
3 "Endovascular Valve Edge-to-Edge Repair".tw. (34)
4 ("edge-to-edge" and (endovascular* or percutaneous*)).tw. (274)
5 or/1-4 (991)
6 Mitral Valve/su [Surgery] (14176)
7 Mitral Valve Insufficiency/su, th [Surgery, Therapy] (16357)
8 Mitral Valve Prolapse/su, th [Surgery, Therapy] (1667)
9 Mitral Valve Annuloplasty/ (1387)
10 ((mitral adj2 (valv* or insufficien* or incompeten* or prolaps* or regurgitat*)) and (surger* or surgical* or repair* or angioplast* or annuloplast* or catheter* or prothes?s or prosthetic* or plication*)).tw. (38202)
11 or/6-10 (52526)
12 Surgical Instruments/ (33792)
13 (clip* or clamp*).tw. (197878)
14 Heart Valve Prosthesis Implantation/is, mt [Instrumentation, Methods] (5300)
15 Surgical Procedures, Minimally Invasive/is, mt [Instrumentation, Methods] (8411)
16 Cardiac Catheterization/is, mt [Instrumentation, Methods] (7494)
17 exp Endovascular Procedures/is, mt [Instrumentation, Methods] (27158)
18 exp Angioplasty/is, mt [Instrumentation, Methods] (16279)
19 Mitral Valve Annuloplasty/is, mt (203)
20 exp Suture Techniques/is, mt [Instrumentation, Methods] (3816)
21 or/12-20 (277090)
22 11 and 21 (3682)
23 5 or 22 (4287)
24 exp Animals/ not (exp Animals/ and Humans/) (7994187)
25 23 not 24 (4106)
26 limit 25 to systematic reviews [Limit not valid in Embase; records were retained] (1593)
27 meta analysis.pt. (43391)
28 exp meta-analysis as topic/ (24364)
29 (meta-analy* or metanaly* or metaanaly* or met analy* or integrative research or integrative review* or integrative overview* or research integration or research overview* or collaborative review*).tw. (140645)
30 (systematic review* or systematic overview* or evidence-based review* or evidence-based overview* or (evidence adj3 (review* or overview*)) or meta-review* or meta-overview* or meta-synthes* or "review of reviews" or technology assessment* or HTA or HTAs).tw. (172486)
31 exp Technology assessment, biomedical/ (20762)
32 (cochrane or health technology assessment or evidence report).jw. (25663)
33 or/27-32 (326529)
34 25 and 33 (39)

35 26 or 34 (1600)
36 (comment or editorial or interview or letter or news).pt. (2758368)
37 35 not 36 (1564)
38 37 use prmz (55)
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40 (Mitraclip? or Mitralclip? or (mitra adj clip?) or (mitral adj clip?)).tw. (719)
41 (Alfieri and (technique? or surger* or surgical* or repair*)).tw. (163)
42 "Endovascular Valve Edge-to-Edge Repair".tw. (34)
43 ("edge-to-edge" and (endovascular* or percutaneous*)).tw. (274)
44 or/39-43 (997)
45 mitral valve/su [Surgery] (14176)
46 mitral valve regurgitation/su, th [Surgery, Therapy] (16357)
47 mitral valve prolapse/su, th [Surgery, Therapy] (1667)
48 mitral annuloplasty/ (1471)
49 ((mitral adj2 (valv* or insufficien* or incompeten* or prolaps* or regurgitat*)) and (surger* or surgical* or repair* or angioplast* or annuloplast* or catheter* or prothes?s or prosthetic* or plication*)).tw. (38202)
50 or/45-49 (52538)
51 exp clip/ (28609)
52 (clip* or clamp*).tw. (197878)
53 suturing method/ (29026)
54 (sutur* adj3 (method* or technique*)).tw. (12984)
55 or/51-54 (254732)
56 50 and 55 (2480)
57 44 or 56 (3047)
58 exp animals/ or exp animal experimentation/ or exp models animal/ or exp animal experiment/ or nonhuman/ or exp vertebrate/ (37404701)
59 exp humans/ or exp human experimentation/ or exp human experiment/ (28288098)
60 58 not 59 (9118152)
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64 "systematic review"/ (68978)
65 "meta analysis (topic)"/ (11251)
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67 (systematic review* or systematic overview* or evidence-based review* or evidence-based overview* or (evidence adj3 (review* or overview*)) or meta-review* or meta-overview* or meta-synthes* or "review of reviews" or technology assessment* or HTA or HTAs).tw. (172486)
68 biomedical technology assessment/ (19668)
69 (cochrane or health technology assessment or evidence report).jw. (25663)
70 or/63-69 (359716)
71 61 and 70 (30)
72 62 or 71 (31)
73 72 use emez (19)
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77 76 use prmz (51) [MEDLINE UNIQUE RESULTS]
78 76 use emez (10) [EMBASE UNIQUE RESULTS]

Economics: Review and Primary Studies

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>, Embase <1980 to 2014 Week 04> Search Strategy:

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2 (Alfieri and (technique? or surger* or surgical* or repair*)).tw. (163)
3 "Endovascular Valve Edge-to-Edge Repair".tw. (34)
4 ("edge-to-edge" and (endovascular* or percutaneous*)).tw. (274)
5 or/1-4 (991)
6 Mitral Valve/su [Surgery] (14176)
7 Mitral Valve Insufficiency/su, th [Surgery, Therapy] (16357)
8 Mitral Valve Prolapse/su, th [Surgery, Therapy] (1667)
9 Mitral Valve Annuloplasty/ (1387)
10 ((mitral adj2 (valv* or insufficien* or incompeten* or prolaps* or regurgitat*)) and (surger* or surgical* or repair* or angioplast* or annuloplast* or catheter* or prothes?s or prosthetic* or plication*)).tw. (38202)
11 or/6-10 (52526)
12 Surgical Instruments/ (33792)
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14 Heart Valve Prosthesis Implantation/is, mt [Instrumentation, Methods] (5300)
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18 exp Angioplasty/is, mt [Instrumentation, Methods] (16279)
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20 exp Suture Techniques/is, mt [Instrumentation, Methods] (3816)
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25 23 not 24 (4106)
26 exp "Costs and cost analysis"/ (425259)
27 exp *Economics/ (269659)
28 ec.fs. (3740909)
29 (cost or costs or costing or economic*).tw. (959132)
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33 "Quality of Life"/ (356209)
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39 37 not 38 (255)
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44 "Endovascular Valve Edge-to-Edge Repair".tw. (34)

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47 mitral valve/su [Surgery] (14176)
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49 mitral valve prolapse/su, th [Surgery, Therapy] (1667)
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52 or/47-51 (52538)
53 exp clip/ (28609)
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57 or/53-56 (254732)
58 52 and 57 (2480)
59 46 or 58 (3047)
60 exp animals/ or exp animal experimentation/ or exp models animal/ or exp animal experiment/ or nonhuman/ or exp vertebrate/ (37404701)
61 exp humans/ or exp human experimentation/ or exp human experiment/ (28288098)
62 60 not 61 (9118152)
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75 73 not 74 (180)
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Cochrane Library
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Description: 2014 Jan 26

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#12 [mh "Surgical Instruments"] 596
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#17 [mh "Endovascular Procedures"/is,mt] 1868
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#20 [mh "Suture Techniques"/is,mt] 143
#21 {or #12-#20} 10964
#22 #11 and #21 89
#23 #5 or #22 from 2004 to 2014 65

DSR – 0
DARE – 4
CENTRAL – 59
HTA – 2

Effectiveness and Harms: Primary Studies
Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>, Embase <1980 to 2014 Week 05>
Search Strategy:
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4 ("edge-to-edge" and (endovascular* or percutaneous*)).tw. (275)
5 or/1-4 (997)
6 Mitral Valve/su [Surgery] (14212)
7 Mitral Valve Insufficiency/su, th [Surgery, Therapy] (16411)
8 Mitral Valve Prolapse/su, th [Surgery, Therapy] (1673)
9 Mitral Valve Annuloplasty/ (1398)
10 ((mitral adj2 (valv* or insufficien* or incompeten* or prolaps* or regurgitat*)) and (surger* or surgical* or repair* or angioplast* or annuloplast* or catheter* or prothes?s or prosthetic* or plication*)).tw. (38309)
11 or/6-10 (52652)
12 Surgical Instruments/ (33869)
13 (clip* or clamp*).tw. (198385)
14 Heart Valve Prosthesis Implantation/is, mt [Instrumentation, Methods] (5339)
15 Surgical Procedures, Minimally Invasive/is, mt [Instrumentation, Methods] (8438)

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19 Mitral Valve Annuloplasty/is, mt (206)
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Cochrane Library
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Description: 2014 Jan 26

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#7	[mh "Mitral Valve Insufficiency"/su,th]	108
#8	[mh "Mitral Valve Prolapse"/su,th]	7
#9	[mh "Mitral Valve Annuloplasty"]	12
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#11	{or #6-#10}	603
#12	[mh "Surgical Instruments"]	604
#13	(clip* or clamp*):ti,ab,kw	4091
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#20	[mh "Suture Techniques"/is,mt]	147
#21	{or #12-#20}	11378
#22	#11 and #21	99
#23	#5 or #22 from 2013 to 2014	8

Appendix 2: Evidence Quality Assessment

Table A1: Mitral Valve Clip Versus Mitral Valve Surgery for Mitral Regurgitation—Mortality in Randomized Controlled Trials

Quality Assessment							Summary of Findings				
Participants (Studies) Follow-Up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence (GRADE)	Study Event Rates (%)		Relative Effect (95% CI)	Anticipated Absolute Effects	
							With Surgery and/or Conservative Treatment[a]	With Mitral Valve Clip		Risk with Surgery and/or Conservative Treatment[a]	Risk Difference with Mitral Valve Clip (95% CI)
1-Year Mortality, EVEREST II RCT (25)											
270 (1 study)	Very serious[b]	No serious inconsistency	Very serious[c]	Very serious[d]	Undetected	⨁⨀⨀⨀ VERY LOW[b,c,d] due to risk of bias, indirectness, imprecision	5/89 (5.6)	11/181 (6.1)	RR 1.08 (0.39–3.02)	56 per 1,000	4 more per 1,000 (from 34 fewer to 113 more)
4-Year Mortality, EVEREST II RCT (25)											
234 (1 study)	Very serious[e]	No serious inconsistency	Very serious[c]	Very serious[d]	Undetected	⨁⨀⨀⨀ VERY LOW[c,d,e] due to risk of bias, indirectness, imprecision	13/73 (17.8)	28/161 (17.4)	RR 0.98 (0.54–1.77)	178 per 1,000	4 fewer per 1,000 (from 82 fewer to 137 more)

Abbreviations: CI, confidence interval; EVEREST, Endovascular Valve Edge-to-Edge Repair Study; GRADE, Grading of Recommendations Assessment, Development and Evaluation; RCT, randomized controlled trial; RR, relative risk.

