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Transcatheter and surgical intervention for secondary mitral regurgitation (Protocol)

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[Intervention Protocol]

Transcatheter and surgical intervention for secondary mitral regurgitation

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ABSTRACT

Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

To assess the effects in secondary mitral regurgitation of:

1. Surgical mitral valve intervention and coronary artery bypass graft versus coronary artery bypass graft alone; and
2. Transcatheter mitral valve intervention and medical therapy versus medical therapy alone.

BACKGROUND

Description of the condition

Mitral regurgitation (MR) is the reversal of blood flow through the left side of the heart, such that blood leaks through the mitral valve from the left ventricle (the main cardiac chamber) to the left atrium (one of the smaller chambers). Under normal conditions, this is prevented by closure of the two mitral valve leaflets. However, effective closure can be prevented by diseases that affect the left ventricle (LV) or the mitral apparatus, consisting of the mitral leaflets, chordae tendinae (strings that keep the leaflets taught), and papillary muscles (pillar-like structures attached to the LV, into which the chordae tendinae insert). During the normal filling phase of the cardiac cycle, left atrial (LA) pressure exceeds LV pressure, causing the mitral valve leaflets to open into the LV. Once LV pressure exceeds LA pressure, the mitral valve leaflets passively close, and are prevented from inverting back into the LA by the tension of the chordae tendinae, exerted by the papillary muscles. MR is the consequence of any disruption to this process, resulting in failure of leaflet coaptation (union) (Harb 2017).

Types of MR (primary versus secondary)

Mitral regurgitation (MR) can be categorised as primary or secondary, according to the underlying aetiology. Primary MR is the most common type, and is caused by age-related degeneration that alters leaflet shape, or fibroelastic deficiency that alters motion. The LV and papillary muscles are generally unaffected, and primary MR is characterised by echocardiographic findings of thickened leaflets with reduced mobility, ruptured chordae, or flail leaflets (leaflets that have lost their connection with the chordae tendinae, which means they move freely and therefore, do not function).

In contrast, secondary MR is characterised by relatively normal leaflets and chordae, but LV dysfunction (e.g. following a heart attack), or dilatation (e.g. dilated cardiomyopathy when the heart muscle has weakened and the heart has enlarged). These processes displace the papillary muscles, distorting the subvalvular geometry, such that the leaflets are tethered in the open position by the chordae tendinae (Harb 2017). This review will focus on the the role of intervention in secondary MR, for which the respective roles of transcatheter and surgical intervention are less well defined.

Consequences of MR

Left untreated, MR contributes to LA and LV volume overload, resulting in progressive chamber dilatation and contractile failure (Gaasch 2008). Without intervention, people with MR will develop progressive exercise limitation and impaired quality of life. The estimated five-year survival of people with severe secondary MR is less than 40% (Rossi 2011).

Assessment of MR

The first line investigation to diagnosis MR is transthoracic echocardiography (cardiac ultrasound (Vahanian 2021)). International guidelines recommend a multiparametric approach to the quantification of MR that combines qualitative, semi-quantitative, and quantitative measures (Kron 2017; Lancellotti 2013; Zoghbi 2017).

Qualitative parameters include:

- Regurgitant jet area by colour flow Doppler (a technique that colour codes the flow of blood in a region of interest to determine direction of flow)
- Jet density and shape (denser jets, and those that are triangular, as opposed to the usual parabolic shape, are associated with more severe regurgitation)
- Size of the flow convergence zone (a hemispheric zone where the regurgitant blood converges, the size of which correlates with the volume of regurgitant blood)

Semi-quantitative parameters include:

- Pulmonary vein flow (blood flow in the vein leading to the LA)
- Mitral inflow pattern (blood flow across the mitral valve, mapped over time)
- Vena contracta width (the width of the regurgitant jet at the origin and narrowest point)

Quantitative measures include:

- Proximal isovolumetric surface area (PISA) – a measurement of the size of the flow convergence zone
- Effective regurgitant orifice area (EROA) – an estimate of the area of the valve that is leaking
- Regurgitant volume (RVol) – a measure of the volume of leaking blood
- Regurgitant fraction (RF) – the proportion of the total LV volume leaking into the LA

Table 1 summarises the echocardiographic parameters that define MR severity, as determined by the American Society of Echocardiography (ASE) (Nishimura 2017; Zoghbi 2017), and the European Association of Cardiovascular Imaging (EACVI (Lancellotti 2013)). Due to discrepancies between international guidelines defining the severity of secondary MR, we will examine people with at least moderate (2+) MR in this review. The severity of MR may differ in low-flow or high-flow states. There remains controversy regarding the definition of 'severe' secondary MR (Grayburn 2014).