[a]Valve repair or replacement surgery and/or conservative medical treatment.

[b]High risk of bias—confounding by co-intervention as 21% of patients with mitral valve clip had subsequent surgery.

[c]Relatively good surgical candidates; comparator is surgery or conservative medical management.

[d]Wide CI and optimal information size criteria not met.

[e]High risk of bias—confounding by postintervention surgery and 25% attrition, unaccounted for in analysis.

Table A2: Mitral Valve Clip Versus Mitral Valve Surgery for Mitral Regurgitation—Mortality in Cohort Studies

Quality Assessment							Summary of Findings				
Participants (Studies) Follow-Up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence (GRADE)	Study Event Rates (%)		Relative Effect (95% CI)	Anticipated Absolute Effects	
							With Surgery and/or Conservative Treatment[a]	With Mitral Valve Clip		Risk with Surgery and/or Conservative Treatment[a]	Risk Difference with Mitral Valve Clip (95% CI)
1-Year Mortality, Cohort Study (Paranskaya et al, Germany) (29)											
50 (1 study)	Very serious[b]	No serious inconsistency	Very serious[c]	Very serious[d]	Undetected	⨁⊖⊖⊖ VERY LOW[b,c,d] due to risk of bias, indirectness, imprecision	0/26 (0)	2/24 (8.3)	Could not estimate –sparse data		—
1-Year Mortality, Cohort Study (Ajello et al, Italy) (30) (better indicated by lower values)											
160 (1 study)	Very serious[e]	No serious inconsistency	Serious[f]	Serious[g]	Undetected	⨁⊖⊖⊖ VERY LOW[e,f,g] due to risk of bias, indirectness, imprecision	55	105	Actuarial survival = 88.9% (3.5) vs 69.5% (7.3); *P* = 0.002	See comment	See comment
2-Year Mortality, Cohort Study (Ajello et al, Italy) (30) (better indicated by lower values)											
160 (1 study)	Very serious[e]	No serious inconsistency	Serious[f]	Serious[g]	Undetected	⨁⊖⊖⊖ VERY LOW[e,f,g] due to risk of bias, indirectness, imprecision	55	105	Actuarial survival = 80.2% (5.2) vs 57.0% (8.1); *P* = 0.002	See comment	See comment

Quality Assessment							Summary of Findings				
Participants (Studies) Follow-Up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence (GRADE)	Study Event Rates (%)		Relative Effect (95% CI)	Anticipated Absolute Effects	
							With Surgery and/or Conservative Treatment[a]	With Mitral Valve Clip		Risk with Surgery and/or Conservative Treatment[a]	Risk Difference with Mitral Valve Clip (95% CI)
1-Year Mortality, Cohort, EVEREST II HRS (27)											
114 (1 study)	Very serious[h]	No serious inconsistency	No serious indirectness	Serious[i]	Undetected	⨁⊖⊖⊖ VERY LOW[h,i] due to risk of bias, imprecision	16/36 (44.4)	19/78 (24.4)	RR 0.55 (0.32–0.94)	444 per 1,000	200 fewer per 1,000 (from 27 fewer to 302 fewer)

Abbreviations: CI, confidence interval; EVEREST, Endovascular Valve Edge-to-Edge Repair Study; GRADE, Grading of Recommendations Assessment, Development and Evaluation; HRS, High Risk Study; RR, relative risk.
[a]Valve repair or replacement surgery and/or conservative medical treatment.
[b]High risk—prognostic imbalance and variable duration of patient follow-up.
[c]Relatively good surgical candidates; comparator is surgery or conservative medical management.
[d]Wide CI and optimal information size criteria not met.
[e]High risk of confounding and section bias (a subset of data from 2 groups was analyzed).
[f]Mixed risk population, with 38% at less than NYHA class III/IV.
[g]Although significant difference in actuarial survival, sample size is too small for confidence in this estimate (160 patients).
[h]Selection bias (post hoc control group), information bias, and confounding by indication.
[i]Fragile estimates and small sample size.

Table A3: Mitral Valve Clip Versus Mitral Valve Surgery for Mitral Regurgitation—Predicted Versus Observed Mortality

Quality Assessment							Summary of Findings				
Participants (Studies) Follow-Up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence (GRADE)	Study Event Rates (%)		Relative Effect (95% CI)	Anticipated Absolute Effects	
							With Surgery and/or Conservative Treatment[a]	With Mitral Valve Clip		Risk with Surgery and/or Conservative Treatment[a]	Risk Difference with Mitral Valve Clip (95% CI)
1-Year Mortality, Predicted Versus Observed Mortality (Before-After), Buzzatti et al (32)											
135 (1 study)	Serious[b]	No serious inconsistency	Serious[c]	Serious[d]	Undetected	⨁⊖⊖⊖ VERY LOW[b,c,d] due to risk of bias, indirectness, imprecision		0/135 (0)	Risk reduction: functional MR = 9.1% (95% CI, 3.1–15.1); degenerative MR = 11.1% (95% CI, 19.7–41.9)	See comment	—
2-Year Mortality, Predicted Versus Observed Mortality (Before-After), Buzzatti et al (32)											
135 (1 study)	Serious[b]	No serious inconsistency	Serious[c]	Serious[d]	Undetected	⨁⊖⊖⊖ VERY LOW[b,c,d] due to risk of bias, indirectness, imprecision		0/135 (0)	Risk reduction: functional MR = 12.1% (95% CI, 3.1–15.1); degenerative MR = 22.2% (95% CI, 4.8–69.2)	See comment	—
1-Year Mortality, Predicted Versus Observed Mortality (Before-After), Schau et al (Companion—Neuss et al, 2013), Germany (31;61)											
155 (1 study)	Serious[b]	No serious inconsistency	No serious indirectness	Serious[d]	Undetected	⨁⊖⊖⊖ VERY LOW[b,d] due to risk of bias, imprecision		0/155 (0)	Qualitative results: all-cause survival rate for the whole cohort comparable to prediction of the SHFM	See comment	—

Abbreviations: CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development and Evaluation; MR, mitral regurgitation; SHFM, Seattle Heart Failure Model.
[a]Valve repair or replacement surgery and/or conservative medical treatment.
[b]Unclear risk of bias—some concerns about completeness of data and validity of SHFM.
[c]Unclear surgical risk—70% with functional MR (MR3+/4+ NR).
[d]Significant but small sample size.

Table A4: Mitral Valve Clip Versus Mitral Valve Surgery for Mitral Regurgitation—Quality of Life

Quality Assessment							Summary of Findings				
Participants (Studies) Follow-Up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence (GRADE)	Study Event Rates		Relative Effect (95% CI)	Anticipated Absolute Effects	
							With Surgery and/or Conservative Treatment[a]	With Mitral Valve Clip		Risk with Surgery and/or Conservative Treatment[a]	Risk Difference with Mitral Valve Clip (95% CI)
Quality of Life (Physical Component), EVEREST II (25) (measured with SF-36; range, 0–100; better indicated by higher values)											
192 (1 study) 1 y	Very serious[b]	No serious inconsistency	Very serious[c]	No serious imprecision	Undetected	⨁⊖⊖⊖ VERY LOW[b,c] due to risk of bias, indirectness	60	132	—	Mean quality of life (physical component) score in control group was 4.4	Mean quality of life (physical component) in intervention groups was 0 higher (3.1 lower to 3.1 higher)
Quality of Life (Mental Component), EVEREST II (25) (measured with SF-36; range, 0–100; better indicated by higher values)											
196 (1 study) 1 y	Very serious[b]	No serious inconsistency	Very serious[c]	No serious imprecision	Undetected	⨁⊖⊖⊖ VERY LOW[b,c] due to risk of bias, indirectness	60	136	—	Mean quality of life (mental component) score in control group was 3.8	Mean quality of life (mental component) in intervention groups was 1.9 higher (1.2 lower to 5 higher)

Abbreviations: CI, confidence interval; EVEREST, Endovascular Valve Edge-to-Edge Repair Study; GRADE, Grading of Recommendations Assessment, Development and Evaluation; SF-36, Short Form Health Survey.
[a]Valve repair or replacement surgery and/or conservative medical treatment.
[b]High risk of bias because of detection bias, attrition bias, and confounding.
[c]Relatively good surgical candidates; comparator is surgery or conservative medical management.

Table A5: Mitral Valve Clip Versus Mitral Valve Surgery for Mitral Regurgitation—1-Year and 4-Year NYHA Class III/IV and Readmission Rates

Quality Assessment							Summary of Findings				
Participants (Studies) Follow-Up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence (GRADE)	Study Event Rates (%)		Relative Effect (95% CI)	Anticipated Absolute Effects	
							With Surgery and/or Conservative Treatment[a]	With Mitral Valve Clip		Risk with Surgery and/or Conservative Treatment[a]	Risk Difference with Mitral Valve Clip (95% CI)
Patients in NYHA Class III/IV at 1 Year, EVEREST II (25)											
218 (1 study) 1 y	Very serious[b]	No serious inconsistency	Very serious[c]	Serious[d]	Undetected	⊕⊖⊖⊖ VERY LOW[b,c,d] due to risk of bias, indirectness, imprecision	9/67 (13.4)	3/151 (2)	RR, 0.15 (0.04–0.53)	134 per 1,000	114 fewer per 1,000 (from 63 fewer to 129 fewer)
Patients in NYHA Class III/IV at 4 Years, EVEREST II (25)											
153 (1 study) 4 y	Very serious[b]	No serious inconsistency	Very serious[c]	Very serious[e]	Undetected	⊕⊖⊖⊖ VERY LOW[b,c,e] due to risk of bias, indirectness, imprecision	3/48 (6.3)	6/105 (5.7)	RR, 0.91 (0.24–3.5)	62 per 1,000	6 fewer per 1,000 (from 47 fewer to 156 more)
Readmission Rates—Zero Evidence											

Abbreviations: CI, confidence interval; EVEREST, Endovascular Valve Edge-to-Edge Repair Study; GRADE, Grading of Recommendations Assessment, Development and Evaluation; NYHA, New York Heart Association; RR, relative risk.

[a]Valve repair or replacement surgery and/or conservative medical treatment.

[b]High risk of bias—confounding by postintervention surgery and 25% attrition, unaccounted for in analysis.

[c]Relatively good surgical candidates; comparator is surgery or conservative medical management.

[d]Fragile estimates and small sample size.

[e]Wide CI and optimal information size criteria not met.

Table A6: Mitral Valve Clip Versus Mitral Valve Surgery for Mitral Regurgitation—Recurrent Mitral Regurgitation 3+/4+ at 1 and 4 Years, 1-Year End-Systolic Volume, and 1-Year Serious Adverse Events

Quality Assessment							Summary of Findings				
Participants (Studies) Follow-Up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence (GRADE)	Study Event Rates (%)		Relative Effect (95% CI)	Anticipated Absolute Effects	
							With Surgery and/or Conservative Treatment[a]	With Mitral Valve Clip		Risk with Surgery and/or Conservative Treatment[a]	Risk Difference with Mitral Valve Clip (95% CI)
Patients with MR 3+/4 at 1 and 4 Years, EVEREST II (25)											
270 (1 study) 1 y	Serious[b]	No serious inconsistency	Very serious[c]	Very serious[d]	Undetected	⊕⊖⊖⊖ VERY LOW[b,c,d] due to risk of bias, indirectness, imprecision	18/89 (20.2)	38/181 (21)	RR, 1.04 (0.63–1.71) No important change in precision at 4 y (RR = 0.88, 95% CI 0.54–1.45)	202 per 1,000	8 more per 1,000 (from 75 fewer to 144 more)
End-Systolic Volume (1 Year), EVEREST II (25) (measured with echocardiography; better indicated by lower values)											
210 (1 study) 1 y	Very serious[e]	No serious inconsistency	Very serious[c]	No serious imprecision	Undetected	⊕⊖⊖⊖ VERY LOW[c,e] due to risk of bias, indirectness	66	144	—	Mean end-systolic volume (1 y) in the control group was −5.6 mL	Mean end-systolic volume (1 y) in the intervention groups was 0.10 higher (5.49 lower to 5.69 higher)
1-Year Serious Adverse Events (Unadjudicated), EVEREST II (25)											
279 (1 study) 1 y	Very serious[f]	No serious inconsistency	Very serious[c]	Serious[g]	Undetected	⊕⊖⊖⊖ VERY LOW[c,f,g] due to risk of bias, indirectness, imprecision	46/95 (48.4)	93/184 (50.5)	RR, 1.04 (0.81–1.34)	484 per 1,000	19 more per 1,000 (from 92 fewer to 165 more)

Abbreviations: CI, confidence interval; EVEREST, Endovascular Valve Edge-to-Edge Repair Study; GRADE, Grading of Recommendations Assessment, Development and Evaluation; MR, mitral regurgitation; RR, relative risk.
[a]Valve repair or replacement surgery and/or conservative medical treatment.
[b]High risk of bias—confounding by co-intervention as 21% of patients with mitral valve clip had subsequent surgery.
[c]Relatively good surgical candidates; comparator is surgery or conservative medical management.
[d]Wide CI and optimal information size criteria not met.
[e]High risk of bias—confounding by postintervention surgery and 25% attrition, unaccounted for in analysis.
[f]High risk of detection and confounding bias.
[g]Wide CI.

Table A7: Mitral Valve Clip Versus Mitral Valve Surgery for Mitral Regurgitation—30-Day Mortality, Blood Transfusion, Reoperations by 4 Years, and Any Major Adverse Event (30 Days)

Quality Assessment							Summary of Findings				
Participants (Studies) Follow-Up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence (GRADE)	Study Event Rates (%)		Relative Effect (95% CI)	Anticipated Absolute Effects	
							With Surgery and/or Conservative Treatment[a]	With Mitral Valve Clip		Risk with Surgery and/or Conservative Treatment[a]	Risk Difference with Mitral Valve Clip (95% CI)
30-Day Mortality, EVEREST II (25)											
274 (1 study) 30 d	No serious risk of bias	No serious inconsistency	Very serious[b]	Very serious[c]	Undetected	⨁⨀⨀⨀ VERY LOW[b,c] due to indirectness, imprecision	2/94 (2.1)	2/180 (1.1)	RR, 0.52 (0.07–3.65)	21 per 1,000	10 fewer per 1,000 (from 20 fewer to 56 more)
Blood Transfusion ≥ 2 Units, EVEREST II (25)											
274 (1 study) 30 d	No serious risk of bias	No serious inconsistency	Very serious[b]	No serious imprecision	Undetected	⨁⨁⨀⨀ LOW[b] due to indirectness	42/94 (44.7)	24/180 (13.3)	RR, 0.30 (0.24–0.37)	447 per 1,000	313 fewer per 1,000 (from 281 fewer to 340 fewer)
Reoperations by 4 Years, EVEREST II (25) **(Post Hoc)**											
234 (1 study) 4 y	Serious[d]	No serious inconsistency	Very serious[b]	No serious imprecision	Undetected	⨁⨀⨀⨀ VERY LOW[b,d] due to risk of bias, indirectness	4/73 (5.5)	40/161 (24.8)	RR, 4.53 (1.68–12.2)	55 per 1,000	193 more per 1,000 (from 37 more to 614 more)
Any Major Adverse Event (30 Days), EVEREST II (25) **(Post Hoc)**											
274 (1 study) 30 d	No serious risk of bias	No serious inconsistency	Very serious[b]	Serious[e]	Undetected	⨁⨀⨀⨀ VERY LOW[b,e] due to indirectness, imprecision	45/94 (47.9)	27/180 (15)	RR, 0.31 (0.21–0.47)	479 per 1,000	330 fewer per 1,000 (from 254 fewer to 378 fewer)

Abbreviations: CI, confidence interval; EVEREST, Endovascular Valve Edge-to-Edge Repair Study; GRADE, Grading of Recommendations Assessment, Development and Evaluation; RR, relative risk.
[a]Valve repair or replacement surgery and/or conservative medical treatment.
[b]Relatively good surgical candidates; comparator is surgery or conservative medical management.
[c]Wide CI and optimal information size criteria not met.
[d]Substantial risk because of attrition.
[e]Fragile estimates and small sample size.

Table A8: Risk of Bias Assessment for Different Outcomes in EVEREST II Trial[a]

Follow-Up Period	Specific Outcomes	Random Sequence Generation	Allocation Concealment	Blinding of Participants/ Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Reporting	Other Bias (Confounding)
1 y	All other outcomes with data	Low risk of bias[b]	Low risk of bias[c]	Low risk of bias[d]	Low risk of bias[e]	Low risk of bias	Unclear risk of bias[i]	High risk of bias[j]
1 y	Quality of life	Low risk of bias[b]	Low risk of bias[c]	Low risk of bias[d]	High risk of bias[f]	High risk of bias[h]	Unclear risk of bias[i]	High risk of bias[j]
1 y	Total serious adverse events	Low risk of bias[b]	Low risk of bias[c]	Low risk of bias[d]	High risk of bias[f]	Unclear risk of bias	Unclear risk of bias[i]	High risk of bias[j]
1 y	NYHA III/IV, end-systolic volume	Low risk of bias[b]	Low risk of bias[c]	Low risk of bias[d]	Low risk of bias[e]	High risk of bias[h]	Unclear risk of bias[i]	High risk of bias[j]
4 y	All outcomes with data	Low risk of bias[b]	Low risk of bias[c]	Low risk of bias[d]	Low risk of bias[e]	High risk of bias[h]	Unclear risk of bias[i]	High risk of bias[j]
4 y	Postintervention surgery	Low risk of bias[b]	Low risk of bias[c]	Low risk of bias[d]	Low risk of bias[e]	High risk of bias[h]	Unclear risk of bias[i]	Unclear risk of bias
30 d	Transfusion, stroke, and mortality	Low risk of bias[b]	Low risk of bias[c]	Low risk of bias[d]	Low risk of bias[e]	Low risk of bias	Low risk of bias	Low risk of bias
30 d	Major adverse events	Low risk of bias[b]	Low risk of bias[c]	Low risk of bias[d]	Unclear risk of bias[g]	Low risk of bias	Unclear risk of bias[i]	Low risk of bias

Abbreviation: NYHA, New York Heart Association.
[a]Mauri et al, 2013, (25) and its companion studies.
[b]Randomization was administered in random blocks.
[c]Interactive voice response system.
[d]No blinding or incomplete blinding, but the review authors judged that the outcome was not likely to be influenced by lack of blinding.
[e]No blinding of outcome assessment, but the review authors judged that the outcome measurement was not likely to be influenced by lack of blinding.
[f]No blinding of outcome assessment, and the outcome measurement was likely to be influenced by lack of blinding.
[g]Insufficient data to reach a judgment.
[h]Substantial attrition (25%).
[i]The study protocol is available and all of the study's prespecified (primary and secondary) outcomes that are of interest to the review were reported in the prespecified way. Also at risk of selective analysis reporting bias because the original planned was per-protocol to minimize null effect of an intention-to-treat analysis on both efficacy and safety outcomes. What was later done was an ITT analysis. Also problematic is the composite nature of outcomes—for example, a patient who in the mitral valve clip arm had postintervention surgery could have failed on 1 component of the composite efficacy outcome, but gained on 2 other (death from any cause and moderate-severe [3+] or severe [4+] MR at 12 mo).
[j]Time-varying co-intervention effect was not taken into account as some patients who underwent the mitral valve clip procedure later had additional surgical repair (up to 20–25%, depending upon time point of assessment) but were counted in the intervention group.

Table A9: Risk of Bias Assessment for Different Outcomes in Observational Studies

Authors, Year of Publication	Outcome Category	Specific Outcomes	Selection Bias	Explanation	Confounding Bias	Explanation	Information/ Measurement Bias	Explanation
Conradi et al, 2013 (26)	All	Mortality 30 d, 3+/4+ MR, postintervention surgery, stroke 30 d, transfusion, and NYHA class III/IV	Low risk of bias		High risk of bias	See footnote[a]	Low risk of bias	
Conradi et al, 2013 (26)	Specific	Mortality at 6 mo	Low risk of bias		Low risk of bias	See footnote[b]	Low risk of bias	
Conradi et al, 2013 (28)	All	30-day mortality; redo cardiac surgery	High risk of bias	See footnote[c]	High risk of bias	See footnote[d]	Unclear risk of bias	See footnote[e]
Paranskaya et al, 2013 (29)	All	Postintervention surgery; MR3+ last follow-up or 1 y; NYHA class at follow-up; stroke at 30 d; important procedure-related complications (various adverse clinical events); mortality at 30 d; mortality at last follow-up or 1 y; LVESV at last follow-up (mL)	High risk of bias	Patients had variable lengths of follow-up, while most data were analyzed as proportions	High risk of bias	Unadjusted estimates with major prognostic imbalance between groups	Low risk of bias	
Buzzatti et al, 2013 (32)	All	Predicted minus observed mortality in functional and degenerative MR population	Unclear risk of bias	Some concerns about missing data	Unclear risk of bias	See footnote[f]	Unclear risk of bias	Reliability and completeness of patient data for the model not reported
Ajello et al, 2013 (30)	All	NYHA at last follow-up; MR ≥ 3+ at last follow-up	High risk of bias	See footnote[g]	High risk of bias	See footnote[h]	Low risk of bias	
Schau et al, 2013 (31)	All	Survival	Unclear risk of bias	Insufficient data	Unclear risk of bias	See footnote[i]	Unclear risk of bias	Insufficient data