In cases of indeterminate MR (e.g. due to poor echocardiography quality or discordant quantitative and qualitative parameters), 3D echocardiography, or cardiovascular magnetic resonance imaging can be used to further clarify MR severity (Bonow 2020).

An emerging theory is that determing the severity of the MR alone is insufficient to select people with secondary MR who will benefit from intervention. In theory, people with secondary MR may benefit from indexing the severity of secondary MR to the extent of LV dilatation or impairment, or both. People with significant MR may be more suitable for interventions targeting the mitral valve than those with mild LV dilatation or dysfunction. In contrast, people with less severe MR and more significant LV dilatation may be more suitable for medical therapy, aimed at treating heart failure (Grayburn 2019).

Description of the intervention

Interventional approaches for MR can be classified as transcatheter or surgical. Mitral regurgitation is the second most frequent indication for valve surgery in Europe (Ancona 2019), and traditionally, surgery has been the mainstay of treatment, and

remains the first line option (Vahanian 2021). However, with recent advances in transcatheter devices and techniques, transcatheter approaches are increasingly used.

Surgical treatment

Surgical treatment for secondary MR involves either repair or complete replacement of the valve. Both techniques require general anaesthesia and usually cardiopulmonary bypass, a procedure during which the beating heart is stopped and drained of blood, and oxygenated blood is mechanically circulated around the body by a pump. Surgery is performed via a median sternotomy (large midline scar), or lateral thoracotomy (smaller scar) for minimally invasive approaches. Mitral valve repair involves re-suspending the mitral leaflets or implanting an annuloplasty ring (which may be intentionally restrictive due to under-sizing), or both, to restore annulus size and shape. In cases where repair is not feasible, the valve is entirely replaced by a biological or mechanical prosthesis, with preservation of the subvalvular apparatus. Both repair and replacement are major surgical procedures (Acker 2014).

Transcatheter treatment

Transcatheter mitral valve repair has the advantage of avoiding cardiopulmonary bypass, and although these procedures are predominantly performed under general anaesthesia, they can also be performed under conscious sedation or even without any sedation (Ates 2020; Ledwoch 2016). The procedure is less invasive, and is usually carried out through a catheter (small tube), into a major vein in the leg. Current generation devices focus mainly on edge-to-edge repair of the mitral valve leaflets to reduce the effective regurgitant orifice area (e.g. MitraClip(R), Abbott Laboratories, Illinois, USA and Pascal system, Edwards Lifesciences, California, USA). These devices mimic the surgical treatment strategy described by Alfieri and colleagues (Alfieri 1995), in which a stitch is placed in the anatomical middle of the two mitral valve leaflets, reducing one large regurgitant orifice area to two smaller orifices. Future emerging devices, which have already gained CE approval, may improve on the current generation therapies by offering transcatheter ring annuloplasty repair (Cardioband (R), Edwards Lifesciences), or complete transcatheter mitral valve replacement (Tendyne (R), Abbott Laboratories), similar to the surgical treatments currently offered.

How the intervention might work

Medical therapy is limited to treating heart failure; there are no proven drug therapies that reduce the severity of MR. Cardiac resynchronisation can reduce secondary MR by up to one grade, but non-interventional therapies are otherwise limited (van Bommel 2011). In people with severe MR, mitral valve intervention is the treatment of choice. The interventions work by reducing the regurgitant orifice area of the mitral valve, and thereby, decreasing the severity of MR.

Surgical intervention

Indications, methods, and outcomes from surgical intervention vary considerably according to the aetiology of MR. The rationale for surgery is that correction of the secondary MR should reduce the burden of regurgitation on the LV, and thereby, improve symptoms and prognosis.

Indications

n primary MR, symptomatic severe disease is a class I indication to perform surgery, since it reduces symptoms and improves life expectancy. By contrast, guidelines do not generally recommend surgery in severe secondary MR, unless there is a need to perform concurrent cardiothoracic surgery such as coronary artery bypass grafting (CABG) (Vahanian 2021)). This approach is based on a number of studies that demonstrated that correcting the secondary MR failed to improve survival (Fattouch 2009; Kang 2009; Michler 2016), or improve echocardiographic characteristics (Bouchard 2014).

Methods

Surgery for MR is usually performed under general anaesthesia, with cardiopulmonary bypass, via a midline sternotomy. For people with primary MR, mitral valve repair (compared to replacement) is currently the recommended gold standard treatment, based on studies that showed better survival than mitral valve replacement (Lazam 2017). However, for people with secondary MR, trials did not find that survival was improved by either repair or replacement. Moreover, MV replacement was shown to provide a more durable correction, and there was more recurrence of MR in the repair group (Acker 2014; Goldstein 2016). Consequently, the optimal treatment option between repair and replacement in people with secondary MR is not well understood.

Outcomes

Outcomes following surgery are less favourable in secondary MR. In primary MR, MV repair significantly improves survival (Kang 2009), and 70% of people remain free of recurrent moderate or severe MR at 20 years (David 2013). By contrast, in secondary MR, reduced mortality has only been observed in one study (Deja 2012), but not in prospective RCTs (Chan 2012; Fattouch 2009; Michler 2016), or other non-RCT studies (Mihaljevic 2007). The durability of surgical repair in secondary MR is inferior to that seen in primary MR; only 75% of people remain free of recurrent moderate or severe secondary MR at two years (Glaveckaite 2018).

Transcatheter intervention

Transcatheter intervention is currently reserved for people with contraindications to surgery (Vahanian 2021), in select people, there appear to be a survival benefit over medical therapy alone (Stone 2018). Compared to surgery, transcatheter intervention has a better safety profile (Feldman 2011), and among people with secondary MR, transcatheter and surgical mitral valve repair may have equivalent outcomes (Guerrero 2016). The efficacy of transcatheter repair in people with secondary MR remains unclear, as two seminal studies published contemporaneously, demonstrated conflicting results (Obadia 2018; Stone 2018).

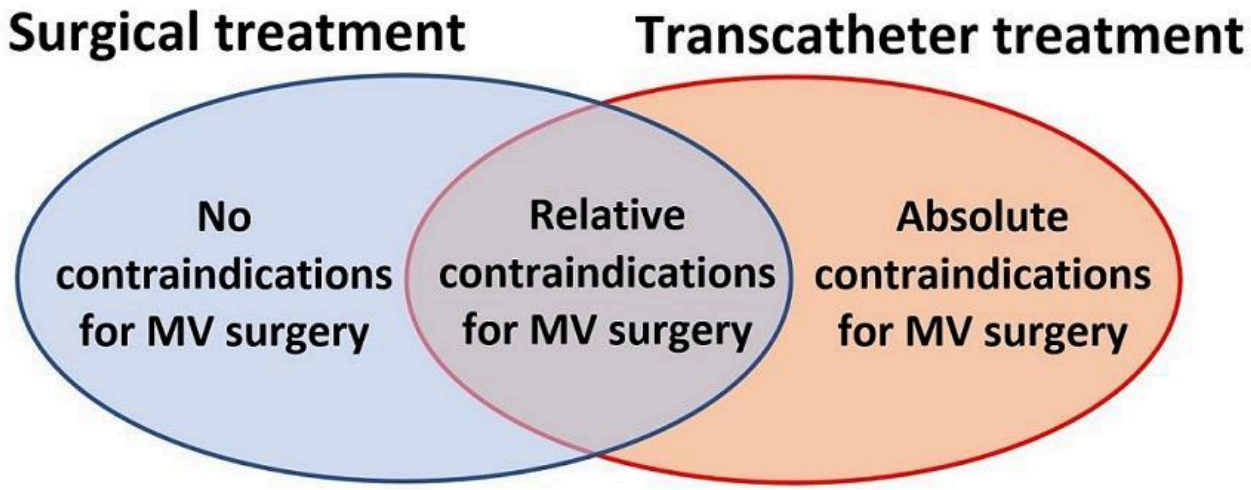
Why it is important to do this review

Mitral regurgitation is the most common valve disease diagnosed worldwide. As life expectancy improves, prevalence is only expected to increase, particularly as MR most commonly affects those over 65 years of age (Nkomo 2006). Without intervention, those affected develop progressive exercise limitation and impaired quality of life.

While surgical treatment has historically been the mainstay of treatment, in recent years, transcatheter treatment has come to

the fore as a credible alternative. As interventional techniques evolve, identifying the respective roles of transcatheter and surgical intervention for MR becomes increasingly important. In many cases, it is unclear which treatment modality is best suited to the person, particularly amongst those with higher surgical risk (Figure 1).

Figure 1. Overlapping indications for surgical and percutaneous mitral valve repair



International guidelines currently recommend surgery as the first line treatment for severe MR of all types, and transcatheter treatment is reserved for people who are inoperable, or high surgical risk (Nishimura 2017; Vahanian 2021). However, strict definitions or criteria constituting high operative risk are lacking. This 'one-size fits all' strategy may be inappropriate for people with secondary MR, as they are a heterogenous group, with a range of ages, risk factors (such as diabetes, hypertension, dyslipidaemia), MR volumes, LV structure and function. They often also have varying co-morbidities, which include prior myocardial infarction, cardiomyopathy, stroke, peripheral vascular disease, and liver or renal failure. These factors significantly influence the optimal treatment strategy and consequential outcomes. This is underscored by the European Society of Cardiology 2021 Valvular Heart disease guidelines, which suggest that "additional studies are needed to identify patients who will benefit" from transcatheter intervention and that "the evidence supporting surgical interervention [in secondary MR} remains limited". An evolving theory is that outcomes from MR intervention are particularly sensitive to selecting the right person (Grayburn 2018); identifying subcohorts with factors that promote favourable outcomes is paramount. However, there are no recent meta-analyses in this field; the last two date from 2013 and 2016 (Takagi 2016; Wan 2013).