Authors, Year of Publication	Outcome Category	Specific Outcomes	Selection Bias	Explanation	Confounding Bias	Explanation	Information/ Measurement Bias	Explanation
Whitlow et al, 2012 (27)	All	All-cause mortality; 30-d mortality	High risk of bias	See footnote[j]	High risk of bias	See footnote[k]	High risk of bias	See footnote[l]

Abbreviations: LVESV, left ventricular end-systolic volume; MR, mitral regurgitation; NYHA, New York Heart Association.
[a]For all outcomes other than mortality at 6 mo, the study is at high risk of confounding by indication—significantly more patients in the mitral valve clip arm were older, males, with higher logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE), lower ejection fraction, proportionately more NHYA class III or IV, and history of previous cardiac surgery.
[b]Adjusted for age and ejection fraction. However, there might be some residual confounding due to not considering comorbidities.
[c]High risk. No information on missing outcome data; but more importantly, the investigators excluded from analysis, both in the preintervention and postintervention periods, all patients who presented with MR irrespective of eligibility for surgery and the mitral valve clip procedure. A valid time series would show the change in outcomes effected by the introduction of the mitral valve clip program for the entire MR population presenting to the hospital by analyzing data for those who did and did not undergo surgery in the preintervention period, and all who underwent surgery, the mitral valve clip procedure, and no procedure in the postintervention period.
[d]Confounding by secular trends (e.g., independence of intervention to other time-varying covariates was not ensured).
[e]Unsure whether introduction of intervention affected data collection.
[f]Because of some concerns about the reliability of Seattle Heart Failure Model (SHFM) mortality prediction— only 10% of patients in the model were treated in specialized care centres. (63)
[g]Crude analyses that do not account for patients in Group A who did not receive a mitral valve clip (n = 35 of 140) and as such might be systematically different from the whole cohort of group A (this can also be viewed as attrition bias).
[h]Because baseline data were analyzed for the full group A and group B cohorts while outcome data originates in a subset of these patients.
[i]Because of some concerns about the reliability of SHFM mortality prediction because only 10% of patients in the model were treated in specialized care centres. (63)
[j]Twenty-two otherwise-eligible patients could not be included in the comparator group due to lack of site institutional review board approval to include patients in the comparator group, lack of patient informed consent, or inability to contact the patient. If these were patients more or less likely to experience the outcome and were obviously ineligible for the mitral valve clip procedure, then the potential of collider/selection bias cannot be ignored. Further, 8 patients would have been otherwise eligible for one or the other intervention group but either they did not elect to enroll or the enrollment had ended.
[k]The comparator group was one that was anatomically ineligible for the mitral valve clip procedure because of either reasons of mitral valve anatomy (which may be associated with the degree of MR) or reasons other than anatomy (in 42% of patients), for example, ejection fraction < 20%, presence of cardiac thrombus, acute myocardial infarction within 2 wk, etc. These differential characteristics are indicative of confounding by indication.
[l]The comparator or standard care exposure is likely to have a high coefficient of variation. In this study 86% and 14% of the control group were medically and surgically treated, respectively.

Table A10: Quality Assessment Based on Phillips Checklist for Cost-Effectiveness, for the Reynolds Study[a]

Quality Criteria	Questions for Critical Appraisal	Response	Comments
S1	Is there a clear statement of the decision problem?	Yes	
	Is the objective of the evaluation and model specified and consistent with the stated decision problem?	Yes	
	Is the primary decision-maker specified?	No	
S2	Is the perspective of the model stated clearly?	No	
	Are the model inputs consistent with the stated perspective?	Unclear	
	Has the scope of the model been stated and justified?	No	
	Are the outcomes of the model consistent with the perspective, scope, and overall objective of the model?	Unclear	
S3	Has the evidence regarding the model structure been described?	No	
	Is the structure of the model consistent with a coherent theory of the health condition under evaluation?	Unclear	
	Are the sources of data used to develop the structure of the model specified?	Yes/no	Unclear where costs for rehabilitation and long-term care are sourced
S4	Are the structural assumptions transparent and justified?	n/a	Not a model
	Are the structural assumptions reasonable given the overall objective, perspective, and scope of the model?	n/a	Not a model
S5	Is there a clear definition of the options under evaluations?	Yes	
	Is there justification for the exclusion of feasible options?	No	Not discussed
S6	Is the chosen model type appropriate given the decision problem and specified causal relationship within the model?	n/a	Not a model
S7	Is the time horizon of the model sufficient to reflect all important differences between options?	n/a	Not a model
	Are the time horizon of the model, the duration of treatment, and the duration of treatment effect described and justified?	n/a	Not a model
S8	Do the disease states (state transition model) or the pathways (decision tree model) reflect the underlying biological process of the disease in question and the impact of interventions?	n/a	Not a model
S9	Is the cycle length defined and justified in terms of the natural history of disease?	n/a	Not a model
D1	Are the data identification methods transparent and appropriate given the objectives of the model?	Yes/no	Reporting lacks clarity as only available in abstract
	Where choices have been made between data sources, are these justified appropriately?	No	
	Has particular attention been paid to identifying data for the important parameters in the model?	n/a	Not a model

Quality Criteria	Questions for Critical Appraisal	Response	Comments
	Has the process of selecting key parameters been justified and systematic methods used to identify the most appropriate data?	Unclear	
	Has the quality of the data been assessed appropriately?	Unclear	
	Where expert opinion has been used, are the methods described and justified?	Unclear	
D2	Is the premodel data analysis methodology based on justifiable statistical and epidemiological techniques?	Unclear	
D2a	Is the choice of baseline data described and justified?	n/a	Not a model
	Are transition probabilities calculated appropriately?	n/a	Not a model
	Has a half-cycle correction been applied to both cost and outcome?	n/a	Not a model
	If not, has this omission been justified?	n/a	Not a model
D2b	If relative treatment effects have been derived from trial data, have they been synthesized using appropriate techniques?	Unclear	Unclear how quality of life from 1 mo through to 12 mo was calculated
	Have the methods and assumptions to extrapolate short-term results to final outcomes been documented and justified?	Unclear	See above
	Have alternative extrapolation assumptions been explored through sensitivity analysis?	n/a	Not extrapolation of data
	Have alternative assumptions regarding the continuing effect of treatment been explored through sensitivity analysis?	n/a	Not extrapolation of data
D2c	Are the utilities incorporated into the model appropriate?	Unclear	See above
	Is the source for the utility weights referenced?	Yes	Derived from clinical trial
	Are the methods of derivation for the utility weights justified?	Unclear	
D3	Have all data incorporated into the model been described and referenced in sufficient detail?	No	Brief summary within abstract
	Has the use of mutually inconsistent data been justified (i.e., are assumptions and choices appropriate)?	Unclear	
	Is the process of data incorporation transparent?	No	
	If data have been incorporated as distributions, has the choice of distribution for each parameter been described and justified?	n/a	
	If data have been incorporated as distributions, is it clear that second-order uncertainty is reflected?	n/a	
D4	Have the 4 principal types of uncertainty been addressed?	No	
	If not, has the omission of particular forms of uncertainty been justified?	No	
D4a	Have methodological uncertainties been addressed by running alternative versions of the model with different methodological assumptions?	n/a	
D4b	Is there evidence that structural uncertainties have been addressed via sensitivity analysis?	n/a	

Quality Criteria	Questions for Critical Appraisal	Response	Comments
D4c	Has heterogeneity been dealt with by running the model separately for different subgroups?	n/a	
D4d	Are the methods of assessment of parameter uncertainty appropriate?	Unclear	Limited reporting of sensitivity analyses
	If data are incorporated as point estimates, are the ranges used for sensitivity analysis stated clearly and justified?	n/a	
C1	Is there evidence that the mathematical logic of the model has been tested thoroughly before use?	n/a	
C2	Are the conclusions valid given the data presented?	Yes	
	Are any counterintuitive results from the model explained and justified?	No	RCT favoured surgical treatment
	If the model has been calibrated against independent data, have any differences been explained and justified?	n/a	
	Have the results of the model been compared with those of previous models and any differences in results explained?	No	Results not put into context with previous literature

Abbreviations: n/a, not applicable; RCT, randomized controlled trial.
[a]Reynolds et al, 2012. (38)

Table A11: Quality Assessment Based on Phillips Checklist for Cost-Effectiveness, for the Mealing Study[a]

Quality Criteria	Questions for Critical Appraisal	Response	Comments
S1	Is there a clear statement of the decision problem?	Yes	"As patients within the EVEREST II HRS trial were old and infirm and the cost of the implant is incurred on day 1, it is important to know if these individuals incur enough benefit to overcome the initial expenditure"
	Is the objective of the evaluation and model specified and consistent with the stated decision problem?	Yes	"To assess the cost-effectiveness of the MitraClip therapy compared to medical management (MM) in patients with severe MR, for whom surgery is not an option due to high operative risk, with the primary data source being the EVEREST II High Risk Study"
	Is the primary decision-maker specified?	Yes	UK National Health Service
S2	Is the perspective of the model stated clearly?	Yes	Health care system
	Are the model inputs consistent with the stated perspective?	Yes	
	Has the scope of the model been stated and justified?	Yes/no	Presurgical costs were not incorporated within the model. The authors justify this based on the fact that the difference in workup costs between the 2 treatment arms would have to be greater than £9,600 to alter the cost-effectiveness decision
	Are the outcomes of the model consistent with the perspective, scope, and overall objective of the model?	Yes	Cost per QALY gained
S3	Has the evidence regarding the model structure been described?	Yes	Underlying assumptions validated by advisory panel and experienced clinicians
	Is the structure of the model consistent with a coherent theory of the health condition under evaluation?	Yes	Similar to other models within this area
	Are the sources of data used to develop the structure of the model specified?	Yes	Efficacy: from EVEREST HRS II for mitral valve clip; from historical matched controls for the medical management group Costs: standard references for drug costs, hospital costs, adverse event costs, valve cost Utilities: from published literature sources
S4	Are the structural assumptions transparent and justified?	Yes/no	Mortality long term is not transparent—it appears that the difference in mortality between the 2 groups is assumed to continue for the duration of the model, although the clinical trial data for mitral valve clip are for 12 mo
	Are the structural assumptions reasonable given the overall objective, perspective, and scope of the model?	Yes/no	Concerns regarding long-term mortality differences, as detailed above
S5	Is there a clear definition of the options under evaluation?	No	Mitral valve clip versus MM; MM is not clearly defined
	Is there justification for the exclusion of feasible options?	Yes	Patients are not eligible for surgery due to high risk of mortality
S6	Is the chosen model type appropriate given the decision problem and specified causal relationship within the model?	Yes	Markov model, 2 segments, short-term 30-d horizon with 1-d cycle, long-term 5-y horizon with 1-mo cycles