The American Heart Association 2020 guidelines have also acknowledged the expanding role of transcatheter treatment, and summarised that treatment with an edge-to-edge device "has expanded from the treatment of severely symptomatic people with primary severe MR who are poor operative candidates, to carefully selected people with secondary MR with persistent heart failure symptoms" (Bonow 2020).

This review aims to better define the roles of transcatheter and surgical mitral valve intervention in moderate and severe secondary MR, and provide evidence to enable clinicians to offer people the appropriate management, thus maximising effectiveness of these costly and invasive procedures.

OBJECTIVES

To assess the effects in secondary mitral regurgitation of:

1. Surgical mitral valve intervention and coronary artery bypass graft versus coronary artery bypass graft alone; and
2. Transcatheter mitral valve intervention and medical therapy versus medical therapy alone.

METHODS

Criteria for considering studies for this review

Types of studies

We will include all randomised controlled trials (RCTs) that fulfill the following comparisons:

1. Surgical mitral valve intervention and coronary artery bypass graft (CABG) versus CABG alone (control group)
2. Transcatheter mitral valve intervention and medical therapy vs control group (medical therapy alone)

We will include studies published as full text, abstract only, and those that are unpublished. For the purpose of this review, we anticipate that sufficient RCTs have been conducted to answer this clinical question, and therefore, we will not include any non-randomised studies.

We do not anticipate that we will encounter any cluster-randomised trials. However, if we identify such trials, we will include them. We will not consider cross-over trials, as once a person undergoes the intervention (e.g. surgery), they cannot go into another arm.

Types of participants

We will include adults 18 years of age and older, with a diagnosis of moderate or severe secondary mitral regurgitation (MR), who are eligible for a mitral valve intervention by transcatheter or surgical procedures. We will only include trials with participants with who do not fit our inclusion criteria, if they include a subset of eligible participants, and then, only if separate data for the eligible participants are available, or the majority of participants (i.e. more than 80%), meet our inclusion criteria.

Types of interventions

Surgical mitral valve intervention includes mitral valve replacement or repair (including all leaflet or annuluplasty repairs) performed through the midline sternotomy or lateral thoracotomy appproach.

Coronary artery bypass grafting involves the attachment of an autologous coronary graft (radial artery, saphenous vein, or internal mammary artery).

Transcatheter intervention uses the transcatheter approach to repair or replace the mitral valve via the femoral approach (excluding hybrid procedures).

Medical therapy includes all medical treatment for heart failure, such as beta blockers, angiotensin converting enzyme (ACE) inhibitors, angiotensin-2 receptor blockers (ARB), mineralocorticoid receptor blockers (MRA), angiotensin receptor-neprolysin inhibitor (ARNI), or diuretics.

People with device therapy (pacemakers and defibrillators), and exercise or dietary treatments will be eligible, given that they are equally available to all participants.

Types of outcome measures

We will use the definitions and measurement of clinical events outlined in the individual trials. We will assess outcomes at 12 months ± 3 months, and at longest follow-up. We have chosen these specific outcome follow-up periods, as some known trials in this area report outcomes at one year (Takagi 2016; Wan 2013); however, longer follow-up data are also available from some trials.

We are interested in the number of study participants with at least one event, rather than the number of events.

Reporting one or more of the outcomes of interest is not an inclusion criterion for the review. When a publication does not appear to report one of these outcomes, we will access the trial protocol and contact the trial authors, to ascertain whether the outcomes were measured but not reported. We will include relevant trials, which measured these outcomes but did not report any data, or data that were not in a usable format, as part of the narrative.

Primary outcomes

- Mortality
- Hospitalisation for heart failure

Secondary outcomes

- Re-intervention for mitral valve dysfunction
- MR grade ≥ 3+
- End-diastolic volume (mL) on echocardiography
- End-systolic volume (mL) on echocardiography
- Ejection fraction on echocardiography
- Quality of life, using the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36; scores range from 0 to 100; higher scores indicate better quality of life). We will use other scales, such as the Sickness Impact Profile or Nottingham Health Profile, if available, and the SF-36 survey was not used
- New York Heart Association (NYHA) functional classification (I to IV)

Adverse events:

- renal failure
- new onset atrial fibrillation
- gastrointestinal complications requiring surgery
- mechanical ventilation for longer than 48 hours
- major bleeding events (defined as those requiring a transfusion of ≥ 2 units of blood products)
- major stroke
- sepsis
- Left ventricular outflow tract (LVOT) obstruction
- access site complications

Search methods for identification of studies

Electronic searches

We will identify trials through systematic searches of the following bibliographic databases:

- Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library, current issue
- MEDLINE Ovid (1946 to search date)
- Embase Ovid (1980 to search date)
- Science Citation Index Expanded on the Web of Science (Clarivate Analytics; 1900 to search date)

The preliminary search strategy for MEDLINE Ovid will be adapted for use in the other databases (Appendix 1). The Cochrane sensitivity-maximising RCT filter will be applied to MEDLINE Ovid, and adapted for the other databases, except CENTRAL (Lefebvre 2019).

We will also conduct a search of ClinicalTrials.gov (www.ClinicalTrials.gov), the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) Search Portal (apps.who.int/trialsearch/), and Clinical Trials Register EU (www.clinicaltrialsregister.eu) for ongoing or unpublished trials.

We will impose no restriction on language of publication or publication status.

We will not perform a separate search for adverse effects of the interventions (transcatheter or surgical) used for the treatment of secondary MR. We will consider adverse effects described in the included studies only.

Searching other resources

We will also search the International Medical devices database (medicaldevices.icij.org/), and the FDA website (www.fda.gov/medical-devices/products-and-medical-

procedures/device-approvals-denials-and-clearances), which cover the majority of medical devices.

We will check reference lists of all included studies, and any relevant systematic reviews identified, for additional references to trials. We will also examine any relevant retraction statements and errata for included studies. We will contact trial authors for missing data, and authors of ongoing trials for a status update, by email.

Data collection and analysis

Selection of studies

Two review authors will independently screen titles and abstracts of all the potential studies we identify as a result of the search, and code them as 'retrieve' (eligible or potentially eligible or unclear) or 'do not retrieve'. If there are any disagreements, a third review author will be asked to arbitrate. We will retrieve the full-text study reports or publications, and two review authors will independently screen the full-text to identify studies for inclusion, and identify and record reasons for exclusion of the ineligible studies. We will resolve any disagreement through discussion, or if required, we will consult a third person.

We will identify and exclude duplicates, and collate multiple reports of the same study, so that each study, rather than each report, is the unit of interest in the review. We will record the selection process in sufficient detail to complete a PRISMA flow diagram and 'Characteristics of excluded studies' table (Liberati 2009).

Data extraction and management

We will use a data collection form for study characteristics and outcome data, which we will pilot with at least one included study. We will extract the following study characteristics.

1. Methods: study design, total duration of study, number of study centres and location, country in which study is published, study setting, and date of study
2. Participants:
   a. General: N randomised, N lost to follow-up or withdrawn, N analysed, mean age, age range, gender, inclusion criteria, and exclusion criteria
   b. Method of randomisation: allocation random, allocation sequence concealed, baseline differences between intervention groups (comments), and what analysis was done to estimate the effect of assignment to intervention
   c. Comorbidities and risk factors: smoking status (risk factor), hypertension, diabetes mellitus, hypercholesterolaemia, history of cardiovascular disease, history of previous reduced LV function, atrial fibrillation, chronic obstructive pulmonary disease (COPD), previous coronary artery bypass surgery
   d. Severity of symptoms: NYHA functional class, SF-36 score
   e. Severity of MR: classification (1+ to 4+), regurgitant volume (RVol; mL/beat), effective regurgitant orifice area (EROA; cm^2)
   f. Aetiology of MR: secondary MR: ischaemic, functional (due to annular dilatation)
3. Interventions: type of intervention (surgical; repair or replacement; transcatheter; type of device used), medications used, including ACE inhibitors, ARB, beta blockers, MRA, diuretics, digoxin
4. Outcomes: primary and secondary outcomes specified and collected, time points reported, measurement methods and thresholds reported; we will also record whether there are missing data
5. Notes: study funding and notable conflicts of interest of trial authors

One review author will extract study characteristics from included studies; a second review author will spot-check study characteristics for accuracy against the trial report. Two review authors will independently extract outcome data from included studies. We will resolve disagreements by consensus, or by involving a third person. One review author will transfer data into the Review Manager 5 file (Review Manager 2020). We will double-check that data are entered correctly by comparing the data presented in the trial report with the data extraction form.