Quality Criteria	Questions for Critical Appraisal	Response	Comments
S7	Is the time horizon of the model sufficient to reflect all important differences between options?	Yes	Base-case time horizon is 5 y; other durations tested in sensitivity analyses, including 2 y and 10 y
	Are the time horizon of the model, the duration of treatment, and the duration of treatment effect described and justified?	Yes/no	It is unclear how long-term survival was derived and if differences between treatments were assumed; "the cumulative survival estimates were extrapolated into the future and used to derive daily or monthly transition probabilities using standard formulas during all model cycles"
S8	Do the disease states (state transition model) or the pathways (decision tree model) reflect the underlying biological process of the disease in question and the impact of interventions?	Yes	
S9	Is the cycle length defined and justified in terms of the natural history of disease?	Yes	Daily cycle length during the 30-d short-term model, and 1-mo cycle lengths during the long-term 5-y period of the model
D1	Are the data identification methods transparent and appropriate given the objectives of the model?	Yes	Efficacy for mitral value is from EVEREST II HRS; for MM it is from a historical cohort Costs—standard sources Mortality—long-term follow-up from EVEREST II HRS; assumptions regarding medical management tested in sensitivity analyses Utilities—published literature
	Where choices have been made between data sources, are these justified appropriately?	Yes	
	Has particular attention been paid to identifying data for the important parameters in the model?	Yes	
	Has the process of selecting key parameters been justified and systematic methods used to identify the most appropriate data?	Yes/no	The application of 2-y NYHA class distribution data from the EVEREST II study that was not in patients ineligible for surgery may not be justified. Concerns regarding the assumptions in the MM group specific to long-term mortality, NYHA classification, and comparability of patients
	Has the quality of the data been assessed appropriately?	Yes/no	See above
	Where expert opinion has been used, are the methods described and justified?	Yes	
D2	Is the premodel data analysis methodology based on justifiable statistical and epidemiological techniques?	Yes/no	The equivalence of the treatment group and the historical control may be of concern; 58% of historic controls did not meet 1 of the inclusion criteria for the treatment group
D2a	Is the choice of baseline data described and justified?	Yes	Assumed to have the same mix of NYHA classification
	Are transition probabilities calculated appropriately?	Unclear	Difficult to assess
	Has a half-cycle correction been applied to both cost and outcome?	No	
	If not, has this omission been justified?	No	

Quality Criteria	Questions for Critical Appraisal	Response	Comments
D2b	If relative treatment effects have been derived from trial data, have they been synthesized using appropriate techniques?	No	Treatment effects were derived from EVEREST HRS II. The patients were matched with historical controls. The equivalence of the groups may be a concern
	Have the methods and assumptions to extrapolate short-term results to final outcomes been documented and justified?	Unclear	Methods for long-term mortality are unclear
	Have alternative extrapolation assumptions been explored through sensitivity analysis?	Yes/no	In some cases
	Have alternative assumptions regarding the continuing effect of treatment been explored through sensitivity analysis?	No	
D2c	Are the utilities incorporated into the model appropriate?	Yes	
	Is the source for the utility weights referenced?	Yes/no	Utility values are not sourced directly from patients undergoing procedure; rather, they are derived from published literature that reports utility decrements associated with NYHA classifications, decrements associated with ICU and non-ICU stays, treatment-related adverse events, and mitral valve regurgitation For MR, the article references 2 studies, both measured quality of life: 1 in patients with cardiomyopathy and 1 in patients undergoing mitral valve repair or replacement; however, neither study reported the disutility value used within this analysis
	Are the methods of derivation for the utility weights justified?	Yes/no	The derivation of the disutility associated with mitral regurgitation is unclear A disutility appears to have been applied for both MR and NYHA class, which may lead to an overestimation of the disutility
D3	Have all data incorporated into the model been described and referenced in sufficient detail?	Yes/no	Some details regarding the transition probabilities, mortality, and utilities are unclear
	Has the use of mutually inconsistent data been justified (i.e., are assumptions and choices appropriate)?	n/a	
	Is the process of data incorporation transparent?	Yes/no	In most cases
	If data have been incorporated as distributions, has the choice of distribution for each parameter been described and justified?	No	Distributional assumptions were not reported
	If data have been incorporated as distributions, is it clear that second-order uncertainty is reflected?	Yes	Results of PSA are presented as a cost-effectiveness acceptability curve

Quality Criteria	Questions for Critical Appraisal	Response	Comments
D4	Have the 4 principal types of uncertainty been addressed?	No	See details below under D4a to D4d
	If not, has the omission of particular forms of uncertainty been justified?	No	See details below under D4a to D4d
D4a	Have methodological uncertainties been addressed by running alternative versions of the model with different methodological assumptions?	Yes	Different discount rates and time horizons have been incorporated. Some alternative values for health deficits have been considered; however, the methods are unclear
D4b	Is there evidence that structural uncertainties have been addressed via sensitivity analysis?	Yes/unclear	Assumptions regarding long-term mortality with treatment do not appear to have been tested in sensitivity analyses. Assumptions regarding long-term mortality with MM were examined in sensitivity analyses, as were different utility valuations and varying decrements
D4c	Has heterogeneity been dealt with by running the model separately for different subgroups?	No	
D4d	Are the methods of assessment of parameter uncertainty appropriate?	Unclear	Assumptions regarding parameter distributions within the PSA are unclear
	If data are incorporated as point estimates, are the ranges used for sensitivity analysis stated clearly and justified?	Yes	Details of the ranges within deterministic sensitivity analyses are provided
C1	Is there evidence that the mathematical logic of the model has been tested thoroughly before use?	Unclear	
C2	Are the conclusions valid given the data presented?	Yes	
	Are any counterintuitive results from the model explained and justified?	Yes	
	If the model has been calibrated against independent data, have any differences been explained and justified?	No	
	Have the results of the model been compared with those of previous models and any differences in results explained?	Yes	

Abbreviations: EVEREST, Endovascular Valve Edge-to-Edge Repair Study; HRS, High Risk Study; ICU, intensive care unit; MR, mitral regurgitation; n/a, not applicable; NYHA, New York Heart Association; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-year.

[a]Mealing et al, 2013. (7)

Appendix 3: Evidence Tables

Table A12a: Evidence Table for Randomized Controlled Trials—General Characteristics

Authors, Year (Authors, Year of Companion)	Analysis Type	Subgroup	Study Design	Maximum Duration of Follow-Up	Total Sample Size	Funding	Conflict of Interest
Mauri et al, 2013 (25)	Main study	n/a	RCT	4 y	279	Industry	Yes
Mauri et al, 2013 (25) (Herrmann et al, 2012 (34))	Companion	Patients with AF	RCT	1 y	279	Industry	Yes
Mauri et al, 2013 (25) (Feldman et al, 2011 (36))	Companion	Patients without AF	RCT	1 y	279	Industry	Yes
Mauri et al, 2013 (25) (Feldman et al, 2011 (36))	Companion	n/a	RCT	1 y	279	Industry	Yes

Abbreviations: AF, atrial fibrillation; n/a, not applicable; RCT, randomized controlled trial.

Table A12b: Evidence Table for Randomized Controlled Trials—General Characteristics (continued)

Authors, Year (Authors, Year of Companion)	Exclusions	Is Study Applicable to My Population of Interest?	Intervention	Comparator
Mauri et al, 2013 (25)	MV area < 4.0 cm^2; severe leaflet/annular calcification; flail width ≥ 15 mm; flail gap ≥ 10 mm; pts with functional etiology having coaptation depth > 11 mm below the annulus or coaptation length < 2 mm	Low applicability	MV clip	Surgery
Mauri et al, 2013 (25) (Herrmann et al, 2012 (34))		Low applicability	MV clip	Surgery
Mauri et al, 2013 (25) (Feldman et al, 2011 (36))		Low applicability	MV clip	Surgery
Mauri et al, 2013 (25) (Feldman et al, 2011 (36))		Low applicability	MV clip	Surgery

Abbreviations: MV, mitral valve, pts, patients.

Table A13: Evidence Table for Randomized Controlled Trials—Population Characteristics

Authors, Year (Authors, Year of Companion)	NYHA Class III or IV	MR 3+ or 4+	Surgical Mortality Risk?[a]	Elderly with History of Cardiac Surgery?	Type of MR	AF?	Pulmonary Hypertension?	Concomitant Severe RV Dysfunction at Baseline?	LVEF < 25% at Baseline?
Mauri et al, 2013 (25)	Not majority	Yes, majority	No	No	Mixed	NR	NR	NR	No
Mauri et al, 2013 (25) (Herrmann et al, 2012 (34))	Not majority	Yes, all	No	No	Mixed	Yes	NR	NR	No
Mauri et al, 2013 (25) (Feldman et al, 2011 (36))	Not majority	Yes, all	No	No	Mixed	Yes	NR	NR	No
Mauri et al, 2013 (25) (Feldman et al, 2011 (36))	Not majority	Yes, majority	No	No	Mixed	NR	NR	NR	No

Abbreviations: LVEF, left ventricular ejection fraction; NR, not reported; RV, right ventricular.
[a]For example, as per Society of Thoracic Surgeons.