Assessment of risk of bias in included studies

Two review authors will independently assess risk of bias for each study using Cochrane's RoB 2, outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019c). We will resolve any disagreements by discussion, or by involving another author. We will assess the risk of bias of specific results of a trial according to the following domains:

- bias arising from the randomisation process;
- bias due to deviations from intended interventions;
- bias due to missing outcome data;
- bias in measurement of the outcome; and
- bias in selection of the reported result.

We will be interested in quantifying the effect of assignment to the interventions at baseline, regardless of whether the interventions are received as intended (the intention-to-treat effect).

We will use the signalling questions in the RoB 2 tool, and rate each domain as low risk of bias, some concerns, or high risk of bias. We will contact the study author(s) to seek clarification, in cases of uncertainty over methodology or data. We will summarise the risk of bias judgements across the same study for each of the domains listed for each outcome. The overall risk of bias for the result will be the least favourable assessment across the domains of bias.

When considering treatment effects, we will take into account the risk of bias for the studies that contribute to that outcome.

We will assess risk of bias for the outcomes planned for inclusion in the summary of findings tables.

We will create a risk of bias table to report bias associated with the included studies.

We will use the ROB 2 Excel tool to carry out our assessment (www.riskofbias.info/welcome/rob-2-0-tool/current-version-of-rob-2). Due to the large amount of data generated by the ROB 2 tool, we will be unable to list all of this in the full review. However, we will list all the consensus decisions for the signalling questions in a supplemental data file.

For cluster RCTs, we will use the RoB 2 tool, and add an additional domain, specific for cluster RCTs, from the archived version of the tool (Domain 1b – bias arising from the timing of identification and recruitment of participants; www.riskofbias.info/welcome/rob-2-0-tool/archive-rob-2-0-cluster-randomized-trials-2016). We

will use the signalling questions from the archived version, and use the guidance in Chapter 23, Section 23.1.2 and Table 23.1.a in the *Cochrane Handbook* (Higgins 2019d). There is new test version for ROB 2 available, which allows analysis of cluster-randomised trials; if possible, we will use it (www.riskofbias.info/welcome/rob-2-0-tool/rob-2-for-cluster-randomized-trials).

Measures of treatment effect

We will analyse dichotomous data as risk ratios, with 95% confidence intervals, and continuous data as mean differences or standardised mean differences, with 95% confidence interval. Our continuous outcomes are:

1. MR grade ≥ 3+
2. End-diastolic volume (mL) on echocardiography
3. End-systolic volume (mL) on echocardiography
4. Ejection fraction on echocardiography
5. Quality of life (SF-36, or similar scales)
6. New York Heart Association functional classification (I to IV)

We will analyse continuous data as mean differences (MD) with 95% CIs, provided the studies have all used the same tool to measure the outcome. If studies have used different tools to measure an outcome (such as QoL, i.e. other scales similar to the SF-36), we will use the standardised mean difference (SMD) with 95% CIs instead. For SMD, we will use Hedges' (adjusted) g, which uses a pooled SD in the denominator – an estimate of the SD using outcome data from intervention groups, based on the assumption that the SDs in the two groups are similar. We will enter data presented as a scale with a consistent direction of effect.

We will use the one-half standard deviation benchmark to assess whether an outcome's change represents a clinically important difference (Farivar 2004) This method takes an improvement of more than one-half of the outcome score's standard deviation to indicate a minimal clinically important difference. In the case of any continuous data provided as a mean difference or change from baseline, we will try to extract data on both change from baseline and post-intervention outcomes, if the required means and SDs are available.

We will narratively describe skewed data reported as medians and interquartile ranges (Higgins 2019a).

Unit of analysis issues

For individually-randomised RCTs, the unit of analysis will be the individual participant who is randomised to each group. In trials with multiple treatment arms (e.g. two different types of transcatheter interventions, or two different types of surgery), we will combine multiple arms to form a single comparison. Regarding multiple observations on patients, we will select the longest reported follow-up from each study (this will apply to both the periods of follow-up).

Multi-arm RCTs and cluster-RCTs will be eligible for inclusion. We will overcome unit of analysis error in cluster-RCTs by conducting the analysis at the same level as the allocation. The data will be analysed considering each cluster as a unit of analysis. However, in cluster-RCTs where the unit of analysis is not reported, we will use an intracluster correlation coefficient (ICC) to calculate the effective sample size. We will include both individual- and cluster-randomised clinical trials and analyse the results separately (Higgins 2019b).

If we identify trials that could contribute multiple correlated comparisons with multiple treatment arms, we will combine groups to create a single pair-wise comparison for analysis. For continuous outcomes, we will carry out multiple pair-wise comparisons, where we split the control group accordingly to avoid double-counting.