Table A14a: Evidence Table for Randomized Controlled Trials—Outcome Specifics

Authors, Year (Authors, Year of Companion)	Domain	Outcome 1 (Prespecified)	Outcome 2 (Not Prespecified but Serves in Main Domain)	Definition of Outcome (How Measured and Categorized)	Qualitative Results	Duration of Observation/ Time Point
Mauri et al, 2013 (25)	Mortality	1-y all-cause mortality	n/a	n/a	n/a	1 y
Mauri et al, 2013 (25)	Mortality	Other	Death	n/a	n/a	4 y
Mauri et al, 2013 (25)	Other	Other	Composite outcome	Freedom from death, MV surgery or reoperation, and MR 3+ or 4+	n/a	4 y
Mauri et al, 2013 (25)	Failure	Postintervention surgery	MV surgery or reoperation	n/a	n/a	4 y
Mauri et al, 2013 (25)	Failure	Other	MR 3+ or 4+ at follow-up	n/a	n/a	1 y
Mauri et al, 2013 (25)	Failure	Other	MR 3+ or 4+ at follow-up	n/a	n/a	4 y
Mauri et al, 2013 (25)	Function/QOL	NYHA class at 12 mo		n/a	n/a	1 y
Mauri et al, 2013 (25)	Function/QOL	Other	NYHA class III or IV at 4 y	n/a	n/a	4 y
Mauri et al, 2013 (25)	Other	Other	Composite outcome in patients with degenerative MR	n/a	n/a	4 y
Mauri et al, 2013 (25)	Other	Other	Composite outcome in patients with functional MR	n/a	n/a	4 y
Mauri et al, 2013 (25)	Ventricular remodelling	Ventricular remodelling (absolute end-systolic volume)	n/a	Left ventricular end-systolic volume	n/a	4 y
Mauri et al, 2013 (25)	Ventricular remodelling	Ventricular remodelling (absolute end-systolic volume)	n/a	Left ventricular end-systolic volume	n/a	1 y
Mauri et al, 2013 (25) (Herrmann et al, 2012 (34))	Mortality	Procedure-related AEs (30-d mortality)	n/a	n/a	n/a	30 d
Mauri et al, 2013 (25) (Herrmann et al, 2012 (34))	Mortality	Procedure-related AEs (30-d mortality)	n/a	n/a	n/a	30 d
Mauri et al, 2013 (25) (Herrmann et al, 2012 (34))	Stroke	Procedure-related AEs (30-d stroke)	n/a	n/a	n/a	30 d

Authors, Year (Authors, Year of Companion)	Domain	Outcome 1 (Prespecified)	Outcome 2 (Not Prespecified but Serves in Main Domain)	Definition of Outcome (How Measured and Categorized)	Qualitative Results	Duration of Observation/ Time Point
Mauri et al, 2013 (25) (Herrmann et al, 2012 (34))	Stroke	Procedure-related AEs (30-d stroke)	n/a	n/a	n/a	30 d
Mauri et al, 2013 (25) (Herrmann et al, 2012 (34))	Harms	Procedure-related AEs (blood transfusion requirement)	n/a	≥ 2 units of blood	n/a	30 d
Mauri et al, 2013 (25) (Herrmann et al, 2012 (34))	Harms	Procedure-related AEs (blood transfusion requirement)	n/a	≥ 2 units of blood	n/a	30 d
Mauri et al, 2013 (25) (Herrmann et al, 2012 (34))	Harms	Total major AEs	n/a	Composite outcome[a]	n/a	30 d
Mauri et al, 2013 (25) (Feldman et al, 2011 (36))	Harms	Total major AEs	n/a	Composite outcome[a]	n/a	30 d
Mauri et al, 2013 (25) (Feldman et al, 2011 (36))	Harms	Major SAEs	n/a	Composite outcome[a]	n/a	30 d
Mauri et al, 2013 (25) (Feldman et al, 2011 (36))	Harms	Other	n/a	Any major AEs	n/a	30 d
Mauri et al, 2013 (25) (Feldman et al, 2011 (36))	Harms	Total SAEs (probably FDA defined)	n/a	n/a	n/a	30 d
Mauri et al, 2013 (25) (Feldman et al, 2011 (36))	Mortality	Procedure-related AEs (30-d mortality)	n/a	n/a	n/a	30 d
Mauri et al, 2013 (25) (Feldman et al, 2011 (36))	Stroke	Procedure-related AEs (30-d stroke)	n/a	n/a	n/a	30 d
Mauri et al, 2013 (25) (Feldman et al, 2011 (36))	Harms	Procedure-related AEs (blood transfusion requirement)	n/a	≥ 2 units of blood	n/a	30 d
Mauri et al, 2013 (25) (Feldman et al, 2011 (36))	Function/QOL	QOL	Physical component summary	n/a	n/a	1 y
Mauri et al, 2013 (25) (Feldman et al, 2011 (36))	Function/QOL	QOL	Mental component summary	n/a	n/a	1 y
Mauri et al, 2013 (25) (Feldman et al, 2011 (36))	Ventricular remodelling	Ventricular remodelling (change in end-systolic volume at 12 mo)	n/a	Change from baseline	n/a	1 y

Authors, Year (Authors, Year of Companion)	Domain	Outcome 1 (Prespecified)	Outcome 2 (Not Prespecified but Serves in Main Domain)	Definition of Outcome (How Measured and Categorized)	Qualitative Results	Duration of Observation/ Time Point
Mauri et al, 2013 (25) (Feldman et al, 2011 (36))	Harms	Overall conclusions about AEs	Renal failure, septicemia, MI, gastrointestinal complications requiring surgery		Renal[b]	30 d

Abbreviations: AE, adverse event; FDA, US Food and Drug Administration; MI, myocardial infarction; MR, mitral regurgitation; MV, mitral valve; n/a, not applicable; NYHA, New York Heart Association; QOL, quality of life; SAE, serious adverse event.

[a]Composite of death, MI, reoperation for failed mitral valve surgery, nonelective cardiovascular surgery for AEs, stroke, renal failure, deep wound infection, mechanical ventilation for more than 48 h, gastrointestinal complication requiring surgery, new-onset permanent atrial fibrillation, septicemia, and transfusion of 2 units or more of blood.

[b]Renal failure (1 vs 0 [*P* = 1]); septicemia (0 vs 0 [*P* = n/a]); MI (0 vs 0 [*P* = NA]); gastrointestinal complications requiring surgery (2 vs 0 [*P* = 0.78]) were in mitral valve clip and surgery arms, respectively.

Table A14b: Evidence Table for Randomized Controlled Trials—Outcome Specifics (continued)

Authors, Year	Intervention				Comparator				Between-Group Comparative Estimates				
	No. of Events	No. Analyzed	Mean	SD	No. of Events	No. Analyzed	Mean	SD	Estimate	SD	LCI	UCI	*P* Value
Mauri et al, 2013 (25)	11	181			5	89			n/a				1
Mauri et al, 2013 (25)	28	161			13	73			n/a				0.914
Mauri et al, 2013 (25)	64	161			39	73			n/a				0.07
Mauri et al, 2013 (25)	40	161			4	73			n/a				<0.001
Mauri et al, 2013 (25)	38	181			18	89			n/a				1
Mauri et al, 2013 (25)	35	161			18	73			n/a				0.745
Mauri et al, 2013 (25)	3	151			9	67			n/a				
Mauri et al, 2013 (25)	6	105			3	48			n/a				
Mauri et al, 2013 (25)	49	117			34	51			−25		−41	−9	
Mauri et al, 2013 (25)	15	44			5	22			11		−11	34	
Mauri et al, 2013 (25)		94	54.46	24.2		41	48.93	27.9	5.5		−4	15	0.247
Mauri et al, 2013 (25)		144	57.54	24.04		66	55.74	31.4	1.8		−6	9.6	0.68
Mauri et al, 2013 (25) (Herrmann et al, 2012 (34))	1	45			1	27			n/a				
Mauri et al, 2013 (25) (Herrmann et al, 2012 (34))	1	130			1	62			n/a				
Mauri et al, 2013 (25) (Herrmann et al, 2012 (34))	1	45			1	27			n/a				
Mauri et al, 2013 (25) (Herrmann et al, 2012 (34))	1	130			1	62			n/a				
Mauri et al, 2013 (25) (Herrmann et al, 2012 (34))	8	45			17	27			n/a				

Authors, Year	Intervention				Comparator				Between-Group Comparative Estimates				
	No. of Events	No. Analyzed	Mean	SD	No. of Events	No. Analyzed	Mean	SD	Estimate	SD	LCI	UCI	*P* Value
Mauri et al, 2013 (25) (Herrmann et al, 2012 (34))	15	130			23	62			n/a				
Mauri et al, 2013 (25) (Herrmann et al, 2012 (34))	10	45			18	27			n/a				
Mauri et al, 2013 (25) (Feldman et al, 2011 (36))	16	130			25	62			n/a				
Mauri et al, 2013 (25) (Feldman et al, 2011 (36))	27	180			45	94			n/a				<0.001
Mauri et al, 2013 (25) (Feldman et al, 2011 (36))	9	180			9	94			n/a				0.23
Mauri et al, 2013 (25) (Feldman et al, 2011 (36))	93	184			46	95			n/a				
Mauri et al, 2013 (25) (Feldman et al, 2011 (36))	2	180			2	94			n/a				0.89
Mauri et al, 2013 (25) (Feldman et al, 2011 (36))	2	180			2	94			n/a				0.89
Mauri et al, 2013 (25) (Feldman et al, 2011 (36))	24	180			42	94			n/a				<0.001
Mauri et al, 2013 (25) (Feldman et al, 2011 (36))		132	4.4	9.8		60	4.4	10.4	n/a				0.002
Mauri et al, 2013 (25) (Feldman et al, 2011 (36))		133	5.7	9.9		60	3.8	10.3	n/a				0.006
Mauri et al, 2013 (25) (Feldman et al, 2011 (36))		144	−5.5	14.5		66	−5.6	21	n/a				
Mauri et al, 2013 (25) (Feldman et al, 2011 (36))													

Abbreviations: LCI, lower confidence interval; n/a, not applicable; SD, standard deviation; UCI, upper confidence interval.

Table A15a: Evidence Table for Observational Studies—General Characteristics

Authors (Year)	Study Design	Single/ Multicentre	Country Status	Maximum Duration of Follow-Up	Sample Size	Funding
Whitlow et al, 2012 (27)	Comparative observational cohort	Multiple	Developed	1 y	150	Industry
Conradi et al, 2013 (26)	Comparative observational cohort	Single	Developed	6 mo	171	Industry
Paranskaya et al, 2013 (29)	Comparative observational cohort	Single	Developed	32 d to 3.8 y (median, 1.3 y)	50	NR
Buzzatti et al, 2013 (32)	Predicted counterfactual comparative study	Single	NR	2 y	144	NR
Ajello et al, 2013 (30)	Comparative observational cohort	Single	NR	October 2008–February 2013	252	NR
Schau et al, 2013 (31)	Predicted counterfactual comparative study	NR	NR	March 2009 and November 2012	155	NR
Conradi et al, 2013 (28)	Before-after (time series)	Single	Developed	6 mo	446	NR

Abbreviation: NR, not reported.

Table A15b: Evidence Table for Observational Studies—General Characteristics (continued)

Authors (Year)	Exclusions	Is Study Applicable to My Population of Interest?	Intervention	Comparator
Whitlow et al, 2012 (27)	See footnote[a]	High applicability	MV clip	Other (explain)
Conradi et al, 2013 (26)	NR	Mix of low to high applicability	MV clip	Surgery
Paranskaya et al, 2013 (29)	Mitral stenosis and endocarditis	Low applicability	MV clip	Surgery
Buzzatti et al, 2013 (32)	NR	Unclear applicability	MV clip	SHFM risk prediction model
Ajello et al, 2013 (30)	NR	Mix of low to high applicability	MV clip	Other (explain)
Schau et al, 2013 (31)	NR	Unclear applicability	MV clip	SHFM risk prediction model
Conradi et al, 2013 (28)	NR	Unclear applicability	Before MV clip procedure	After MV clip procedure

Abbreviations: MV, mitral valve; NR, not reported; SHFM, Seattle Heart Failure Model.
[a]Evidence of acute myocardial infarction within 2 wk; left ventricular ejection fraction 20% and/or a left ventricular end-systolic dimension 60 mm; an MV area 4.0 cm^2; leaflet anatomy that might preclude successful device implantation; history of MV leaflet surgery; echocardiographic evidence of an intracardiac mass, thrombus, or vegetation; or active endocarditis.

Table A16: Evidence Table for Observational Studies—Population Characteristics

Authors (Year)	NYHA class III or IV?	MR 3+ or 4+?	Surgical Mortality Risk?	Elderly with History of Cardiac Surgery?	Type of MR	AF?	Pulmonary Hypertension?	Concomitant Severe RV Dysfunction at Baseline?	LVEF < 25% at Baseline?
Whitlow et al, 2012 (27)	Yes, majority	Yes, all	≥ 12% based on STS and surgeon estimated; mean (17.4–18.2)	Yes, majority	Mixed	NR	NR	NR	No
Conradi et al, 2013 (26)	Yes, majority	Yes, majority	EuroSCORE (33.7 ± 18.7 vs 10.1 ± 8.7%) in MVC vs controls, respectively.	No	NR	NR	NR	NR	No
Paranskaya et al, 2013 (29)	Not majority	Yes, all	EuroSCORE <20%; STS 4.2 ± 4	No	Mixed	NR	NR	NR	No
Buzzatti et al, 2013 (32)	Yes, majority	NR	NR	NR	Mixed	NR	NR	NR	No
Ajello et al, 2013 (30)	Not majority	Yes, majority	EuroSCORE (22.3 ± 16.1% vs 22.1 ± 13.7%); STS (10.8 ± 9.8% vs 7.2+/-7.9%)	NR	Functional	NR	NR	NR	No
Schau et al, 2013 (31)	Strongly suspected	Strongly suspected	NR	NR	Mixed	NR	NR	NR	NR
Conradi et al, 2013 (28)	Yes, majority	NR	EuroSCORE (9.4 ± 10.4 in 2007 vs 9.5 ± 10.5 in 2011)	No	Mixed	NR	NR	NR	No

Abbreviations: AF, atrial fibrillation; EuroSCORE, European System for Cardiac Operative Risk Evaluation; LVEF, left ventricular ejection fraction; MVC, mitral valve clip; MR, mitral regurgitation; NR, not reported; NYHA, New York Heart Association; RV, right ventricular; STS, Society of Thoracic Surgeons.

Table A17a: Evidence Table for Observational Studies—Outcome Specifics

Authors (Year)	Outcome Domain	Outcome 1 (Prespecified)	Outcome 2 (Not Prespecified but Serves in Main Domain)	Definition of Outcome (How Measured and Categorized)	Qualitative Results	Duration of Observation/ Time Point
Whitlow et al, 2012 (27)	Mortality	Procedure-related AEs (30-d mortality)	n/a	n/a	NA	30 d
Whitlow et al, 2012 (27)	Mortality	1-y all-cause mortality	n/a	n/a	n/a	1 y
Conradi et al, 2013 (26)	Mortality	Procedure-related AEs (30-d mortality)	n/a	n/a	n/a	30 d
Conradi et al, 2013 (26)	Mortality	Other	Mortality	n/a	n/a	6 mo
Conradi et al, 2013 (26)	Failure	Other	MR 3+ or 4+	n/a	n/a	Periprocedural
Conradi et al, 2013 (26)	Failure	Postintervention surgery	n/a	n/a	n/a	6 mo
Conradi et al, 2013 (26)	Stroke	Procedure-related AEs (30-d stroke)	n/a	n/a	n/a	30 d
Conradi et al, 2013 (26)	Harms	Procedure-related AEs (blood transfusion requirement)	n/a	Units of RBC	n/a	Periprocedural
Conradi et al, 2013 (26)	Function/QOL	Other	NYHA class III or IV	n/a	n/a	6 mo
Conradi et al, 2013 (26)	Harms	Overall conclusions about AEs	Myocardial infarction	n/a	No significant difference	30 d
Paranskaya et al, 2013 (29)	Mortality	Procedure-related AEs (30-d mortality)	n/a	n/a	n/a	30 d
Paranskaya et al, 2013 (29)	Mortality	1-y all-cause mortality	n/a	n/a	n/a	1 y
Paranskaya et al, 2013 (29)	Stroke	Procedure-related AEs (30-d stroke)	n/a	n/a	n/a	30 d
Paranskaya et al, 2013 (29)	Failure	Postintervention surgery	n/a	n/a	n/a	1 y
Paranskaya et al, 2013 (29)	Failure	Other	MR 3+ at last follow-up or 1 y	n/a	n/a	1 y or last follow-up
Paranskaya et al, 2013 (29)	Function/QOL	NYHA class at 12 mo	n/a	n/a	No significant difference in NYHA class	1 y
Paranskaya et al, 2013 (29)	Harms	Other	Important procedure-related complications (various adverse clinical events)	n/a	n/a	1 y
Paranskaya et al, 2013 (29)	Ventricular remodelling	Ventricular remodelling (absolute end-systolic volume)	LVESV at last follow-up	n/a	n/a	1 y
Paranskaya et al, 2013 (29)	Harms	Overall conclusions about AEs	Myocardial infarction (at 1 y); acute kidney failure (procedure related)	n/a	No significant differences between the groups	1 y
Buzzatti et al, 2013 (32)	Mortality	Other	Predicted minus observed mortality in functional MR population	n/a	n/a	Year 1
Buzzatti et al, 2013 (32)	Mortality	Other	Predicted minus observed mortality in functional MR population	n/a	n/a	Year 2

Authors (Year)	Outcome Domain	Outcome 1 (Prespecified)	Outcome 2 (Not Prespecified but Serves in Main Domain)	Definition of Outcome (How Measured and Categorized)	Qualitative Results	Duration of Observation/ Time Point
Buzzatti et al, 2013 (32)	Mortality	Other	Predicted minus observed mortality in degenerative MR population	n/a	n/a	Years 1 and 2
Ajello et al, 2013 (30)	Function/QOL	Other	NYHA at last follow-up	n/a	Evaluation at last follow-up showed clinical improvement in group A: 9.5% of patients were in NYHA functional classes III–IV vs 32.6% (*P* = 0.029)	Follow-up times: group A, 13.7 ± 12.8 mo; group B, 27.1 ± 22.5 mo
Ajello et al, 2013 (30)	Failure		MR ≥ 3+ at last follow-up	n/a	MR ≥ 3+ in 18.3% vs 36.9% (*P* = 0.043); with comparable ventricular function (EF% MR ≥ 3+ in 18.3% vs 36.9% (*P* = 0.043)	
Ajello et al, 2013 (30)	Mortality	Other	n/a	Actuarial survival	NA	24 mo
Ajello et al, 2013 (30)	Mortality	Other	n/a	Actuarial survival	NA	12 mo
Schau et al, 2013 (31)	Other/mixed domains	Other	Qualitative survival report	n/a	Qualitative survival report: Kaplan-Meier-analysis showed all-cause survival for the whole cohort comparable to prediction of the SHFM. Subgroup of patients with end-stage heart failure and NT-proBNP >10,000 pg/mL had poorer outcome than predicted by SHFM	
Conradi et al, 2013 (28)	Mortality	Procedure-related AEs (30-d mortality)	n/a	n/a	n/a	30 d
Conradi et al, 2013 (28)	Failure	Other	Redo cardiac surgery	n/a	n/a	n/a

Abbreviations: AE, adverse event; EF, ejection fraction; LVESV, left ventricular end-systolic volume; MR, mitral regurgitation; n/a, not applicable; NS, not significant; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; NYHA, New York Heart Association; QOL, quality of life; RBC, red blood cells; SHFM, Seattle Heart Failure Model.

Table A17b: Evidence Table for Observational Studies—Outcome Specifics (continued)

Authors (Year)	Intervention				Comparator				Between-Group Comparative Estimates				
	No. of Events	No. Analyzed	Mean	SD	No. of Events	No. Analyzed	Mean	SD	Estimate	SD	LCL	UCL	*P* Value
Whitlow et al, 2012 (27)	6	78			3	36			n/a				
Whitlow et al, 2012 (27)	19	78			16	36			n/a				
Conradi et al, 2013 (26)	4	95			2	76			n/a				
Conradi et al, 2013 (26)	8	95			4	76			n/a				NS
Conradi et al, 2013 (26)	4	95			1	76			n/a				
Conradi et al, 2013 (26)	3	95			0	76			n/a				
Conradi et al, 2013 (26)	1	95			0	76			n/a				
Conradi et al, 2013 (26)		95	0.5	1.2		76	1.4	1.7	n/a				
Conradi et al, 2013 (26)	29	95			13	76			n/a				
Conradi et al, 2013 (26)	1	95			0	76		1	n/a				
Paranskaya et al, 2013 (29)	0	24			0	26			n/a				
Paranskaya et al, 2013 (29)	2	24			0	26			n/a				
Paranskaya et al, 2013 (29)	0	24			2	26			n/a				0.29
Paranskaya et al, 2013 (29)	3	24			1	26			n/a				
Paranskaya et al, 2013 (29)	0	24			1	26			n/a				0.65
Paranskaya et al, 2013 (29)	1	24			2	26			n/a				
Paranskaya et al, 2013 (29)	8	24			4	26			n/a				0.51
Paranskaya et al, 2013 (29)		24	55.4	19		26	57	15.6	n/a				0.79
Paranskaya et al, 2013 (29)													
Buzzatti et al, 2013 (32)									9.1				0
Buzzatti et al, 2013 (32)									12.1				<0.0001
Buzzatti et al, 2013 (32)													
Ajello et al, 2013 (30)	10	105			37	112							0.03
Ajello et al, 2013 (30)	19	105			41	112			n/a				0.46
Ajello et al, 2013 (30)		105	80.2 ± 5.2			112	57.0 ± 8.1		n/a				0
Ajello et al, 2013 (30)		105	88.9 ± 3.5			112	69.5 ± 7.3		n/a				0
Schau et al, 2013 (31)													

Authors (Year)	Intervention				Comparator				Between-Group Comparative Estimates				
	No. of Events	No. Analyzed	Mean	SD	No. of Events	No. Analyzed	Mean	SD	Estimate	SD	LCL	UCL	*P* Value
Conradi et al, 2013 (28)	14	194			11	252			n/a				0.22
Conradi et al, 2013 (28)									0.52				<0.01

Abbreviations: LCL, lower confidence limit; n/a, not applicable; NS, not significant; SD, standard deviation; UCL, upper confidence limit.