Dealing with missing data

We will contact investigators or study sponsors to verify key study characteristics and obtain missing numerical outcome data, as indicated (e.g. when a study is identified as abstract only). When possible, we will use the RevMan 5 calculator to calculate missing standard deviations (Review Manager 2020), using other data from the trial, such as confidence intervals, based on methods outlined in the *Cochrane Handbook* (Higgins 2019b). When this is not possible, and the missing data are thought to introduce serious bias, we will explore the impact of including such studies in the overall assessment of results, with a sensitivity analysis.

Assessment of heterogeneity

We will inspect forest plots visually to consider the direction and magnitude of effects, and the degree of overlap between confidence intervals. We will use the I^2 statistic to measure heterogeneity among the trials in each analysis, but acknowledge that there is substantial uncertainty in the value of I^2 when there are only a small number of studies.

We will also consider the P value from the Chi^2 test ($P < 0.05$). If we identify substantial or considerable heterogeneity (indicated by an I^2 value greater than 50%), we will report it, and explore possible causes by prespecified subgroup analysis. We will use the following for I^2. (Higgins 2019a)

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

Assessment of reporting biases

If we are able to pool more than 10 trials, we will create and examine a funnel plot, to explore possible small study biases for the primary outcomes.

If we are able to create a funnel plot, we will run a formal statistical test for asymmetry (Egger 1997). If we have a small number of studies, then the ability to detect publication bias is largely diminished, so it will be difficult to exclude the presence of publication bias.

Data synthesis

We will include all studies in the primary analysis, and assess the potential effects of studies at high risk, or high risk/some concerns in a sensitivity analyses, in which we only pool studies at low risk of bias.

We will undertake meta-analyses by pooling the appropriate data using RevMan 5 (Review Manager 2020). We will use a random-effects model to combine data, as we expect some

heterogeneity in the interventions and outcome definitions. We will undertake a meta-analysis only if we judge participants, interventions, comparisons, and outcomes to be sufficiently similar to ensure an answer that is clinically meaningful.

There may be a number of reasons why a meta-analysis cannot be carried out, which we will try and overcome using these non-statistical methods:

- limited evidence for pre-specified comparison: we will group PICO elements;
- different effect measures used across studies: we will calculate the effect estimate and measure of precision for the same effect measure from the available statistics, if possible;
- bias in the evidence: when there are major concerns about bias in the evidence, we will use structured reporting of the available effects, using tables and visual displays;
- clinical or methodological diversity: we will modify planned comparisons, providing rationale for post-hoc changes.

Subgroup analysis and investigation of heterogeneity

We plan to carry out the following subgroup analyses for any outcomes with substantial heterogeneity in participants:

- Age (younger than 75 years, 75 years or older)
- Male versus female
- LV ejection fraction normal (> 50%), mid range (40% to 49%), reduced ejection fraction (< 40% (Ponikowski 2016))
- Regurgitant volume/left ventricular end-diastolic volume ratio (RVol/EDV) > 0.2 (a threshold that has been reported to potentially discern participants at higher risk of mortality (Namazi 2019))
- EROA > 0.2 cm^2 versus > 0.4 cm^2
- RVol > 30 mL versus > 60 mL
- Type of percutaneous intervention (Mitraclip, or Tendyne or Cardioband)
- Surgical approach (valve replacement or valve repair)

We will use the formal test for subgroup differences in RevMan 5, and base our interpretation on this (Review Manager 2020).

Sensitivity analysis

We plan to carry out the following sensitivity analyses, to test whether key methodological factors or decisions affected the main result

1. Only include randomised studies with low risk of bias.
2. Apply a fixed-effect model.
3. We plan to explore the impact of missing data. If we identify studies with missing data that were unobtainable, we will repeat the analyses, excluding them to find their impact on the primary analyses.

Summary of findings and assessment of the certainty of the evidence

We will use the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the certainty of a body of evidence as it relates to the studies that contribute data for the prespecified outcomes. We will use the overall ROB 2 judgement to feed into the GRADE assessment. We will use GRADEpro GDT software to create two summary of findings tables (GRADEpro GDT). We will justify all decisions to downgrade the quality of the evidence using footnotes, and we will make comments to aid readers' understanding of the review where necessary (Schünemann 2019).

Two review authors (MA, HS) will independently make judgements about evidence certainty, and resolve disagreements by discussion, or involving a third author (RS). We plan to extract study data, format our comparisons in data tables, and prepare summary of findings tables before writing the results and conclusions of our review. In case a meta-analysis is not possible, we will present the results as a narrative summary of findings table.

We will have two summary of findings tables, one for each of our two comparisons, and will include the following outcomes, at the longest available follow-up, as this is the most clinically relevant end point (Takagi 2016; Wan 2013).