Appendix 4: List of Included and Excluded Studies

Included Studies

Effectiveness and Harms: Systematic Reviews

For Identifying Primary Studies Only

- 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 2013 Jun 27. [PMID: 23813844]
- 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 2013 Dec 10. [PMID: 24323764]

For Updating—Good Quality Review Serving Our Purpose

- 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 2013 Jun 27. [PMID: 23813844]

Effectiveness and Harms: Primary Studies

- 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 Jul 23;62(4):317–28. [PMID: 23665364]
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Record Had Study Design Issue (Editorial, Protocol, Not a Primary Study, or Noncomparative)

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Record's Full Text Could Not Be Retrieved

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Economics: Primary Studies and Systematic Reviews

Record Did Not Evaluate Cost-Effectiveness of the MitraClip or Percutaneous Mitral Regurgitation Edge-to-Edge Repair

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Record Was an Abstract of a Fully Published Study Already Included in Synthesis

- Mealing S, Eaton JN. MitraClip for patients with mitral regurgitation who are ineligible for surgical repair or replacement: A UK based cost-utility analysis. J Am Coll Cardiol 2011;58(20 Suppl 1):B212.

Appendix 5: Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA—Screening Process)

Search Output from Databases

- Economic database (reviews + primary studies), total n = 141
- Reviews of effectiveness and harms database, total n = 69 + 1 (reviewer nominated)

The screening questions/criteria are listed in Figures A1 to A4.

Results of Level I (Title or Abstract) Screening

Level I Screening: Effectiveness and Harms (SR Evidence)

E = exclude

I = include because this record is an eligible SR. Eligibility criteria:

- Claims to be an SR
- Reports searching the literature or specific database and/or screened literature using reported eligibility criteria
- Pertains to symptomatic patients (NYHA class III or IV) with moderate or severe mitral regurgitation (3+ or 4+) of chronic functional or degenerative etiology who are at high or prohibitive risk for surgical mitral valve repair/replacement
- Investigates repair of the mitral valve with a mitral valve clip

U = uncertain (pass to level 2)

F = flag (e.g., for economic question; or potentially eligible primary study for effectiveness and harms)

Level I Screening: Economic Evaluations (SR or Primary Evidence)

E = exclude

I = relevant full economic evaluation (primary or economic synthesis) of mitral valve clip

F = flag (e.g., for effectiveness and harms)

Figure A1: Screening Criteria and Questions for Level 1 Screening Based on Title or Abstract

Abbreviations: NYHA, New York Heart Association; SR, systematic review.

Potential SRs of mitral valve clip effectiveness and harms (i.e., those passed or flagged while screening the 2 databases above) were these:

- 2 from economic database in reverse (latest to earliest) chronological order (48;49)
- 10 from effectiveness and harms database in reverse chronological order (24;39-47)
- 1 review not picked up in searches but considered reviewer nominated (23)

Potential SRs/primary studies of mitral valve clip economic evaluation (i.e., those passed or flagged in the while screening the 2 databases above) were the following:

- 5 from economic database (7;38;49;64;65)

- None from effectiveness and harms database (because they were already captured in economic searches)

Results of Level II (Full-Text) Screening

Exclude if not SR (i.e., not on topic in terms of population and intervention, or not an SR)

- Yes
- No (stop and do not screen for following screening question)

Include if the search is reliable:

- Yes
- No (stop and do not screen for following screening question)

Note: A reliable search must report at least 2 databases (one of which must be MEDLINE), search end date(s), and key terms/search terms:

- Yes
- No (a final assessment of no leads to clear exclude)

Note: In either case, send off a letter to the corresponding author and probably 1 more author and request for the search strategy in 1 week. Consider coming back to re-evaluate the record for this question if the provisional answer is no.

Does the SR meet the quality standards stipulated below?

- Yes
- No

Note: Quality should be assessed using the following:

- 2 independent reviewers screened or 1 screened and the other verified the records (e.g., if 20% of the records were verified, the result of the verification must be reported)
- Eligibility criteria are appropriate (this question assesses reviewers' judgment about the clinical and/or methodological relevance of included studies for which reviewers may have to look at included study characteristics)
- Some sort of summary of the included study characteristics must be reported
- Some reasonable RoB assessment must be reported
- The overall methods of evidence synthesis are appropriate

Rate the quality additionally using AMSTAR and provide overall score while documenting specific AMSTAR answers. (Note, AMSTAR scores alone do not inform eligibility.)

Figure A2: Screening Criteria and Questions for Level 1 Screening Based on Full Text

Abbreviations: AMSTAR, Assessment of Multiple Systematic Reviews; RoB, risk of bias; SR, systematic review.

- Starting number: n = 13 for questions of effectiveness and harms, and n = 5 for the economic question

Systematic Reviews/Primary Studies for Economic Evaluation

Of the 5 studies, 2 (7;38) were included and 3 (49;64;65) were excluded for the following reasons:

- Record did not evaluate the cost-effectiveness of mitral valve clip or percutaneous MR edge-to-edge repair (49;64)
- Record was an abstract of a fully published study that is already included in the synthesis (65)

Systematic Reviews of Effectiveness and Harms

We started screening in reverse (latest to earliest) chronological order. (23;24;39-49) Because our stopping rule was met, double reviewer screening was not employed for 8 articles (40;42-47;49). Studies were excluded for the following reasons:

- 2 reviewers excluded 2 records that did not qualify as SRs (41;48)
- A single reviewer screened all others and excluded studies for various reasons (2 were duplicates of a poorly reported SR (40;43); 1 was a narrative review (42); 1 (44) was an earlier companion version of 2 studies (40;43); 3 were narrative (45;46;47); 1 was not an SR (49); 1 was deemed as unclear for its comprehensiveness of search strategy (39))

We included 2 SRs. (23;24) These SRs were deemed to have employed reliable search strategies (i.e., at least 2 databases—1 of which should have been MEDLINE—were searched, end dates and key search terms were reported), but their evidence synthesis was not undertaken with a view to minimizing bias across studies. They received AMSTAR scores of 4 and 7, respectively, out of a total of 11. As such, we used these reviews to identify included studies for their search periods. We searched and included additional new primary studies of relevance.

Level I Screening for Primary Studies for the Questions of Effectiveness and Harms

I (include):

- Reports comparative effectiveness of mitral valve clip versus surgery or conservative medical management in patients with mitral regurgitation
- Study design is comparative (two independent groups), experimental, or observational (concurrent, internal control, historical, or external control)
- English language

E (exclude)

F (flag): if potential primary study for economics

Figure A3: Screening Criteria and Questions for Level 1 Screening Based on Title or Abstract for Primary Studies

In this database, studies (n = 521) came from 4 sources:

- 9 were flagged as relevant in the economic database screen (27;36;50-56)
- 36 were included in the 2 identified SRs (or were excluded for the narrower focus of the primary SR, but potentially eligible for our review)
- 469 originated from our searches run on February 7, 2014, with a 6-month overlap with search periods of the 2 included SRs (latest search end date was June 2013 for Vakil et al's SR) (23); we searched Ovid MEDLINE(R), Embase, and the Cochrane Library for the period January 2013 to February 7, 2014
- 7 records from the WHO Trial Registry (grey literature)

After removing duplicates, we were left with a total of 484 records. We passed 36 of 484 records to level II for full-text screening.

Level II Screening for Primary Studies for the Questions of Effectiveness and Harms

Option 1: exclude due to the following (select the first obvious reason):

- Language other than English and no useful information from abstract when in English
- Does not evaluate benefits or harms of the mitral valve clip or percutaneous MR edge-to-edge repair
- Incorrect study design (editorial, protocol, not a primary study, or non-comparative)
- Wrong population (non-MR)
- Wrong intervention (no mitral valve clip or no similar percutaneous MR edge-to-edge repair)
- No surgical or pharmacological treatment as comparator
- Other—text box for reasons that must be recorded if this option is selected

Flag as relevant economic evaluation; this can be selected with option 1 or 2.

Option 2: include because option 1 above is not selected—either this record should clearly be included or its exclusion is unclear

Figure A4: Screening Criteria and Questions for Level II Screening Based on Title or Abstract for Primary Studies of Effectiveness and Harms

Abbreviation: MR, mitral regurgitation.

Of a total of 36 records passed to level II, 1 record was excluded because full text could not be retrieved. (66) We finally included, with consensus, 13 records ((25;26;34), also atrial fibrillation effect modification, (60) and postprocedure repair rate (27-33;36;37)). See Table A18.

Table A18: Included and Excluded Primary Studies for Questions on Effectiveness and Harms of Mitral Valve Clip[a]

Ref ID	Reviewer 1	Reviewer 2	Consensus	Additional Notes
75	I	I	I	
80	I	I	I	
103	E	E	Does not evaluate benefits or harms of mitral valve clip or percutaneous MR edge-to-edge repair (1b)	
104	I	I	I	Also AF effect modification
106	I	I	I	Postprocedure repair rates (serious adverse event?)
517	E	E	Does not evaluate benefits or harms of mitral valve clip or percutaneous MR edge-to-edge repair, but investigates CARILLON Mitral Contour System (1b)	
522	I	I	I	
556	I	E	2 groups, but different populations as descriptive results (1c)	
610	I	I	I	
626	E	E	Descriptive (1c)	
633	E	E	1c	
1,006	E	E	1c	
1,007	E	E	1c	
1,016	E	E	1c	
1,057	E	I	I	Transparently report post hoc inclusion of this design that examines health services/program improvement
1,121	I	E	1c	
1,175	I	I	I	
1,204	E	E	1c	
1,270	U	I	I	
1,271	U	I	I	Transparently report this novel design for a counterfactual comparator
1,282			Full text could not be retrieved	
1,292	I	I	I	
1,326	I	I	I	
1,338	E	E	1c	
1,353	I	I	I	
1,377	E	E	1c	
1,381	E	E	1c	
1,389	E	E	1c	
1,414	E	E	1c	
1,434	E	E	1c	
1,500	E	E	1c	Consider methods for QA assessment
1,502	E	E	1c	Consider
1,503	E	E	1c	Consider

Ref ID	Reviewer 1	Reviewer 2	Consensus	Additional Notes
1,504	E	E	1c	Consider
1,505	E	E	1c	Consider
1,506	E	E	1c	Consider

Abbreviations: AF, atrial fibrillation; E, exclude; I, include; MR, mitral regurgitation; QA, quality assurance; ref ID, reference identification; U, unclear.
[a]n = 36.

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Health Quality Ontario
130 Bloor Street West, 10th Floor
Toronto, Ontario
M5S 1N5
Tel: 416-323-6868
Toll Free: 1-866-623-6868
Fax: 416-323-9261
Email: EvidenceInfo@hqontario.ca
www.hqontario.ca

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