- Mortality
- Hospitalisation for heart failure
- Re-intervention for mitral valve dysfunction
- MR grade $\geq$ 3+
- End-diastolic volume (mL) on echocardiography
- Ejection fraction on echocardiography
- Quality of life

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ADDITIONAL TABLES

Table 1. Quantification of secondary mitral regurgitation severity using a multiparametric approach

	MILD	MODERATE	MODERATE	SEVERE
	(1+)	Mild-to-Moderate (2+)	Moderate-to-severe (3+)	(4+)
QUALITATIVE				
Jet area by colour flow Doppler	Small (< 20% LA area)	Intermediate	Intermediate	Large (>40% LA area - EACVI;

Table 1. Quantification of secondary mitral regurgitation severity using a multiparametric approach *(Continued)*

				>50% LA area - ASE)
Jet density and shape	Faint, Parabolic	Dense, Parabolic	Dense, Parabolic	Dense, Triangular
Size of flow convergence zone	Small	Intermediate	Intermediate	Large
SEMI-QUANTITATIVE				
Pulmonary vein flow	Systolic dominant	Normal or systolic blunting	Normal or systolic blunting	Systolic flow reversal
Mitral inflow	A-wave dominant	Variable	Variable	E-wave dominant
VC width (cm)	< 0.3	0.3 - 0.69	0.3 - 0.69	≥ 0.7
QUANTITATIVE				
PISA (cm)	< 0.3 (ASE) < 0.4 (EACVI)	0.3 - 1 (ASE) 0.4 - 1 (EACVI)	0.3 - 1 (ASE) 0.4 - 1 (EACVI)	≥ 1
EROA (cm^2)	< 0.2	0.20-0.29 (ASE)	0.30-0.39 (ASE)	≥ 0.2 (EACVI) ≥ 0.4 (ASE)
RVol (ml)	< 30	30-44 (ASE)	45-59 (ASE)	≥ 30 (EACVI) ≥ 60 (ASE)
RF (%)	< 30	30 - 39	40 - 49	≥ 50

[+]3 criteria or elliptical orifice should be considered evidence of severe MR (ASE guidelines)

APPENDICES

Appendix 1. Preliminary MEDLINE Ovid search strategy

1 Mitral Valve Insufficiency/
2 (Mitral adj2 regurgitation).tw.
3 1 or 2
4 ((surg* or operation or repair* or replac* or intervention* or transcatheter* or Trans catheter* or percutaneous*) adj3 valve*).tw.
5 3 and 4
6 randomized controlled trial.pt.
7 controlled clinical trial.pt.
8 randomized.ab.
9 placebo.ab.
10 drug therapy.fs.

11 randomly.ab.
12 trial.ab.
13 groups.ab.
14 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
15 exp animals/ not humans.sh.
16 14 not 15
17 5 and 16

CONTRIBUTIONS OF AUTHORS

HS and MA have written the protocol. RS did initial editing and rest of the authors edited and approved.

DECLARATIONS OF INTEREST

HS declares no conflicts on interest

SMB has received a personal grant to attend BSEcho conference, and a grant for the NHS Joint Working from Daichi-Sankyo was given to Portsmouth Hospitals University NHS Trust; received speaker honorarium from AstraZeneca for online webinar about Dapagliflozin

BL declares no conflicts on interest.

KLSK declares no conflicts on interest

SL declares no conflicts on interest

ZT declares no conflicts on interest

DP declares no conflicts on interest

MA works as Cardiology Registrar at the Royal Free Hospital, London, UK

KL declares no conflicts on interest

AB has received research funding from AstraZeneca via his institution to look at the overlap between chronic renal impairment, diabetes, and heart failure; unrelated to the current work. I have control over this grant, and AstraZeneca has no financial interest in the finding of the current review. AB is a Trustee of the South Asian Health Foundation.

BS declares income from private practice (Wessex Cardiology LLP) until July 2019, and published an opinion in Heart about outpatient management of heart valve disease during COVID-19 pandemic.

SM has received payment by Edwards Lifesciences to their institution. SM holds an unpaid position at the British Society for Cardiovascular Magnetic Resonance and has published several research papers on valve disease, including mitral regurgitation. SM works as a Consultant Cardiologist with a specialist interest in heart valve diseases at the Oxford University Hospitals NHS Trust, UK.

BP has received consultancy payments from Anteris, unrestricted educational and research grants from Edwards Lifesciences; payments for lectures from Edwarsd Lifesciences and Abbott; and payment for development of educational presentations from Edwards Lifesciences.

RS has received consultancy payments from Edwards Lifescienes and Freeline Therapeutics; grants from Sanofi Genzyme and Takeda Shire; payment for lectures by AKCEA and payment for the development of educationa presentations from Amicus. RS declares that none of the organisations listed have a financial interest in the interventions/controls assessed in this review.

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